The Hepatitis E Virus

Pigs Might Fly

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This is a true story and is dedicated to Jackie and the memory of her late husband Peter. It's the story of the death of a man in his prime caused by a viral infection normally only seen in Asia, Africa, and Mexico, and the quest to determine why this might have happened.

The important thing is not to stop questioning.
Albert Einstein

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CHAPTER ONE

KATHMANDU VALLEY, 1973

Nepal is one of the poorest countries on earth. Until the early 1950s Nepal was "closed," and to gain entry one needed to first seek approval from the king. This meant that, with the exception of a few notables, foreigners were, to all intents and purposes, excluded. Along with Nepal's geographical isolation and lack of significant export activity, this resulted in a nation which suffered extreme hardship, which it continues to endure. In the 1950s the national infrastructure was virtually non-existent, and even today it is very basic, even by developing countries' standards.

One notable exception to the exclusion of foreigners from Nepal was the British army, who for nearly two hundred years has enlisted young Nepali men to the Gurkha regiments. Every year, the British come to the recruiting stations in the foothills of the Himalayas and, by applying a physically daunting two-week selection regime, sign up the cream of Nepali youth to serve Queen and country. Over the years, the Gurkhas have produced regiments of fighting men with a proud and fearsome reputation dating back to the Indian Mutiny of 1857–8. The Gurkhas have fought all over the globe and sustained forty-three thousand casualties in the two world wars. More recent conflicts that the Gurkhas have been involved in include Malaya, Borneo, the Falklands, Kosovo, Bosnia, East Timor, Sierra Leone, Ivory Coast, and Iraq. At the height of the Second World War there were ten Gurkha regiments and forty battalions. Following the decline of the British Empire there remain just two battalions of Royal Gurkha Rifles, one of which most recently served in the ongoing situation in Afghanistan.

Competition among young Nepali men to gain entry to the Gurkhas is ferocious. In 2011 over twenty-eight thousand applied, but only 230 were enlisted. Some Nepali families have produced recruits to the Gurkhas over three or more generations, and, for many, gaining entry to the Gurkhas is a badge of pride. It really means something. In fact, for most aspirants it means everything. For successful recruits, it is not only a way of seeing the world but provides a steady job and a very handsome income, much of which finds its way back to Nepal.

So, it was with overwhelming joy in his heart that Subash Gurung was enlisted to the Gurkhas in 1964. Subash was eighteen years old and brought up in a remote hill village. Kathmandu was 450 miles away, a two-week journey. It might as well have been Timbuktu—he had never been to either. Although Subash had no first-hand experience of places distant from his home, he had heard about them from his father, who had travelled the world with the Gurkhas and served with them with distinction during the Second World War. Before leaving Nepal, he married Sujata. She was also eighteen, lived in the same village, and the pair always knew they would get married for as long as they could both remember. He was not to see her again for a while. After basic training in England, Subash was posted to Borneo, and fought there in the confrontation between Malaysia and Indonesia. He fought with the pride of his Regiment, his family, and his adopted country. This was jungle warfare, of which Gurkhas are experts. Two days before the end of the conflict, Subash sustained serious battlefield injuries. Although they were not life threatening, he lost his left arm. His career as a Gurkha was over.

Subash returned to Nepal but could not settle into life in his village. He was restless. Privately he was a little ashamed as he felt his service to the Gurkhas fell short of his father's, both in length and distinction. Subash and Sujata moved to Kathmandu and with his pay off from the army Subash set up a business arranging supplies, porters, and travel arrangements for the increasing numbers of visiting mountaineers trying their hand at the Himalayas. His training in the Gurkhas was invaluable. He had been taught logistics the British Army way. His business, although strictly seasonal, flourished. Life in Kathmandu was good and Subash and Sujata were well off by Nepali standards. The main thing missing from their life was family. Home was many miles distant, and despite trying hard to have children, none appeared. Then, after six years, Sujata became pregnant. Both were overjoyed that God had blessed them in this way after so long. It was a precious baby.

Sujata was tired. She thought this was normal as she was eight months pregnant, and the monsoon flooding had caused much extra work both at home and in the business. Sujata thought nothing of it. She did not complain. Eight weeks before she was due to give birth, Sujata became unwell. She was feverish, her muscles ached, and she turned yellow. Like most Nepalis, Sujata did not even consider seeing a doctor. What will be, will be. It was God's will. Sujata got worse. Her skin took on a deep yellow/green colour. She became very confused and disorientated and could not get out of bed. Subash was beside himself with worry. He eventually took Sujata to hospital, but she died two hours after arrival.

Tulbahadur Kunwar came from a family of doctors. His father practised in Kathmandu, as did his father before him. He trained in Delhi and had undergone postgraduate training at the London Hospital in Whitechapel in the 1960s. While in London he was nicknamed—somewhat inevitably, and with scant regard to political correctness—as "the Gurkha." On return to practise in Kathmandu, Tulbahadur became reacquainted with the rainy season and flooding which occurred with monotonous regularity between June and September each year. The rains brought with them many cases of infectious diarrhoea and hepatitis. This was not usually such a big deal, as Nepalis are hardy people, and most recovered with no problem. However, he noticed that when pregnant women developed hepatitis, many of them died very rapidly, along with their unborn child.

The monsoon season in 1973 was longer than usual. It started early, and the rains were much heavier than the norm. In places, the flood water in Kathmandu was over four feet deep, and still the rain came. By early July, Kathmandu was in the middle of an epidemic of hepatitis. There were tens of thousands of cases. Scores of pregnant women died,[1] Sujata among them. In Nepal, it is culturally unacceptable to bury a dead pregnant woman with the unborn baby still inside the corpse. As attending physician, it was Tulbahadur's responsibility to remove the dead babies prior to burial. He had done this many times during the monsoon of 1973. He performed this procedure for Sujata, shortly after death, using a Caesarean section incision. Miraculously, the baby was alive. Tulbahadur was a religious man and thought the baby's survival was God's will. However, as a man of medicine, he did not share the widely held belief that the outbreak of hepatitis was also God's will. He did not know what the cause was.

[1] C. G. Teo, "Fatal Outbreaks of Jaundice in Pregnancy," *Epidemiology and Infection* 140 (5) (2012): 767–87.

CHAPTER TWO

AFGHANISTAN, 1979

Leonid Brezhnev was First Secretary of the Central Committee of the Communist Party and leader of the Union of Soviet Socialist Republics. He was the second most powerful man in the world. Brezhnev was no fool—he was a highly intelligent, ambitious, and uncompromising leader. But he was no student of history. He demonstrated this quite clearly by ordering the Soviet invasion of Afghanistan in December 1979. Up to this point, no invading army had ever managed to tame Afghanistan for any length of time. In the nineteenth century the British tried twice and failed. In 1842, the end of the first Afghan war was marked by the British Army with 16,500 souls being completely destroyed by the Afghans as they retreated across the Gandamak Pass. There was only one survivor, an army doctor. It is said he was spared to tell others what happens when you try it on with the Afghans. Brezhnev should have taken heed.

The Soviet army had plenty of kit, with guns, tanks, artillery, attack helicopters, and planes, along with the Spetnaz, their Special Forces, and they used it all with impunity. However, the Russians did not reckon with the tribal militias, and were ill-equipped both physically and mentally to fight a guerrilla war with the Mujahideen. The Soviets fell into a "bear trap." They left nine years later, the final convoy of heavily loaded planes struggling to make it home over the mountains to the north, spewing out streams of metal chaff in a desperate attempt to avoid the handheld surface-to-air missiles deployed by the enemy, their tails between their legs.

In addition to underestimating the tribal militias, the Soviet army underestimated the Afghani environment, and what effect it might have on its troops. Infectious diarrhoea was rife. Outbreaks of hepatitis could, and often did, incapacitate a battle group for weeks on end. No one knew what caused the outbreaks of hepatitis among Soviet troops fighting in Afghanistan, and tests for all known hepatitis viruses were negative.

CHAPTER THREE

MOSCOW, 1982

The Ilyushin II-76 transport touched down at the military airport facility just outside Moscow. The flight was late. The first snowfalls in Moscow had come early, and the runway had to be cleared before the heavily laden jet could land. On board were numerous pieces of military hardware and returning military personnel, taking a break from the war in Afghanistan. Among them was Gennady Demidov. Gennady was fed up. He had been in Afghanistan for six months as an army medic and hated it. While he was happy to be coming home for a break, it was late, and it would be even later when he got home. Under his seat on the aeroplane was a package he had to deliver to some crazy scientist in downtown Moscow. He would not get home for another four hours, minimum. At six pm Gennady arrived at the Institute of Poliomyelitis and Viral Encephalitis. He was met by Mikhail Balayan, head of the Department of Viral Hepatitis. Gennady handed over the package without ceremony. Conversation was minimal—he wanted out of the door and home as quickly as possible. He did not know what was in the package and cared even less.

Mikhail put the package on the bench in his lab. He did not open it straight away but sat and looked at it for a while. The package looked innocuous enough—it was a small cardboard box taped up in a number of rather haphazard directions to keep the lid secure. There were no labels on it, no named addressee, no attached inventory of contents. This was a special package. Very few people knew the contents, but Mikhail did, and he knew what he was about to do with them. Mikhail was a virus hunter.

Mikhail locked the lab door. Although it was dark outside, he pulled down the blinds. He then returned to the package on the bench, removed the tape, and opened it. Inside were nine capped plastic beakers. He opened them one by one, setting them side by side. The smell was not pleasant as they contained samples of human faeces fresh from Afghanistan, from soldiers laid low with unexplained hepatitis. He ignored the smell, took a deep breath, and kicked into scientist mode. To each plastic beaker he added 50 millilitres of saline. He stirred them one by one.

The contents were then passed through the rudimentary filtration system he had set up earlier that afternoon. The pore size on the filter was quite large—he just wanted to remove the big bits. The filtered fluid was murky, smelly, evil-looking stuff, and was collected in a glass receiver. When all the samples had been processed he was left with just under half a litre of filtered human shit. Mikhail looked at it then turned on his heel and opened the lab fridge. He took out a large carton of yoghurt and opened it before adding it to the filtrated stool suspension, stirring as he went. He took another brief look at the creamy suspension, took another deep breath, and drank the lot in one go, followed immediately by a large glass of vodka.

Two weeks later Mikhail developed hepatitis. He went yellow and felt as though he was going to die, but the scientist in him knew that the chance of fatality was small. Well, smallish. Despite being very off-colour, he was well enough to collect samples of his stool. These were picked up by one of his several assistants and delivered to the lab, where the team were geared up for action. Four weeks later, Mikhail had recovered enough to go to work. The guys had been busy. They all piled into the tiny room housing the electron microscope—a very powerful tool that has a magnification of fifty million times and a resolution down to one ten-millionth of a millimetre. Mikhail pushed his specs onto his forehead, looked down the scope eyepiece, and adjusted the settings slightly. As he did so he saw hundreds of tiny disc-like structures. Mikhail had found himself a new virus, and in so doing joined an increasingly lengthy list of scientists and doctors who have successfully experimented on themselves in the name of medicine.[1]

The virus that Mikhail had found was later named hepatitis E. Not only was it the cause of the hepatitis in the Soviet forces in Afghanistan, but was later shown to be the cause of the outbreaks in many other developing countries. Hepatitis E has subsequently been shown to be a very common infection in some developing countries in the world. It is spread by contaminated drinking water (the so-called oral-faecal route) and is therefore particularly common in areas with poor sanitary arrangements. There have been a number of very large outbreaks, with thousands of young adults affected in the Indian subcontinent, war-torn areas in Africa, and Mexico.[2]

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[1] M. S. Balayan, A. G. Andjaparidze, S. S. Savinskaya, E. S. Ketiladze, D. M. Braginsky, A. P. Savinov, V. F. Poleschuk, et al., "Evidence for a Virus in Non-A, Non-B Hepatitis Transmitted Via the Fecal-oral Route," *Intervirology* 20 (1) (1983): 23–31.

[2] M. S. Khuroo, "Study of an Epidemic of Non-A, Non-B Hepatitis: Possibility of Another Human Hepatitis Virus Distinct from Post-transfusion Non-A, Non-B Type," *The American Journal of Medicine* 68 (6) (1980): 818–24.

CHAPTER FOUR

CORNWALL, 2006

Peter felt ill. Peter never felt ill, and if he did feel a bit off colour he rarely saw his doctor. He was of the generation who did not like to bother doctors—he didn't want to waste their time. He did not like doctors. They patronised him and, secretly, he was frightened of them. Still, he did not feel well at all. He'd tossed and turned all night with fevers and sweats. When he awoke he felt liverish and looking in the mirror he saw that the whites of his eyes had a faint yellow tinge. The muscles of his not inconsiderable torso ached, as though he'd been on the receiving end of a good kicking. He'd not been in a brawl for some years, having given up his part-time job as a bouncer at one of the many local nightclubs when he'd turned forty, at Jackie's insistence.

Peter was fifty-nine years old. He was born in Liverpool, England, and like most scousers had a dry, cutting wit, and said things exactly as he saw them. After school, he'd done various manual jobs, including being a bouncer. Such work was relatively easy to find for a man with Peter's build and acerbic interpersonal skills, as the city of Liverpool at that time was reputed to have the highest concentration of nightclubs in the world. After his first marriage broke up he met the love of life, Jackie, who waited at the tables of a club. They were still young and decided to make a break from their past and moved four hundred miles south to Newquay in Cornwall to settle down. They were happy together. They fought, they kissed and made up. They loved each other.

Peter and Jackie rarely took holidays away from home. They were a bit short of cash when the kids were growing up and, as Cornwall is a major UK tourist destination in the summer, they spent their holidays at home. Newquay becomes stuffed to the gunnels with tourists for eight weeks during school summer holidays. It is popular with working-class families from the midlands, who are catered for by endless caravan parks, cheap hotels, fast-food joints, and nightclubs. It also attracts the surfing brigade due to the large (by UK standards) waves caused by the Atlantic swell. Malibu it is not, but as far as Peter and Jackie were concerned home in Newquay was perfect for a holiday. The beach was just down the road to

keep the kids happy, and their favourite pub was just around the corner. Why spend all that money going abroad? In any case, they didn't much care for foreign food.

Peter smoked, drank, supported Everton football club, and liked practical jokes. He was a man's man. Ten weeks later he was dead. He was killed by the same virus that had caused Sujata's death in Kathmandu, the same virus that had crippled the Soviet army in Afghanistan.

CHAPTER FIVE

THE WORK ETHIC

In the late nineteenth century my great-grandfather was run out of his village in rural Lincolnshire, England, where he worked as a farm labourer. He'd committed the cardinal social sin of failing to doff his cap to the Lord of the Manor—not once, but twice. He'd been warned. He dug his heels in, and as a result he and his family were unceremoniously ejected from their tithed cottage. They began the long trek, with all their worldly possessions, northwest across the Lincolnshire countryside and into the county of the West Riding of Yorkshire. After a hundred-mile journey, it was here they settled. Presumably, my rather pig-headed great-grandfather felt more at home among Yorkshire men who, in general, are straight talking and not infrequently as stubborn as he was.

Max Weber, the nineteenth and twentieth-century German sociologist/philosopher, thought and wrote a lot about religion.[1] To him, religion was a "social construct." What he meant by this was that, by and large, religions flourish and develop to support the existing social order. In India, for example, the caste system has been entrenched for thousands of years. This has allowed the Hindu religion to flourish to support the social order. I have often wondered whether Max Weber visited West Yorkshire when he was developing the theory. West Yorkshire and its heavy woollen industry were at the heart of the Industrial Revolution in Britain in the late eighteenth century. At around the same time, the non-conformist Protestant religion took a major hold in the area, largely through the efforts of the Wesley brothers. The woollen mills and Protestant church (largely, but not exclusively, the Wesleyan branch of the Methodist Church) prospered together in a symbiotic relationship. There was a large body of working men, women, and children who serviced the woollen mills with their labour. They were downtrodden and largely without hope in their lives. Enter the Methodist Church. Hellfire and brimstone if you do not work hard. No drink, no gambling. No idolatry, fornication, or fun. Love your neighbour as yourself, including your beneficent employer.

[1] M. Weber, *The Protestant Ethic and the Spirit of Capitalism* (1905).

Repent all your sins. Do all the above, all the time, always, and you might just avoid the drop into the fiery pit.

I was brought up in the 1960s in the West Yorkshire town that my great-grandfather chose. The Industrial Revolution had waned considerably since its heyday in the Victorian era. Nevertheless, when I was growing up, there were still eighteen Methodist Chapels and forty-five working woollen mills. I recall the latter because of the noise, which was more pronounced on a summer's day when all the windows were open: chuckachucka, chuckachucka, chuckachucka, chuckachucka, chuckachucka. The noise was deafening when walking past the outside of the mill. It must have been almost unbearable inside and, of course, in those days nobody had heard of ear-protectors, let alone wore them. The other thing about the mills was the smell, a slightly heady, perfumed mixture of grease, wool dye, and human sweat.

I was the youngest of five. Dad was a carpenter. Mother was a mill girl but gave it up to raise the family. When we were a bit older she did all sorts of part-time jobs to make ends meet, and there was always "the property," a few one-bedroomed workers' cottages that my dad had scraped enough money together to put a deposit on. He let them out to pay the mortgage. They needed considerable maintenance, and all his spare time seemed to be taken up doing this. When we were old enough (ten years of age or so), we were expected to lend a hand. Hard work it was, too. I still swing a mean paintbrush, but unfortunately none of the carpentry skills rubbed off. I wished I'd paid more attention.

We had one bath every week on a Saturday night to spruce us up for chapel the following morning. The places of worship are known as chapels rather than churches. They were plain and simple, with no stained-glass windows, almost (but not quite) Quaker-like and rejoiced in names such as The Bethel and The Primitive, known locally as The Prim. Two hours of fire and brimstone later, it was home for Sunday lunch. When we got older, us kids prepared the meal and Granny would come over to join us. We always cooked roast meat and two vegetables. The meat was slightly over cooked by today's celebrity chef's standards, particularly so with roast pork as we had it drummed into us by Granny that pork should, under no circumstances, ever be undercooked. How correct she would prove to be. We cremated it.

Life as a kid was not all drudgery. We had fun, and plenty of it. We'd play outside in the street—hide and seek, cricket, soccer. My personal favourite was "kick the can and run." This is essentially a version of hide and seek, but instead of counting to ten or twenty before the seeker could begin his task, one of the "hidees" kicks a can (usually a used tin of

vegetables or soup) as far as he (these were almost invariably boys' only events) could. The seeker then had to go and fetch the can and replace it at the spot from where it was kicked before he could start the search for the other players, who had by now hidden themselves well away. I enjoyed this game most because I perfected the technique of the "lofted can kick." I invariably aimed it into next doors' garden, over a six-foot wall. This meant the seeker had to scramble over the wall to get the can back, and we would be hidden a hundred yards away before it was retrieved. I practised the lofted can kick to perfection, and I could always be relied upon to get any can of any shape, size, or variety over the wall.

As I entered adolescence, play became less frequent. At the age of ten I did a paper round every day. At twelve I had a Saturday job in a butcher's shop. My job was to deliver meat to the homes of the customers. This was done on an old-fashioned butcher's bike with a huge wicker basket on the front. Other jobs included assistant in a tailor's shop, market-stall helper, hospital cleaner, and building-site labourer. Best of all was my last job before going to medical school, which was full assistant at the local pork butchers. One of my tasks was to complete the pork pies by adding the warm jelly through a hole in the top of the pastry. Staff were allowed to each eat one pork pie per day. They were extraordinarily delicious, and people came from miles around to buy them. After extensive deliberation, consideration, and a personal sampling policy that was not completely congruent with house rules, I decided that slightly warm pork pies were best, ninety minutes after coming out of the oven and forty-five minutes after jelly insertion. Yummy. I still love pork pies, but never seem to be able to find ones of the same quality. I did not know it at the time, but by consuming large quantities of these delicious pork pies I was exposing myself to an as yet unidentified hepatotropic virus. The same one that killed Peter.

As I got older, I rebelled. At fifteen I refused to go to chapel and have never been since. However, I'd shown signs of my great-grandfather's independent spirit at a much younger age. One of the golden rules in our household was: "never spend any money on a Sunday." Now, I had a number of issues with this concept, even at the age of eight. I was particularly keen on soccer, and a follower of the local club, Leeds United, who were then in their heyday. A big thing in those days was soccer cards. These were cards featuring the photo and career history of the top UK players of the day, which were sold with chewing gum. I had a good selection but wanted to get the cards of the entire Leeds United team. I had a few important team members missing, including Billy Bremner and

Johnny Giles. Money was tight. What to do? The answer was the collection money.

During every service at chapel there was an offertory—a collection of money from the congregation of worshippers to pay the minister and general chapel overheads. As kids, Mum and Dad gave us each threepence, or occasionally sixpence, to put in the offertory bag. This bag was passed round the congregation and everyone put their hand in the bag with their contribution (a bag was used so that nobody could see what anybody else was coughing up). I mastered the art of the "threepenny-bag-flick." My closed hand would go in the bag. I would then flick the side of the bag with my index finger, making the coins in the bag move as though they had just been joined by another coin. Of course, the threepence was in my pocket and was spent on the way home (rushing ahead of Mum and Dad to cook lunch) on soccer cards and chewing gum. I never did get Johnny Giles.

I'd wanted to be a doctor since about the age of eleven. I'm not entirely sure why, but my dad was very ill around this time and maybe this influenced me. Dad had rheumatoid arthritis. He got this in his early forties and the disease was relentless, progressive, and crippling. He never complained much, and I think his mates at work helped him a lot with the heavy lifting. In his late fifties he became increasingly ill. His main symptom was profound exhaustion. He could not walk to the end of our street without stopping, a distance of barely two hundred yards. Twelve months later, after seeing numerous specialists and having countless tests, he was admitted to hospital for four weeks for further evaluation. He was found to have an unusual condition called constrictive pericarditis. This is very rare indeed, and his case was subsequently written up in the British Journal of Rheumatology. The condition is caused by dense scar tissue forming around the outside of the heart, preventing it from working properly. He was treated by cardiac surgery to remove the scar tissue and was back to his old self in no time. Many years later, when I was in my final year at medical school, he told me how the diagnosis had eventually been arrived at after all those tests and opinions. A bright young doctor, not long qualified, had spotted that the veins in his neck were much more prominent than they should have been. This was due to the fact that the blood in his veins could not properly flow back into his non-compliant heart, which was being crushed by the external scar tissue. I never forgot this.

Unsurprisingly, I worked hard at school, and I did quite well in exams. At the age of eighteen I left home for good and travelled two hundred miles south to study medicine at the Charing Cross Hospital Medical School in London.

CHAPTER SIX

LONDON, 1977

On the first day of medical school we met Professor Tony Glenister. He was in his late fifties, short, bald, and, like many of his generation in the medical profession, had the tendency to peer over his half-moon spectacles when making a particularly salient point. In addition to being the dean of the medical school, he was the Queen's Anatomist. I'm not entirely sure what roles and responsibilities this particular sinecure entails. However, we students knew we would be studying human anatomy, and plenty of it. So it proved to be. We spent nearly fifty percent of the week in the anatomy dissection room during the first two years. By both national and international standards this was excessive. I guess he wanted to ensure that, if Her Majesty enquired, he could confidently reassure her that, should she require the services of the next generation of young doctors, they would certainly be able to find their way around the Royal Frame.

Studying anatomy in those days was a rite of passage. It moved students from the innocence of laity to fledgling, death-corrupted, members of the medical profession. The key to this whole process was the dissection room. This was an enormous room on the fourteenth floor of the medical school. It was light, airy, and had large windows on three of its four sides, with stunning views over the River Thames and to the centre of London, some four miles to the east. It contained twenty human cadavers, laid out neatly on two rows of dissecting tables, ten to a row. There was considerable space around each table to accommodate the six students allocated to each body.

The tradition was that the first-year students were introduced to the dissecting room in general, and their human cadaver in particular, on day one. Most of us, myself included, had never seen a dead body, let alone twenty in one go. The first thing that hit me was the smell, which was very unpleasant, noxious, acrid, and incisive, going straight up to the back of the nose and smacking the back of the palate. This was followed, after a time, by a sickly-sweet lingering aftemote with hints of honey and plenty of malt vinegar. This was the smell of death and formalin, used to embalm and preserve the bodies. The smell was overpowering as soon as the lift

doors opened on the fourteenth floor. When we got into the dissecting room itself, the smell grabbed all the olfactory nerve endings. This was compounded by the gut-wrenching assault on one's visual sensory apparatus of twenty dead bodies laid out in two coldly straight rows. Not surprisingly, a number of my peers fainted or rushed out to be violently sick. I managed to stay on my feet and keep hold of my breakfast. But only just.

We were to spend hours and hours carefully disassembling our cadavers over the next two years. We were not encouraged to use gloves and after a morning's work one's fingers became soft and wrinkled, like when you have spent too long in a hot bath. We all kept our fingernails cut very short. If not, death quite literally got under the skin. As time went by, the smell of formalin and our physical intimacy with death somehow became less obtrusive. The macabre nature of our task in our somewhat surreal surroundings was inevitably offset by lavatorial humour. However, despite apocryphal stories of the "give us a hand, mate" variety, we treated our cadavers with respect. I was particularly conscious that both my parents had left their bodies to medical science and would one day end up on the dissecting table. Indeed, my dad was dissected by students at the medical school in Leeds twenty-five years ago, following his death at the age of seventy. I guess they got a bit of a surprise when they came to his heart.

Today, most medical schools throughout the world teach human anatomy using models and computer simulation. This is so-called "dry" anatomy. In my view, this results in a lack of depth of understanding—not only of structural relationships in the human body, but also the unique physical and metaphysical introduction to death that can only be gained in the dissection room. I acknowledge that this is an old-fashioned view, and that I'm also starting to sound rather like Tony Glenister. He died a few years ago, God rest his soul. Part of the reason for the move to dry anatomy over recent years is the paucity of cadavers, as fewer people now leave their bodies to medical science. However, there are still a few medical schools that continue to teach "wet" anatomy, as my peers and I were taught. Three of my sons went on to study medicine; I tried my best to put them off. They were all taught in the dissecting room and once in a while they would email me some anatomy questions to keep me on my toes. I would send my answers without looking them up. I performed creditably in this exercise, and got a good percentage of the answers correct, but cannot remember anything about the detailed anatomy of the foot. Bearing in mind I have not studied it for nearly forty years, I'm

amazed how much anatomy I can still remember. I offer my, slightly begrudging, thanks to the Queen's Anatomist.

The dean told us we would have to do six hours of bookwork every day, as well as our dissection and lectures. As the work ethic was firmly on my hard drive, this posed no problems to me. In the first year I took his advice literally, and got straight As. I realised I'd overdone it and slackened off a bit afterwards, but always took my studies seriously. Having said that, medical school was not all work by any means. I was free from the constraints of my strict Methodist upbringing and I guess I went a bit wild. We went on cricket tour each year to the sleepy Devon village of Cheriton Fitzpaine, whom the hospital's cricket team has played every year since 1958. We would camp in a field belonging to one of the Cheriton team members and played the match on their tiny pitch. It is so small that scoring two or three runs is quite impossible. Between innings, a traditional Devon high tea would be laid on at the side of the pitch on trestle tables, which sagged and groaned with the weight of the delicious homecooked food.

After the match we repaired to the Half Moon public house for refreshments. In those days, this village hostelry only had two extensions to licensing hours (this allowed drinking after the normal closing time of eleven pm) each year. One was New Year's Eve, the other in July when the "young doc'ers" came down from London to play the village at cricket. They serve a particularly fine scrumpy (a type of homemade cider) at the Half Moon, which has hallucinatory properties in the over-indulgent. Looking back, some of the antics we got up to, particularly on cricket tour, were childish, immature, and puerile. Do I have any regrets? Not really. UK medical students were at that time renown for the amount of alcohol they consumed. I have to say that, although this assertion was accurate at the time I went to medical school, this is not so nowadays. Modem-day students today are more likely to be older, have a previous degree or other life/work experience before starting, and have far more academic work and exams than we ever did, my first year notwithstanding. As a result, they are far more serious, play much less sport, and drink less.

The quality of teaching we received can only be described as indifferent. I was surprised by this, as I had expected better. We had quite a few teachers who were truly awful while most were average, but a handful were quite exceptional. Max Lab, professor of physiology, fell firmly into the latter category. He was in his late thirties and always wore a pinstriped suit with fashionably wide jacket lapels and flared trousers. Even we boys recognised that he was good looking; the girls simpered. However, what was really outstanding about him was that he could make

his at times rather dry subject come completely alive. He did this by illustrating key points with reference to patients, although he was a scientist (physiologist) and not a clinician (physician). I still recall his lecture about the physiology of the heart. He told us the "bread and butter" of how the heart worked, and what happened when it went wrong. This took him thirty minutes or so. He then stopped and told us the following story:

> I was flying across the Atlantic to the United States last year, and the elderly American passenger in the seat behind me had a heart attack. He became very breathless, as his left ventricular function was impaired, and fluid started to dam back into his lungs. He went blue in the face and started frothing at the mouth. There were no drugs on the plane that I could use. What did I do, and what is the physiological reasoning behind the action I took?

Now that's a thought-provoking question. We considered the issues and discussed it between ourselves for five minutes or more. We came up with a number of possibilities, including: "slitting a vein on the patient's arm and taking a pint of blood out." This suggestion was deemed overly dramatic, highly dangerous (as the patient was already likely to have very low blood pressure), and a bit messy for British Airways first class. In fact, what he said he did (I've always assumed it was a true story) was to place tourniquets on both arms and both legs. The tourniquets needed to be given the correct amount of tightness—slack enough to allow arterial blood to enter each limb, but tight enough to prevent blood flow back to heart in the veins in each limb. The net result was that blood was effectively pooled in the patient's arms and legs, which became engorged, swollen, and blue. This reduced the volume of blood in the patient's circulation, so reducing the amount of work the already stressed heart had to do. Neat. We asked him if the patient survived. He declined to answer.

The consultant staff at the hospital who taught us clinical medicine in the last three years were also a mixed bag. There was a strong masonic influence, and a good number of the consultant staff also held part-time appointments at the Royal Masonic Hospital, which was a mile or so down the Road in Hammersmith. We students, and our patients, encountered kindness, brilliance, indifference, incompetence, navel gazing, anal retentiveness, arrogance, and contempt in equal measure. On one occasion, I was so incensed by one consultant surgeon I told him what I thought. Although he treated patients well he didn't care about them. I felt he treated them with no humanity. I told him so in great-grandfather's "eat your heart out" no-uncertain terms. Needless to say, my assessment marks

were adversely affected, and my attitudinal difficulties noted. Thankfully, my academic marks were good, and I avoided having to retake the placement. Perish the thought.

Our first clinical attachment was to the neurology service. We saw patients with all manner of weird neurological problems. The unit was a national centre for motor neurone disease, and at any one time half the ward was full of patients with this dreadful disease. Motor neurone disease causes a wasting of the motor nervous system, causing the muscles of the body to waste away, so in the end the patient is unable to move at all. The worst thing about it is that the sensory nervous system is completely intact, so the patient can hear, smell, taste, and feel pain just like the next person. Thus, at the end of the disease the patient becomes "locked in," with a completely intact sensory nervous system but unable to respond to the environment. There is no cure. It was very depressing to see patients with this inexorably progressive disease with no hope but a horrible death. Also, one of the first symptoms is muscle twitching. We all thought we were coming down with the disease, until we realised an odd twitch in a muscle is quite normal. This was one of several diseases I thought I was developing during the course of my studies, an experience shared with many of my peers.

One of the consultants who ran the service was quite brilliant. Patients came from all over the United Kingdom to see him, and he had an international reputation for research. He was an excellent clinician. He always got the diagnosis correct, although quite how he did this baffled me at the time. He used to run a morning teaching clinic every week, which is where I first met him. He'd see four or five patients in an hour and ask them two or three questions, but rarely more. He examined their eye movements and gait. Then he tested a couple of the patients' reflexes with a tendon hammer, and when in a rush I saw him do the arm reflexes by bashing their arm with the hammer with the patient still wearing a coat! He'd then ask us what we thought the diagnosis was. He'd tease us a bit, tell us what it was, and then move on to the next case. At just past ten am he'd put on his coat and hat and go out the door, climb into his Rolls Royce, and drive off to Harley Street. The senior registrar would finish the clinic. Although he was a first-rate diagnostician, I had about as much respect for him as he showed his (NHS) patients.

Quite a different kettle of fish was Keith Reynolds. He was an East-End boy made good, and a consultant surgeon. Although he was extraordinarily fearsome, wore formal morning wear on his ward rounds (tail coat, striped trousers—the whole nine yards), and was completely demanding of his staff, there was another side to him. He was a quite

brilliant bedside teacher. Coming up to our final exams he would come in on a Saturday morning in his own time and do some clinical teaching, with patients in attendance. The lecture theatre would be packed, a full house every time. Yes, he was arrogant. Yes, he shouted, and very loudly too. However, underneath the crusty exterior he was kind and cared deeply about the patients in his charge. I'll never forget the way he set a terrified patient at her ease. She was going to the operating theatre for emergency surgery, to identify and hopefully stop the source of severe internal bleeding. The way he spoke to her turned a terrified old lady into a serene, contented, and completely trusting patient. Keith died a few years ago. I was sorry to hear of his passing.

CHAPTER SEVEN

KASHMIR, 1979

One of the highlights of my medical-school years was a trip to northern India. I went there with a couple of student friends for two months in the long summer break before starting our clinical training. We'd spent the six weeks before working all hours God sent on a building site in order to finance the trip. India—what a remarkable place. An assault on the senses—heat, humidity; the colours, the food. Teeming with people, with monsoon rain, with filth. We did India on the cheap—no five-star hotels; no air-conditioned buses; no guided tours. Yes, we went to the usual places: Delhi, Jaipur, Agra, and the Taj Mahal. But we did it on a student budget. Queuing to get a train ticket at Delhi train station ticket office was not a question of getting in line. It was world-class rugby scrummaging that went on for hours. Naturally, you can hire local agents to do this for you, but we did it ourselves. In general, we travelled third class by train, often with a hundred people on the roof of our carriage.

At medical school I was introduced to curry. I grew a taste for it. Just as well, as on our budget we had curry for breakfast, lunch, and supper, although I never did quite get used to having curry first thing in the morning. Being relatively impecunious students, we ate at some fairly dodgy eateries, including some roadside fast curry joints. We all got "Delhi-belly," myself quite badly—eighteen bowel movements in one day was my record. The problem was, there was only a twenty-second warning as there was absolutely no way of deferring the defecatory reflex. I lost two stone in weight during the trip, and my bowel has never quite been the same since.

The highlight of the trip was Kashmir, a wondrous valley surrounded by white-capped Himalayan peaks. It was much loved by the British who, in the times of the Raj, would decamp to its cool climate to escape the oppressive summer heat. They were partial to staying on "houseboats" on Lake Srinagar, the provincial capital. We thought that was a good idea and stayed on a downmarket version of the same. Lake Srinagar is stunningly beautiful, and home to several hundred houseboats. These are like large canal barges permanently moored on the lake and are effectively small

floating hotels. We used to sit out on the roof in the evening and watch the sun go down behind the Himalayan peaks, the closest thing to heaven on earth. Now, sadly, because of the troubles, it's too dangerous to visit.

One of my friends, in addition to the trots, developed another illness while in Kashmir. He reckons it all started after a dodgy masala dosa, a kind of spicy Indian pancake. He became rather listless and tired. We thought it was the heat. This proved inaccurate, as a few days later he became jaundiced. The whites of his eyes went bright yellow. He had hepatitis. He remained unwell for a further three weeks, the jaundice fading after ten days. In the end, he made a complete recovery. I wasn't to know it at the time, but he may well have been my first experience of a case of hepatitis E. At this time, although the infectious agent was yet to be discovered, Kashmir was in the middle of an epidemic of waterborne hepatitis. During 1978–9 there were over twenty thousand cases in the Kashmir valley. In all, 436 pregnant women died, along with their unborn children. This epidemic was subsequently shown to be caused by hepatitis E,[1] the same virus that killed Sujata in Kathmandu and crippled the Soviet army in Afghanistan. The same virus that killed Peter in Cornwall twenty-six years later.

[1] M. S. Khuroo, "Study of an Epidemic of Non-A, Non-B Hepatitis: Possibility of Another Human Hepatitis Virus Distinct from Post-transfusion Non-A, Non-B Type," *The American Journal of Medicine* 68 (6) (1980): 818–24.

CHAPTER EIGHT

LONDON, 1984

After qualification I had the somewhat dubious honour of being selected as house physician to the Professorial Medical Unit at the Charing Cross Hospital. The medical team of five doctors in various stages of postgraduate training and known as "The Firm," of which I was the most junior member, was headed by Professor Abe Guz who specialised in chest medicine, which in reality meant a ward full of patients with end-stage emphysema. The Firm worked as a team. We were all on call together, and we looked after virtually all the patients we admitted to hospital. They were our patients, they belonged to us. If a patient died, that was The Firm's responsibility. This ethos taught me how to look after my patients. It was very personal. If I messed up, the patient died.

Emphysema is caused primarily by smoking, but also occurs in patients who have not smoked as they age, particularly those from an urban environment. In rare cases, a genetic enzyme deficiency causes the disease, and such patients present in their thirties or forties. The main symptom is breathlessness. Patients have over-expanded non-compliant lungs and find it particularly hard to breathe out. To help with the breathing process, patients typically adopt a sitting posture, and generally have to sleep sitting upright. They also breathe through pursed lips and use their so-called "accessory muscles" to help them. The latter are muscles attaching the neck to the top of the chest wall which contract and relax with each breath to try to get air in and out of the lungs. This is a very tiring process for the patient, and towards the end very distressing. In those days, there was nothing much we could do to arrest their gradual decline, and I was asked by more than one to put them out of their misery, which I never did.

Despite my genetically acquired work ethic, even I found the work very demanding. These were the days of the "1 in 3" rota. What this meant was that one was expected to work a normal day (this was often eight am to eight pm) during the week. In addition, one was on call for emergency admissions one day in three, and one weekend in three. The weekends were the killer. Work would start at eight am on Friday, which was a

normal working day. Emergency admissions would then follow from five pm Friday until eight am Monday morning. One was expected to work right through, often with little or no sleep, and then do a normal day's work on Monday. It was thus possible to work eighty hours straight, with no sleep. No time off was given to recover. When I arrived, I found I was rostered on call for three weekends on the trot. I did it, but nearly went psychotic with sleep deprivation, and only left the hospital once during that time, to get my haircut. I undoubtedly made many sleep-deprived errors, a common occurrence in UK hospitals in those days. Things have now changed, and quite rightly so. Doctors in training, at least in the United Kingdom, can now no longer work more than fifty-six hours per week, allegedly.

Among many rather onerous tasks I had to do I recall two in particular. First up, every morning I did the "sputum run." What this meant was that I had to run around the ward and get every patient to cough up their respiratory secretions into a small white pot. A tedious, time-consuming, and not altogether pleasant job. It also had to be completely fresh, of the "Dalton: I mean still at body temperature" variety. Twenty-five patients later, I would run down three floors to the microbiology laboratory clutching a bag with twenty-five pots of putrid spit and make my way to the "hot bench." This was where samples such as sputum were plated up on dishes containing culture media, and staffed by a young Scottish Microbiologist. It was her job to plate up the sputum and incubate them (usually at 37°C) for forty-eight hours to see if they contained any bacteria. It was quite unnecessary to do sputum culture on every patient every day. She knew this and told me so, very nicely. I could see her argument; Abe could not.

My second task was worse, but thankfully had to be done only twice a week. Before each of Abe's ward rounds it was my job to make sure all the patients' chest x-rays were on the ward, neatly filed with each patient's case notes. It sounds easy, but the reality was somewhat different. This task meant a trip down to the x-ray department, in the bowels of the hospital. The first time I did it I arrived in a bit of a rush and asked the receptionist where I might find the x-rays of my list of patients. She took me around the corner to the so-called "reporting room." This small office was a complete mess with paperwork and, more pertinently, x-rays were scattered all over the place. She pointed to two piles of x-ray packets in the corner, which were so huge they nearly reached the ceiling.

"They are in there, or at least I think they are," she said.

"Thanks."

One-and-half-hours later I had found all but one of my patients' chest x-rays. These days, we don't have old-fashioned x-ray films or x-ray packets. All the images are stored on computer—no lost films, no hunting through piles. All my house physician has to do is a click a button. *Plus ça change.*

Abe Guz was a very scary man. He was very short and very bald, and when he put one of The Firm on the spot (a regular occurrence on his ward rounds) he would invade one's personal body space. This was a really quite intimidating manoeuvre he employed and involved him getting as close to his "victim" as he possibly could, without touching, and locking eyes. Unfortunately, as Abe was so short, he invariably had to extend his neck back and look up, as his "victim" was almost invariably considerably taller than he. In my case, this resulted in him looking straight up my nostrils—very anxiety-provoking.

Abe is one of the brightest doctors I have ever met, either during the course of my undergraduate studies or in the subsequent thirty-five years I have spent practising since qualifying as a doctor. To me, his head somehow always seemed slightly out of kilter with the rest of his body. This, perhaps, is as a result of his short stature making his head look disproportionately oversized. On the other hand, his head may very well have been larger than average to contain his brain, which was intellectually the size of a planet. Abe was, in many ways, the archetypal "mad professor." He could often be seen patrolling up and down outside the medical-school buildings, a bundle of papers under his arm, head slightly bowed, brow furrowed, deep in thought. He was also highly strung and, when he got particularly excitable, would stick the end of his tie in his mouth and chew it. One evening he was spotted in the medical-school bar talking to the professor of surgery. They had just been to some academic administrative meeting, at which there must have been some kind of contretemps as the conversation was animated, and Abe was doing his old personal-space invasion trick. Abe grew really quite agitated and, as was his want, reached for his tie and put it in his mouth. He started to chew the end of it vigorously. He continued to munch with gusto until it was pointed out that the tie, in fact, belonged to the professor of surgery.

Abe could also be quite forgetful. He is said to have once been taking his kids home in the car when he stopped at the newsagent around the corner from his local tube station, leaving the kids as he popped in to get a newspaper. Following this, his mind completely elsewhere, he proceeded to the station, down the steps, and caught the tube home. You can just imagine the scene when he got home as he greeted Mrs Guz:

"Had a nice day, honey?"

"Abe?"
"Hmm?"
"Aaaabe?"
"Hnnnmmm?"
"How did you get home?"
"Er … oh, on the tube."
"Abraham?"
"Yes sweet pea?"
"Where are the kids?"
(The reality dawns on Abe who, in true Woody Allen style, smacks his forehead with the flat of his hand and murmurs to himself.)
"Ah, Abe, you schmuck."

But Abe was no fool. He had a worldwide research reputation in his field of respiratory medicine, was a very, very able clinician, and his diagnostic work is among the best I have ever witnessed. Given his ability, the only time I ever saw him get the diagnosis wrong sticks in my mind. It was with a very tricky patient with all sorts of unusual symptoms, with nothing much to find on the physical examination. However, the patient had bought himself a sphygmomanometer (a very unusual thing for a patient to do at that time) and had been checking his own blood pressure at least four times a day. He had dutifully recorded his blood pressure readings on a graph, beautifully annotated with his neat copperplate script. This showed that his blood pressure was all over the place—sometimes normal, sometimes very high indeed. Abe was convinced he had a rare condition called a phaeochromocytoma.

In ninety-five percent of patients, high blood pressure is "primary" (i.e. there is no specific cause) and is aggravated by being overweight and a high salt intake. In five percent of patients with high blood pressure, it is secondary to another cause. For example, patients with kidney disease often get high blood pressure, which is caused by their kidney trouble. There is a fairly lengthy list of other conditions that can also cause high blood pressure. Phaeochromocytoma is right at the bottom of the list, in small print. It is caused by a small, often benign, tumour in the adrenal gland that secretes adrenaline and adrenaline-like substances into the patient's blood stream. The hallmark of this condition is bursts of very high blood pressure, often associated with quite bizarre symptoms, caused by the intermittent release of adrenaline by the tumour. To give an idea how rare this is, I have only seen three cases in my career as a practising internal physician.

Abe was convinced this patient had a "phaeo." He did his usual ward round, full entourage in tow. He told us his clinical diagnosis. He then told all the assembled members of The Firm that he was off to China for a six-week sabbatical to study acupuncture and Chinese herbal medicine, that he

was completely sure of the diagnosis, and that we were to confirm it before he returned. Oh dear.

The way to make the diagnosis of a "phaeo" is to measure the adrenaline levels in the blood stream. The problem is that the adrenaline is often released in bursts, and such peaks in serum adrenaline are often very transitory. What this meant in practice was that, over the next six weeks, the poor patient had a very large number of blood tests. The first week I took eight separate samples (at differing times of day and night) and sent them up to the laboratory for analysis. I got a call on the Monday of the following week. I was required to explain to the Head of Biochemistry Department why we had sent so many samples for testing, whether I realised how much each test cost, if I understood how short-staffed his department was, and if I really thought the patient had a "phaeo" now that all eight samples showed normal adrenaline levels. I talked this through with the senior registrar, a very nice man. He had been on The Firm quite some time and was looking for a consultant post. To succeed in his quest, he would need Abe's support and reference. He needed to get this case right.

"OK, Harry, here's the plan. We'll put the patient on continuous blood pressure monitoring and get the nursing staff to do it every fifteen minutes. When it goes up you come and take his blood, day or night. OK?"

Fifty-six negative blood tests later, we agreed that this patient did not have a phaeochromocytoma. In addition to taking all fifty-six samples, I got the job of plotting the graph showing his blood-pressure measurements over the six-week period with the corresponding adrenaline levels (all normal) taken at the time the patient's blood pressure went up. Even Abe could not deny that we'd been scrupulously thorough and had plenty of evidence that argued against the diagnosis of phaeochromocytoma. The head of biochemistry went potty with Abe when he returned from China. The patient's symptoms resolved, and the blood pressure settled. We never did find out what was wrong with him, but he sure as hell did not have a "phaeo."

One of Abe's best gifts was his ability to make sense of the patient's "history"—their account of their illness. Patients come in all shapes and sizes, from all different backgrounds. Their ability to give a cogent account of their symptoms also varies widely, from the succinct to the wandering ramble. Unpicking the latter is often a challenge, and Abe was an expert. One evening I admitted a twenty-six-year-old man to our ward. He had a number of symptoms I could not quite understand, including nausea, malaise, and tingling in his hands and feet. When I examined him, he had loss of sensation to pin pricks (elicited by lightly jabbing the patient with a sterile pin) in his hands and feet. I was unsure of the diagnosis. Abe came to see him the following morning on his ward round.

He talked to the patient for three minutes, repeated the pin-prick test on their feet, and checked the blood-test and chest x-ray results (all normal). He turned to me and said: "Dalton. Check his thallium levels. This is thallium toxicity."

I duly did, and it duly was. Brilliant! Abe's ears had pricked up when the patient said he was a scientist, and he'd spent the three minutes mainly asking about the chemicals the patient had been in contact with. It turns out that two weeks previously he had been using thallium as a catalyst in some experiments he was doing. Thallium is a heavy metal (atomic weight 204 $g.mol^{-1}$) and is used in the manufacture of glass with a high index of refraction, infrared optical materials, low-temperature thermometers, and semi-conductors. When first discovered it was used as a rat poison and in humans as a hair-removing cream, until it was realised how toxic it was. Its use is now very strictly limited. Thallium is very water soluble, easily adsorbed through the skin, and extraordinarily toxic to humans. Shortly after ingestion it causes nausea, vomiting, and diarrhoea. Over the next few days, it causes damage to the nervous system, including numbness and tingling in the hands and feet, hair loss, muscle wasting, cardiac damage, convulsions, coma, and death. As thallium is colourless and odourless, and thallium poisoning very difficult to diagnose, it has gained the epithet "the poisoner's poison." It has been used in numerous celebrated poisonings over the last century, including an alleged plot to assassinate Fidel Castro, and features as the chosen poison in Agatha Christie's "The Pale Horse."[1] More recently, when the former Russian spy Alexander Litvinenko became ill in London in November 2006, it was initially thought he had been poisoned with thallium.[2] It wasn't until some bright young doctor waved a Geiger counter at him that it became clear that thallium poisoning was not the cause. Litvinenko was killed by acute radiation sickness caused by polonium 210, traces of which were found in several spots in London and two British Airways planes.

The patient on the ward recovered in the end, and I learned "Abe's dictum" the hard way: "Dalton, listen carefully to the patient: they are trying to tell you the diagnosis, and the key to good medicine is a correct diagnosis." This was his way of telling me that, in making a diagnosis, eighty-five percent of the diagnostically useful information comes from the patient's history (what the patient tells you), five percent from the physical examination, and ten percent from the tests you order. I determined to always pay particular attention to the patient's history.

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[1] A. Christie, *The Pale Horse* (London: CollinsCrimeClub, 1961).

[2] Alexander Litvinenko: Profile of murdered Russian spy. https://www.bbc.co.uk/news/uk-19647226

CHAPTER NINE

XINJIAN PROVINCE, 1988–9

Xinjian Province is in the far northwest of China. The people are poor, the province's infrastructure even poorer, and sanitary arrangements and sewerage systems are rudimentary in the extreme. In 1988–9 there was the biggest outbreak of hepatitis E in recorded human history, when over 120 thousand people were infected with the hepatitis E genotype 1 virus. The source of infection, as in all such epidemics in developing countries, was contaminated drinking water. Hundreds of pregnant females perished.[1]

[1] C. G. Teo, "Fatal Outbreaks of Jaundice in Pregnancy," *Epidemiology and Infection* 140 (5) (2012): 767–87.

Chapter Ten

Clapham, 1988

After working with Abe, I spent six months in the accident and emergency department (known in the United Kingdom as A&E, the equivalent of ER in the United States) at Charing Cross Hospital, London. There was never a dull moment. We never knew what was going to come through the door. Patients came with a full spectrum of illnesses, accidents, and problems; all shapes and sizes; new-born infants, the middle aged, the elderly; stockbrokers, pawnbrokers, down and outs. The lot. One patient that sticks in my mind from that time is an elderly Jewish woman who was a Nazi concentration-camp survivor. I can't recall what was wrong with her, but the thing that struck me about her was the way she looked. She was in her late eighties, but from the end of the bed one would have guessed her age to be about mid-fifties. The Nazi doctors had experimented on her during the Second World War. I don't know what they did to her at that time (and neither did she), but she looked remarkably young for her age.

Working in the A&E department involved plenty of blood and gore. The most serious cases were taken directly into the "resus" (resuscitation) room, an enormous room with six patient bays and all manner of medical equipment that one might require when treating desperately sick patients. It opened directly onto the ambulance bay via huge sliding double doors for ease of access. I learned a lot of medicine in that room. With the blood and guts went a black sense of humour, a necessary part of the personal survival kit for people working in that kind of environment.

One of the less-pleasant tasks I had to do while working here was to certify the "DOAs"—patients who are bought to hospital by ambulance, but who are dead on arrival. Rather than be brought into hospital, such cases were seen in the ambulance by a doctor. If they were certified as dead, instead of being brought into the department, they were transported directly to the mortuary. A common scenario would be an elderly patient found dead at home. Often, the patient had been dead for a day or two. Certifying death in such circumstances was relatively easy. They were cold and blue and rigor mortis had already set in. It would have been easy to perform a perfunctory examination in such cases, but I always did it

properly. From time to time, patients who had been certified as "dead" woke up in the mortuary, although this was a very, very rare event. Nevertheless, I did not want this to happen to one of my cases. The only time I completed this task in anything less than a meticulous manner was one day when I was asked by an attending ambulance crew to certify a D●A in the back of their vehicle. I was ushered in by one of the ambulance crew to be met by his colleague holding several plastic bags. I peered in. The bags were full of dismembered human body parts and congealed blood.

"This one threw himself under a train on the underground, Doc. Do you think he's dead...?"

During my six months in A&E I worked with a great bunch of colleagues, including a guy called Richie. Richie was a very loud and very Northern Irish. He had a whacky sense of humour. His main hobby was his car, which was a "souped-up" Cadillac of gargantuan proportions. Every Saturday evening, when he was not on duty, he would take it on the "King's Road Cruise." This consisted of a caravan of large numbers of similar vehicles driven through Chelsea, horns blazing, music blasting. ●ne Saturday night at about three am, I was on night duty. The department was empty. The usual Saturday evening rush had been seen and sent on their way to the bowels of the hospital, or home for the ones with less serious problems. Suddenly, there was a loud, prolonged, and insistent car hom just outside the resus doors from the ambulance bay. It was Richie in his Cadillac, with a big grin on his face. He was showing off. He poked his head out the window.

"Have yer been busy tonight?" He shouted.

"No" came the reply. "The place is empty."

With that, he put his foot on the gas and revved the engine. The electrically-operated doors of resus flew open, and the Cadillac came to rest in the middle of the room, stereo on full blast. After a moment of stunned silence, we all fell about laughing. It was a bizarre sight, to say the least.

After my six months in A&E were up, I took a position as senior house officer (this grade of doctor was unique to British medicine and lies between the US equivalents of intern and resident) in General Internal Medicine at the Royal Cornwall Hospital in Truro, Cornwall. I took this post as I had decided that I wanted to be a hospital doctor, and I needed a period of general training before deciding which specialty to practice. Working in Truro would offer me very good hands-on experience. I spent eighteen months working in Cornwall seeing patients with heart attacks, strokes, pneumonias, jaundice, and all manner of other general medical

problems. One of the attractions of Cornwall was that the hospital was renowned for how busy it was. The job was a "1 in 3" on call, equating to a seventy-two-hour working week as a minimum. When on call for the weekend, then it was more like 112 hours per week. I did not complain. In fact, the thought never crossed my mind—at the time, these kinds of hours were the norm for young doctors throughout the United Kingdom. Yes, it was tiring, but I saw a lot of patients and I learned a lot of medicine by doing so.

To progress my career as a hospital specialist, I would have to sit some postgraduate examinations. I needed to sit the Membership of the Royal College of Physicians clinical exam, known in the profession as "the membership." I spent eighteen months working in Cornwall, the first six and the last six at the main hospital in Truro. It was just too busy to do any meaningful academic study in these two periods. However, the middle six months were spent at a much smaller "slow stream" institution called Tehidy Hospital, near Cambome. The work was much quieter, the pace much slower. It was time for some serious bookwork.

Tehidy Hospital was originally the family estate of a wealthy Cornish family, the Bassett's. At the beginning of the twentieth century, the mansion and grounds were left in perpetuity to the people of Cornwall to be used as a hospital. The mansion was set in grounds and woodlands amounting to hundreds of acres, several miles from the nearest town of Camborne and adjacent to the wild north Cornish coast clifftops. At the beginning of the twentieth century, tuberculosis was a very common problem. In those pre-antibiotic days, many patients with tuberculosis were treated at isolation hospitals. The treatment consisted of strict attention to diet, plenty of fresh air, and some gentle exercise. Occasional resort to surgery on the affected lung was made in patients who showed no response to treatment. Tehidy estate was the perfect setting for an isolation hospital, and that's what it became. Looking at the archives of the patients treated there (and at countless other such places throughout the developed world) makes sobering reading. Patients often spent very protracted periods at the hospital undergoing treatment. In some cases, this amounted to years. The other striking thing is the very large number of patients who died from tuberculosis while there. Even in the mid-1980s when I worked there, it was not uncommon to hear patients expressing the opinion that they would not want to go there as a patient. When asked why, the response would invariably be that a number of relatives had perished at Tehidy years ago from fulminant tuberculosis.

When I worked at Tehidy Hospital during the winter of 1984–5, I think it is true to say that the hospital was long past its heyday, and it would

close ten years later. Effective antibiotic therapy introduced forty years previously had more-or-less conquered the ravages of tuberculosis. There was little need for isolation hospitals, and Tehidy had largely ceased performing that function more than twenty years previously. The size of the hospital had shrunk dramatically, and when I worked there only one ward was open. This was used to care for patients recovering from strokes, or very elderly patients who needed time to recover from other complaints before becoming strong enough to be allowed to go home. It was a nice place for the patients to recover, with beautifully manicured gardens and extensive views across the rolling Cornish countryside. The pace of life and medicine was slow. Emergency admissions to Tehidy Hospital in those days were uncommon, as patients requiring emergency treatment were generally sent to the main hospital in Truro, some fifteen miles away.

Occasionally, however, we would get the odd emergency, usually an elderly patient with a stroke. One emergency admission I dealt with will always stick in my mind. She was in her mid-eighties and had suffered a stroke that had left her weak down one side but had not affected her speech. For reasons that escape me, she was airlifted by a helicopter "air ambulance" from her home thirty miles away, the chopper landing on the front lawn of the old mansion block. For the journey she had been strapped, *M*A*S*H*-style, to a stretcher in a small patient "pod" at the side of the helicopter. This lady had never travelled by plane, helicopter, or any other form of aerial transport come to that. Neither had she travelled outside of her home county of Cornwall at any stage during her life. When she arrived, and the helicopter engine was switched off, she was understandably a little bemused. I went to see her in the helicopter's pod. She thought she had arrived at the pearly gates, bless her soul.

While working at Tehidy, whenever possible, I tried to finish my clinical duties by lunchtime. That would leave me the whole afternoon and evening to do some reading. I never read past ten pm, as I've always found the quality of my academic work decays exponentially as midnight looms. At the start, I had to decide which text to read. I nosed round the tiny hospital library at Tehidy. It did not take me long. There was only one decent textbook on medicine on the shelves—the *Oxford Textbook of Medicine*.[1] This is a premier text covering the whole of general internal medicine including cardiology (heart disease), neurology (nervous disease), gastroenterology (bowel disease), nephrology (kidney disease), infectious diseases, etc. In those days, the *Oxford Textbook of Medicine*

[1] D. J. Weatherall, J. G. G. Ledinghman, D. A. Warrell et al. (eds.), *The Oxford Textbook of Medicine* (Oxford: Oxford University Press, 1983).

ran to two volumes and was just shy of 1,100 pages. I flicked inside the front cover—it was relatively up to date, as the edition had been published only three years previously. Also, inside the front cover was the library label, indicating when the book should be returned. In the years it had been on the shelves at Tehidy it had not been taken out at all. Not even once. I kept the book out for four months and read the whole lot from cover to cover. For a multi-author text, it was surprisingly well written—the quality of the English was excellent, and the content fascinating. I then sat my "membership" exam. Perhaps predictably, I passed first time. I was now a Member of the Royal College of Physicians of London. When I went up to London to receive my award my mum came to watch. She was very proud.

After I passed my exams it was time to get thinking about what area of medicine I would like to specialise in and obtain a registrar post (the equivalent to a US resident). I decided I would go back to London. I was fortunate enough to be appointed medical registrar at St George's Hospital in London. The latter is a leading London Teaching Hospital and used to be situated in a magnificent building on Hyde Park Comer in Knightsbridge, which is now a hotel. However, when I was there it had decamped to the rather less salubrious surroundings of Tooting, London. I spent the next three years as a medical registrar at St George's and allied hospitals. It was an interesting experience and carried considerable responsibility. One of the primary duties was to see, assess, diagnose, and treat the emergency admissions when on call, while supervising the work of the more junior members of the team. Asking the Consultant to come in was almost unheard of. An occasional phone call to one's boss for advice about a tricky case, preferably before eleven pm, was okay. The chief on his or her next ward round reviewed all the patients with all The Firm in attendance. The registrar's ability was largely determined by their performance in dealing with such emergency patients.

My ability with emergencies underwent one of the severest of all possible challenges while working at St George's. On Monday December 12, 1988 I received a phone call in the on-call room at eight am. I was coming to the end of my weekend on call and had been on duty continuously since nine am on the Saturday morning. I answered the phone in my underpants, my mouth still full of toothpaste.

"Harry Dalton, medical registrar." I said, lightly spraying the bathroom mirror and the phone with flecks of white toothpaste.

"This is the accident and emergency consultant. We have a MAJAX [major accident/incident]. This is not a drill. Come to resus now. I repeat, this is not a practice. Come now!"

"I'm on my way!" I replied, producing more flecks of toothpaste on the telephone handset in the process, but she'd already hung up.

Bloody hell! No time to shave. No time to wash. I spat the remaining toothpaste out. I pulled on some trousers, a shirt, and shoes, grabbed my white coat, and charged out the door. I pitched up in resus two minutes later: unshaven, hair all over the place, wearing no socks, and a white rim of toothpaste round my lips.

"What's up?" I asked the first person who I came across, an A&E nurse.

"There's been a train crash. Multiple casualties, and they are coming here."

This was the day of the Clapham rail disaster.

In those days, the role of the medical registrar in any MAJAX was, in conjunction with other colleagues, to run the resus room. Doctors specialising in general internal medicine such as myself were not trained in dealing with trauma *per se*, but were trained in resuscitating sick patients, from whatever cause. I was in the resus room, anxiously waiting for the first casualties. Word came through that they were due in ten minutes. More anxious waiting. More checking of the kit. During this time, a steady stream of colleagues started arriving to give a hand. This included staff from all over the hospital arriving at work, expecting a normal day. Very soon, there was a very long line of medical and nursing staff that had pitched up to help. This included a significant number of the consultant staff, a sight rarely seen in those days in A&E. Even before the first casualties arrived, we had numerous highly trained doctors and nurses for each patient-bay in resus. We were ready.

The call came in. One minute to the arrival of the first ambulances. Six patients, all with serious injuries, two in cardiac arrest. The resus doors pinged open. The first casualty came to my bay. A middle-aged man in a pinstriped suit. Multiple trauma. No blood pressure. No pulse. His clothes were cut off him in ten seconds. IV lines in. Monitors on. ET tube down. O-negative blood running. Cardiopulmonary resuscitation commenced. All within another minute, a textbook example of how to deal with such a patient. I was concentrating hard but could not fail to notice other casualties coming through the door. At first a few, followed by a flood. The resus room was working flat out on the serious casualties. The less serious and the "walking wounded" were being dealt with next door. We did everything we could for our patient. His ECG remained flat. No pulse. We tried some more. No response. This patient was dead. All the team looking after the patient agreed—we could do no more, and to try further would not only be pointless, it might put another potentially salvageable

casualty at risk. As quick as a flash, the porters arrived and removed the dead patient from our resus bay, ready for our next casualty.

Next up was a young woman. She had considerable abdominal pain, especially at the top of the abdomen on the left. Pulse 120 beats per minute (normal is about 72), blood pressure 70/40 mm Hg (normal is about 120/80). Monitors on. Lines in. O-neg blood running. Within ten minutes she was a bit better, and her blood pressure had improved to 90/60. She was assessed by the surgeon at our "station." Diagnosis—ruptured spleen. She was whisked upstairs to the operating theatre. All non-emergency operations had been cancelled. Teams of surgeons awaited, ready to go.

Next up. Elderly male with multiple trauma. Two broken legs, a broken arm, and some broken ribs. Easy.

Eventually, the steady stream of casualties slowed down. In the end, it stopped altogether. I'd done my very best and was proud to have been part of the team in resus. However, resus was now empty. It was time for me to move on. I went up to the intensive care unit (ICU) because I thought they might well need a hand, and so they did. The ICU was full of patients requiring ventilation and intensive medical therapy *before* the MAJAX. It was now controlled mayhem. I spent the rest of the day there helping out. By the time eight pm came I'd done all I could. I was also knackered. I'd been on duty continuously since Saturday morning at nine am—a total of seventy-one hours. I went home, had a long shower and a bowl of pasta, and fell asleep watching the day's events unfold on the national news. I was physically and mentally spent.

Looking back now on this tragic episode, a couple of things strike me. The first thing to say is that, although I had never been involved in a MAJAX before, I was utterly impressed by the quality of medicine and the speed at which it was delivered, under the most trying of circumstances, and the team spirit it engendered. I feel both privileged and proud to have paid my small part. The second thing that strikes me relates to the timing of the accident. There is never a "good" time to have a disaster like the Clapham rail crash. Such incidents come "out of the blue" and are simply a catastrophe for the families of the thirty-five people who died and over one hundred who sustained serious injury. However, from a medical/MAJAX point of view, the timing could have been very much worse.

If you had to choose the time of a disaster such as the Clapham rail crash, you could not choose a better one than eight am, Monday morning. Large numbers of hospital staff, rested from a weekend not on duty, were already arriving at the hospital. The day's work had not yet begun in earnest. They all lent a hand. As a result, we were extremely well staffed, and could cope with just about anything. Consider, for a moment, if this

accident had happened at nine pm on a Sunday evening. The medical staff on duty would have been few, and a fraction of those who instantly turned up to help in the event would have been available. Also, the much smaller number of on-call medical staff might well have been on duty since nine am Saturday morning, and some might have been continuously on duty since nine am Friday morning. Thus, the wave of casualties would have been met, at least initially before other staff could be called in from home, by a small number of medical staff who were already exhausted.

Another point about the timing of the disaster is as follows. Had the accident occurred two weeks earlier, I think the MAJAX response at St George's may have been far short of the magnificent and efficient effort that was delivered, whatever the time of day or night it happened. The reason for this is that St George's had just commissioned and opened a brand-new A&E department. It was large and state of the art, with all the latest medical bells and whistles. It was in this environment that the casualties were treated. It was opened the week before the disaster. The department that it replaced was a standalone, pre-fabricated building constructed in the 1930s. It was tiny, fifty years out of date, and would not have coped. A couple of days after the MAJAX I was talking to an ambulance driver who had been involved in the emergency services response to the Clapham crash. We naturally exchanged stories and experiences. He was an old hand and had been delivering emergencies to St George's for the best part of twenty-five years.

"It's a good job it didn't happen in the old Unit," he said.

"You're right there," I replied.

"Still, it was quite some way to christen the new place ..."

It was during the second year of my registrar position that I eventually decided on a specialty that I would pursue as a career. I spent this year working at St Helier Hospital in Carshalton, which is in suburban South London. The hospital has very close links with St George's and educates many of its students. It is also staffed by junior staff on rotation from the "Ivory Towers." The hospital itself is an impressive but rather scruffy 1930s art deco edifice standing high on a hill over South London. From the top floor there is a magnificent view of the metropolis sprawling for miles to the north. The German Luftwaffe used the hospital as a landmark when bombing London in the Second World War. During this process, they blasted the East End of the city to bits. After the war, many of the previous inhabitants of the East End were subsequently rehoused on the infamous and enormous Rose Hill estate, situated adjacent to the hospital. They were rough and ready and stood no nonsense. They were a pleasure to look after as patients.

I had to decide what to do as a career. I wasn't sure. I seriously considered the idea of being a specialist in infectious diseases, but ultimately, I decided the career prospects were bleak, as there were very few consultant posts in infectious diseases in the United Kingdom. In the end, I decided to be a gastroenterologist. This is a specialist concerned with the illnesses of the stomach, gut, pancreas, and liver. One of the consultant staff I worked for at St Helier's was a guy called Robin Orchard. It was due to his influence that I decided where my career was headed. Robin was a first-class gastroenterologist, and he showed me the nuts and bolts. He taught me how to use an endoscope. Most importantly, he taught me the true "art" of medicine.

Robin had a fantastic bedside manner. I witnessed first-hand how he worked and was very impressed. He never sat me down and told me how one should act at the bedside, it was learning by watching a master at work. He had a great knack of putting patients at ease. It's quite difficult to describe how he did so in the written word. However, he exuded a great sense of confidence and experience, and transmitted this to his patients. He made them feel safe. He judged the background and personality of his patients extremely well and tailored the level of the consultation accordingly. He was on their wavelength. Patients felt they could talk to him and know he would listen and they would not be patronised. He used humour and jokes extremely effectively at the bedside, and I've never seen this done better before or since. I could see how important it was to make patients smile, even (and perhaps especially) when they are sick. His approach was part poetic, part balletic, part lavatorial, and part thespian. Robin knew his audience and played them quite brilliantly. His bedside manner, however, was much more than an act. He really did connect with his patients, but this was not in the stage-managed artificial way employed by actors treading the boards. It had an authenticity given to it by the immediacy of the patient's illness.

In summary, Robin showed me how he got the patient "on his side." I did not fully understand the importance of this art of medicine until much later.

CHAPTER ELEVEN

OXFORD, 1991

After three years at St George's I needed to go off for a couple of years and do some research in my chosen field. I was lucky enough to be appointed research fellow to the gastroenterology unit in Oxford, under Professor Derek Jewell. I spent just over two-and-a-half years with Derek. Looking back, it was a great privilege to study in that environment. Derek specialised in inflammatory bowel diseases (Crohn's disease and ulcerative colitis). I spent the next two-and-a-half years doing some basic research aimed at trying to understand the mechanisms of what caused the severe inflammation in the gut found in these conditions. This involved a good deal of laboratory work with test tubes and pipettes, isolated white blood cells from patient gut and blood, and a little bit of clinical work to keep my hand in. In addition to being an excellent scientist, Derek was also a first-class clinician. In years to come, when I got stuck with a tricky clinical problem, I would ring him up and ask his advice, or send the patient up to see him for an opinion. He always gave a balanced, sensible, and practical view.

At Oxford we had distinguished colleagues from all over the world who came to visit, and when they did they would give us a lecture or a chat about their ideas and experience. Also, the laboratory was full of peers from all over the world. While I was there I worked with contemporaries from the United Kingdom, Australia, Japan, Singapore, Sri Lanka, India, Bolivia, Nigeria, Italy, Spain, Greece, and Belgium. All were under the tutelage of Derek, who chucked us all in together. However, he did not do so without a good deal of thought. He ensured that the atmosphere was right. It was permissive, enquiring, friendly, and encouraging, but with a demanding core of solid steel. The result of the combination of a faciliatory ambience and a bunch of bright young medics from the United Nations was awesome. Our combined research output far exceeded the sum of the individual parts, and international friendships established at this time have lasted a professional lifetime.

While in Oxford I had the good fortune to meet one of the greatest gastroenterologists of the twentieth century, Dr Sidney Truelove. Sidney

used to come to the lab every Monday for an hour or so. He would sit and have a chat with Derek, smoke his woodbines, and talk to the young research fellows, me included. He had retired ten years previously and was in his late seventies at that stage but had spent thirty years in Oxford studying ulcerative colitis. It was he who established Oxford as one of the world's premier units for studying and managing patients with diseases of the gut. He achieved this by his intellect, rigorous observation and reporting of his findings, and willingness to do what he felt to be right, whatever anybody else said. I've always enjoyed a game of snooker, and I soon learned that Sidney did too. We went out every week for a few games. Sidney was not as good at snooker as when he was younger. He had a bit of a tremor in his hands, which made delicate shots difficult. I usually beat him, but every once in a while, he would produce a magnificent shot from one end of the table to the other, which made me realise that had we been playing twenty years earlier I would not have had a prayer.

Although Sidney was not as sharp at snooker as he once was, his intellectual capacity was intact. One of the great things about snooker (at least at our very amateur level) is that the game takes quite some time. It would not be unusual for us to spend forty to fifty minutes playing a frame. During the course of our play we would talk. I was particularly interested in Sidney's accounts of some of the clinical studies he had done when he was younger. In the early 1940s, the mortality rate from severe ulcerative colitis was twenty percent. At that time, there was no specific treatment for ulcerative colitis apart from bed rest. Sidney was involved in setting up the first trial of a new treatment, with cortisone (a steroid) injections for this condition. The study was one of the first placebo-controlled trials (patients were randomly allocated to cortisone injections or placebo/dummy injections) ever conducted. It showed that patients receiving cortisone did far better than those who received placebo injections.[1] As a result of this work, which was published in *The British Medical Journal* in 1955, steroid injections became the standard treatment for severe ulcerative colitis. The mortality rate around the world almost instantly dropped from twenty percent to less than one percent.

This was remarkable for a number of reasons. I have read his original articles from the 1950s several times, and each time I am struck by the very clear accounts Sidney gave of the outcome of the cases of patients with severe ulcerative colitis who received the dummy preparation.

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[1] S. C. Truelove and L. J. Witts, "Cortisone in Ulcerative Colitis: Final Report on a Therapeutic Trial," *British Medical Journal* 2 (4947) (1955): 1041–8.

Torrential, progressive, bloody diarrhoea, all day and all night; circulatory collapse and bowel perforation. Many of these patients died. They were often young men and women in their twenties or thirties. These patients did not die in vain as they helped prove the efficacy of steroid injections in ulcerative colitis, and so establish this as the treatment of choice. This has subsequently saved the lives of three generations of patients with this condition. At the time, however, some of the medical establishment felt that it was unethical to do such a trial in which patients randomly received a dummy preparation. During the course of the study, Sidney was contacted by doctors from around the United Kingdom asking for their patients with ulcerative colitis to be given cortisone, but not the dummy. Sidney, quite rightly, said no. This would have fundamentally undermined the double-blind nature of the study and compromised the scientific quality of the result. Had he said yes to these many requests, the ultimate outcome would have been to make the study not generalisable. This was not good enough for Sidney, but he got a lot of stick at the time from some of his peers. The double-blind trial has been the accepted way of proving the efficacy of a new treatment ever since. Well done Sid.

After two years and two terms, I submitted my DPhil thesis (this is called a PhD in every other university except ●xford). I did not find the cause for ulcerative colitis, but I made some original observations about the mechanisms of the uncontrolled inflammation in the gut in such patients. My thesis was approved, and my DPhil awarded six months later.

●ne of my tasks while at ●xford was to teach the undergraduate medical students. I did this regularly, and I enjoyed it. Just before I left, I was due to give a lecture on inflammatory bowel disease to the students. I turned up early and listened to the lecture that preceded mine. This was on viral hepatitis and given by one of the consultant staff in ●xford at that time, Dr Roger Chapman.

Roger explained to the students that there are five types of viral hepatitis. Each is given a letter of the alphabet (I've never been quite sure why).

Hepatitis A. This virus is spread by the oral-faecal route (i.e. it is caught by eating food or drinking water contaminated with the virus). It affects young adults and causes a self-limiting illness with jaundice (a yellow discolouration of the skin and eyes) that lasts four to six weeks. Travellers visiting areas such as Asia and North Africa not uncommonly catch it. Rarely (one case in a thousand), it results in acute liver failure and death. There is now a very effective vaccine available (although there wasn't at the time of Roger's lecture), and travellers visiting high-risk areas should always consider having a shot before departing.

Hepatitis B. This virus is spread parenterally (by the intravenous route, e.g. contaminated blood transfusion, intravenous drug users sharing needles etc), sexually, or vertically (from mother to baby). Acute hepatitis B infection causes hepatitis, jaundice, and an illness that last about six weeks. Most individuals who become ill like this clear the virus, and there are no long-term effects. However, in a minority the virus continues to multiply in the body and is not cleared by the normal human defence mechanisms. This results in long-term carriage of the virus in the liver, causing liver inflammation, scarring (cirrhosis), and liver cancer. Such "chronic" carriage of hepatitis B is common in patients who have been infected from their mother during childbirth. This is an important cause of death in the Far East. There is a very effective vaccine available which prevents individuals becoming infected.

Hepatitis C. This is also spread parenterally (by the intravenous route) or sexually. Patients rarely have symptoms from an acute infection, but fifty percent of patients who come across the virus become chronically infected. Such patients include recipients of blood transfusions, the blood from which unknowingly carried the virus (common before the mid-1980s, now very rare), and intravenous drug users who share injecting needles. There is a high rate of liver cirrhosis and liver cancer in the patients who harbour the virus. There is no vaccine, but chronic hepatitis C infection is now treatable with modern, but very expensive antiviral therapy.

Hepatitis D. This is seen only in the context of patients who carry the hepatitis B virus. It is uncommon in the United Kingdom but seen more frequently in EU countries such as Italy. It causes liver failure and death and is very difficult to treat.

Hepatitis E. A very recently discovered virus. It occurs primarily in large outbreaks involving many thousands of cases in places such as Nepal, Kashmir, and India. Hepatitis E is not seen in developed countries such as the United Kingdom.

Roger's lecture lasted forty minutes; his coverage of hepatitis E lasted two. He got the last bit hopelessly wrong.

CHAPTER TWELVE

CORNWALL, 1994

After Oxford, I spent two years as a senior registrar (equivalent to senior resident in the United States) in Leeds, West Yorkshire. In some ways, it was nice to be home, in others not. It had been fifteen years since I left to go to medical school, and a lot had happened to me in the interim. While my view about life had not changed, my professional attitudes had. I did feel an empathy with my patients when I worked in Leeds. I could sense what they were thinking, what they were feeling. I had grown up in their community. However, I knew in my heart that I would not spend very long there. And so it proved to be. I had now completed a total of eleven years postgraduate training and was ready to be a chief. A consultant post came up in Truro, Cornwall, a lovely place to live, work, and bring up my family. Nice colleagues and a decent hospital. The only reservation I had was that it was rather isolated, both geographically and intellectually. I had been interested in the academic side of medicine since my time in Oxford and going to work in Cornwall would severely limit my opportunity to do research, or so I thought at the time.

Cornwall is a beautiful place. It has a stunning coastline—wild and rugged in a winter storm, captivatingly attractive during the crowded, sunny summer months. My favourite time of year in Cornwall has always been the spring, before the hordes of tourists (known locally as emmets, which is an Old English term for ants) descend. The daffodils come out at the end of February, and there are still quite a number of daffodil farms dotted around the county. Driving around the countryside on a sunny day, with the smell of spring and cut grass in the air, suddenly coming across fields and fields of golden daffodils in bloom is truly a magnificent site.

Working in Cornwall meant looking after Cornish men and women. The Cornish are a proud people, but then they have a lot to be proud about. The Cornish are also renowned for their independent spirit, their stubbornness, their distrust of outsiders, and their warmth and generosity of spirit. These qualities are born of generations of geographical isolation, poverty, hard work, and abuse by English authority. Following the unsuccessful Cornish rebellions of 1497 and 1549, Cornishmen were hung,

drawn, and quartered in their scores.[1] The Cornish largely watched the Monmouth rebellion of 1685 (put down at the battle of Sedgemoor) from the side lines, and mostly escaped the attention of the infamous Judge Jeffreys and his Bloody Assizes. However, this did not stop this barbaric judge from making occasional forays into Cornwall to deal with the unruly Cornish. He held court hearings in the Dolphin Inn in Penzance, and "tis said that his ghost still haunts the place." He was certainly a "hang 'em and flog 'em" type.

More recently, the Cornish people have been on the receiving end of some of the worse urban and rural poverty in Europe due to a combination of factors. Geographically isolated, Cornwall has been largely ignored by UK central government and has suffered chronic underfunding going back many generations. This is due, in part, to the fact that Cornwall, until very recently, has been a stronghold of liberal, independent political thinking and nearly always returns members of parliament belonging to the Liberal/Liberal Democrat party. As the political influence of the Liberals in the United Kingdom went into decline in the early twentieth century, so did the political voice of Cornwall. The tin mines, a source of great wealth in the eighteenth and nineteenth centuries, have all closed, while the European Union Fisheries Policy and the quota system have decimated the Cornish fishing industry.

Although the Cornish fishing fleet is now a fraction of the size it was forty years ago, it is still active and vibrant. There's nothing better to my mind than watching the fleet come in early in the morning to Newlyn harbour and land their catch. A magnificent sight. The fishermen are, of course, strictly regulated by European Union law. They have a quota of fish they are allowed to catch. If they land over their quota they are in deep trouble. This has led to the hideous practice of the surplus catch been dumped over the side to feed the seagulls. What a waste of the planet's resources. It must break the heart of the guys who have to do it.

The Cornish have never been on the best of terms with the Spanish. I suspect this enmity goes back centuries, to the days of marauding Spanish galleons that in those days would intermittently raid the Cornish coast for a quick bit of murder, rape, and pillage. The present-day Cornish fisherman has a particular dislike for Spanish fishermen. The Spanish are renowned for bending the strict EU fishing rules. They are suspected of fishing with nets with too-small meshes, which, instead of allowing the minnows to escape, hoover up everything. They have, quite legally,

[1] P. Payton, *Cornwall: a History* (Truro: Cornwall Editions, 2004).

registered Spanish vessels with Spanish crew in the United Kingdom, so purloining some of the Cornish fish quota.

A few years ago, some of the Spanish fishing fleet crossed the Atlantic. They were intending to fish off Newfoundland, Canada—a very good place for Atlantic cod. The Canadians thought otherwise. They sent a coastguard and a couple of warships to meet the Spanish fleet, who were told in no uncertain terms to "fish elsewhere." This went down rather well in Cornwall. Immediately after this happened, Canadian flags were to be seen flying all over the place. This was particularly so in and around the main fishing port at Newlyn, at the southwest tip of Cornwall. Here, virtually every building had a Canadian flag on it. In fact, there was such a run on purchasing Canadian flags from Cornwall that the supply of flags in the United Kingdom soon became exhausted. Extra flags were flown in from Canada and, if memory serves, the Canadian Ambassador himself made the trip down to Cornwall to present some and to ask what all the fuss was about. The Canadian flags continued to fly for several months, and every time I took a trip down to the west of the county I saw them and grinned from ear to ear.

In more recent years, Cornwall has started to change. Cornwall was always a popular place for people to retire to—well off yachty-types, and the less well off, often from the midlands towns around Birmingham. Since 9/11, there has been a positive exodus of people from London to Cornwall. These are not people of retirement age but well-heeled business types decamping to the country for a better quality of life to an area with no perceived terrorist threat. They bring their Porsches, BMWs, and businesses, often internet-based, with them. If they need to go up to town they simply hop on a flight from Newquay airport and are in London in fifty minutes. This immigration has caused the price of houses to skyrocket well in excess of the national average increase. As a result, buying a house is now sadly not possible for many ordinary working people.

Alongside this demographic change, Cornwall has had a vast amount of EU money pumped into it, in recognition of its previously unenviable status as one of the most economically deprived areas in Europe. Despite this, the three biggest sources of employment are still tourism, farming, and the National Health Service (NHS). The tourist season peaks for eight weeks during the UK school summer holidays in July and August, with the aged and couples without children coming either side of this period. The local economy is geared around tourism, and it is not uncommon to hear a patient who works in this industry say they would prefer to avoid any hospital appointments between June and September. Farming is also

important to the local economy. The farms are largely beef and dairy, the latter the source of the world-famous Cornish clotted cream---delicious, but almost guaranteed to fur up your arteries in no time at all if you over indulge.

By far and away the biggest single employer in Cornwall is the good old NHS, itself the largest single employer in the EU. The NHS in Cornwall employs well over five thousand people, including doctors, nurses, radiographers, and occupational therapists—the list goes on. There are two NHS hospitals in Cornwall. The Royal Cornwall Hospital in Truro is a very large institution with over eight hundred beds and serves as the main hospital for the community of approximately four hundred thousand souls. There is a small hospital in Penzance known as the West Cornwall Hospital, situated in the far west of the peninsula. It has about fifty inpatient beds on two wards. One ward is for "medical" patients and one ward for "surgical" patients. It has been threatened with closure or "downgrading" on countless occasions in recent years. This has been vociferously, and successfully, opposed by the local community. An example of Cornish single-mindedness and unwillingness to accept diktats from bureaucrats if ever there was one.

The Cornish have a reputation for being insular. I think this is unfair. They do, however, have a healthy mistrust of outsiders. Bearing in mind their history, who can blame them? It takes time for the Cornish to accept an outsider. The length of time varies from individual to individual. In general, once they have decided you are not going to "stiff them one," they will accept you. They are warm, friendly, and generous. Although they will accept you, you will not be Cornish. No, that takes a generation or more. I recently met a man in my clinic. He was from the midlands town of Burton upon Trent. He had fallen in love with a Cornish girl, married her, and moved to Cornwall when they were married forty years earlier. I asked him if he liked living in Cornwall. He said "of course." I asked him if he was now an honorary Cornishman after forty years. His wife butted in: "Not quite."

I have looked after Cornish patients now for nearly twenty-five years. What are they like as patients? Well, like anywhere else there is a spectrum of individuals from the good to the bad to the ugly. Two things strike me, though, about Cornish men and women as patients. Firstly, they are tough. I realise this is a generalisation, but to my mind your average Cornish person has a higher pain threshold than your average patient from elsewhere. I have no scientific evidence to back up this claim, merely my observations from over thirty years looking after patients from differing places in the United Kingdom and one year in New Zealand. The other

thing that strikes me about the Cornish is to do with trust. A Cornish patient is, on the whole, slower to give their doctor their trust. However, when they do they are very, very unlikely to take it away again. I feel very honoured to have had the duty of looking after so many marvellous patients during my career, none more so than the people of the lovely county of Cornwall.

CHAPTER THIRTEEN

BOTTOMS UP

When I took up my consultant post in Cornwall over twenty years ago, there was quite a bit of sorting out to do. I joined another gastroenterologist who had run the service single-handedly for a long time. I was keen to help improve the existing service. New clinics were started, and a new endoscopy unit was commissioned. Despite my best efforts, the waits for patients to be seen remained interminably long. I enjoyed my work immensely, although the hours were long and the patients many. Each week I would do two ward rounds, which involved reviewing each patient under my care who was an inpatient in the hospital. Most of these patients had been admitted as an emergency, with quite a wide range of conditions. In addition, I saw specialist referrals from other teams. A typical number of patients seen on a ward round would be twenty-five each time, for a subtotal of fifty inpatient consults per week.

In a typical week I would do two (or sometimes three) outpatient clinics. At each clinic there would be me and two other junior doctors (residents). A typical clinic would be fifty patients. I would see about twenty patients personally, and the remainder would be seen by the junior members of the team. I supervised their work, and they frequently popped in to ask for advice about what to do. This was a subtotal of forty to sixty outpatient consults per week. I also did endoscopy lists two or three times per week. These lists consisted of procedures to examine the stomach (gastroscopy), colon (colonoscopy), or bile duct (ERCP). It would not be uncommon to do a total of twenty-five procedures in a week for a subtotal of twenty-five patient endoscopies. In addition to the above, there was the on-call work. At consultant level there was no necessity to be resident in the hospital, but there was a responsibility to review all the patients admitted as an emergency when on call. This usually consisted of a very extended ward round that could go on for hours and hours. Over a weekend on call it would not be uncommon to see fifty patients in total, for an A&E ward round subtotal of fifty consults per weekend when on call.

Totting up all the above adds up to a lot of work. In a normal week, when not on call, I would see well over one hundred patients. On an on-call weekend it could be as much as 165 patients per week, possibly more. That's a lot of patients. Each produced an enormous amount of paperwork that had to be dealt with. Work started at eight am and often did not finish until after seven pm. I did not complain, and I enjoyed doing it. However, it left very little time for anything else, and no time to do much research. What little time I had to myself in the week was spent doing some private medicine.

One of the reasons, but not the only one by any means, for doing private practice was financial. The salary of an NHS consultant was good by national UK standards, but certainly not over-generous. It just about covered the mortgage. Then there were the school fees to think about, and the bills. Another reason for doing private practice was that it allowed medicine to be practised as it should be. The most important thing it gives to medicine, in my view, is time. During my working week in the NHS, time was a very precious commodity. There were always very large numbers of patients to be seen, and this could lead to very functional consultations in order to get to the nuts and bolts of the case as quickly as possible and move onto the next. In contrast, private practice affords the "luxury" of being able to spend time with a patient. It allows one to get to know patients, their fears, their worries, and anxieties. Only when you know all this can you deliver care that is individually tailored to meet a patient's needs. I enjoyed doing private medicine mainly because it allowed me to deliver care of the highest quality.

Shortly after starting work as a Consultant in Cornwall, there was a major issue regarding the reputation of the NHS hospital in Truro. There had been a number of "scandals" hyped up in the UK national press. These included the "needle in the baby" and "nurse appendicectomy" scandals. The former was a case of a baby who was found to have a needle in their body. It was not clear at the time how this could have got there. It was assumed by many to have somehow got there accidentally due to an oversight or mistake by the medical/nursing staff. It made front-page news in the tabloids. The other story that made front-page news related to one of the senior theatre nurses who is said to have performed part of an appendicectomy operation. I'm unsure of the details of the case, but I understand the patient came to no harm. Nevertheless, the hospital was pilloried.

These scandals understandably had an adverse effect on the morale of the staff that worked at the hospital. In addition, it meant that bright young doctors were choosing not to come and work in Cornwall due to the

incorrect perception that the quality of work was poor. The net result was that for eighteen months or more I had a number of young doctors working on my team who were less than satisfactory. I didn't think that was good enough and I resolved to do something about it. I thought about this issue for some time. In the end, I came up with what I have always referred to as the "bottom-up strategy."

Final-year medical students from the University of Bristol had, for many years, come to Truro to study clinical medicine. It was a good place to study medicine, as there was plenty of clinical material and they were made welcome by the staff, who were happy to see them. They came in groups of eight at a time, meaning the patient/student ratio was 100/1. This is an important point, and meant that, unlike in the established teaching hospitals that have a patient/student ratio of less than one, students were not "competing" for patients. Thus, the commonly expressed attitude in many teaching hospitals (from staff and patients alike) of "oh no, not another medical student" was absent in Truro.

I like having students around, they keep me on my toes. What I teach has to be correct and up to date. The students are generally very bright and, having few preconceptions, often ask really quite innocent but penetrating questions: "Why *do* we do it that way?" Having them around makes me think about the way I practice medicine and wonder about the received wisdom of modem-day practice. I taught the students from Bristol when they came to Truro and enjoyed it immensely. I realised very early on that the students were important for the future of medicine in Cornwall in the long term, and the particular problem about attracting quality staff in the short term. This was the basis of the "bottom-up strategy," the conceptual details of which were simple, and were as follows:

(1) Teach the students to the highest possible quality
(2) Teach them so well they all pass their final examinations easily
(3) Ensure that they enjoy their time in Cornwall
(4) Choose the best ones and appoint them to the staff once qualified

I started in a small way and did a lot of the teaching myself. This was neither sustainable in terms of my time nor in the breadth of education the students required. I therefore enlisted a group of like-minded consultant colleagues who shared the vision. Two-thirds of the students' week was spent on the wards, working "apprentice-style." The remainder of their time was organised, structured bedside clinical teaching delivered by my consultant colleagues and myself. This level of teaching was not par for

the course by any means. In most medical schools at the time, students were lucky to get one hour per week of consultant-led clinical teaching. And then, of course, there was the surfing. Understandably, the students loved coming to Truro.

More and more students started to come to Truro as the word spread. We started taking students from University College Hospital in London as well. Very soon we were up to about forty students on site at any one time, and the hospital in Truro acquired the moniker of "UCL-on-Sea." The student/patient ratio was still only 2●/1, and the atmosphere thus remained congenial and welcoming. We started taking students from abroad for their "elective" period of study. At first it was just a few German students, but soon became more international and students came from all over the world, including the Czech Republic, Ireland, Sweden, Spain, the United States, Canada, Australia, New Zealand, Fiji, and Japan, to name but a few. The interaction between the students from differing backgrounds and countries was interesting and fruitful—a lesson I learned from Derek Jewell in ●xford.

With all the extra students came some cash from the parent universities. At first this was not much, but it soon increased. Before long we were turning over 25●,●●● pounds per year. Following a vigorous exchange of views with hospital management, it was agreed to have the teaching money "ring fenced." In other words, it would not simply disappear into the "black hole" of the hospital's annual overspend but be spent on supporting the teaching infrastructure. I set up an undergraduate office with two full-time secretaries and appointed clinical staff whose primary responsibility was to teach the students. They were absolutely brilliant. It was great fun. I also completely refurbished the student accommodation. The Ritz it wasn't, but for student hospital accommodation it became easily the best in the country by far. In addition to upgrading the student's study bedrooms I put in a full-sized snooker table, a sauna, and a jacuzzi. Inevitably, I got into a bit of bother over the latter. Thursday nights were the students' night out in town. Every Friday morning my staff would get a call from the accommodation manager. "The students have flooded the jacuzzi room again." Inspecting the room, it was clear they had clearly had a good time as the room was usually three inches deep in water, on top of which floated a multitude of empty beer cans and other flotsam and jetsam. Following my inspection, I always agreed to "speak to the students about it." I never did. Naturally, I got quite a bit of stick about all this, despite my protestations that the jacuzzi was not a jacuzzi, but a whirlpool bath. In the end, it had to be disconnected.

Every year in May I invited a group of ten students to Truro for some intensive bedside teaching to help them prepare for their upcoming final clinical examinations. My staff and I carefully selected these students. They were individuals who we wanted to come and work in Truro, the brightest students with the best interpersonal skills. We had a vested interest in helping them pass their imminent final examinations, and we taught them very well indeed. A number of them gained honours in their finals (a rare distinction), and not a single one failed. I had a great deal of fun doing all this. We got the brightest and best young doctors coming to work in Truro, and I always got the pick of the bunch on my team. It gave me great pleasure to see the students develop and gain confidence on the wards. Some of these youngsters were staggeringly bright and it is gratifying to see that many of them have since gained a consultancy. The "bottom up" strategy had worked very well. In a few short years, we had turned the place around from being in the doldrums to a bright, vibrant institution where everybody wanted to come and work. Job done.

Not quite. When the Labour government came to power in 1997 they were committed to increasing the numbers of doctors trained in the United Kingdom. This meant expanding the places at existing medical schools and creating a number of new ones. The universities of Plymouth and Exeter decided to put in a bid for a new medical school. They had heard of what I had achieved in Truro, and I was invited to sit as the project executive as the representative for Cornwall in the new bid. The new medical school was to be situated in Devon and Cornwall and would be administered jointly by both universities. After a couple of years of endless meetings, the bid was successful, and the Royal Cornwall Hospital in Truro was selected as one of the three main teaching hospitals for the new school, which was named the Peninsula Medical School. A new ten million pound medical-school building was built on the hospital site in Truro. It was extraordinarily gratifying to see the first students from the new school qualifying as young doctors. Job well and truly done.

CHAPTER FOURTEEN

THE JAUNDICE HOTLINE

One of the new services for patients that I set up in Cornwall, not long after I arrived, was a clinic that was named the "jaundice hotline." The idea of this clinic is to enable the rapid assessment of patients who become jaundiced, without admitting them to hospital wherever possible. The reason I was keen to get this clinic going was that, prior to this, the existing management of such patients was a bit of a mess. We looked back over a one-year period and found some rather startling facts. In all, 150 patients with jaundice had been admitted to the hospital in the previous year with an average length of stay of ten days. They had been admitted under sixteen different consultant teams to twelve different wards. The care of these patients was screaming out to be rationalised.

Patients become jaundiced because of a build-up of bile pigments in the eye and skin, giving the patient the characteristic yellow appearance. This is caused by an increased amount of bile in the patient's bloodstream. This build-up of bile in the bloodstream has two main causes:

(1) A blockage or obstruction to the bile duct. This is essentially a plumbing problem with the bile duct. The common causes are cancer of the pancreas and a gallstone which has slipped out of the gallbladder and become lodged in the bile duct
(2) Direct toxic injury to the liver. The liver metabolises bile and when it is damaged it cannot complete this function properly. The commonest cause of this type of liver injury is excessive consumption of alcohol, but viral infections of the liver can also cause the same type of injury

I sat down with a couple of colleagues and we tried to work out a safe, efficient, and patient-friendly way of managing patients with jaundice, avoiding hospital admission wherever possible. The key to the whole process was the ultrasound scan. This scan shows if there is a plumbing problem due to obstruction of the bile duct or not. When the bile duct becomes obstructed the pressure within it goes up, and it dilates. This

shows up on the scan. Patients with obstructed bile ducts need a procedure to relieve the blockage. To do this, we mostly use an endoscopic procedure to gain access to the bottom of the bile duct named ERCP. The endoscope is passed through the sedated patient's mouth and stomach and on to the bottom of the bile duct, which is situated a couple of inches below the outlet of the stomach. It can be performed as a day case, in most patients.

When the liver itself is injured—due to alcohol excess, for example—it usually has a fantastic potential to recover. Most patients with a non-obstructive jaundice can therefore be managed safely on an outpatient basis, provided they are monitored appropriately. Only cases of very severe liver injury require daily monitoring and inpatient care. Using this knowledge, we designed a "one-stop shop." It worked like this:

(1) The patient becomes jaundiced and goes to the general practitioner
(2) The general practitioner phones the jaundice hotline number with the patient's details
(3) The patient is sent an appointment to the next jaundice hotline clinic. These occur twice per week, so no patient should wait more than two working days
(4) When the patient attends they have a clinical assessment, a set of blood tests, and an ultrasound scan
(5) Patients with an obstruction of the bile duct are booked for the unblocking endoscopic procedure as a day case or overnight stay within a week
(6) Patients with jaundice due to injury to the liver itself have further blood tests to work out why and are managed in the clinic
(7) Only patients with severe liver injury, or those who are very elderly/infirm, are admitted to hospital (five percent of the total number of patients assessed)

We introduced this system twenty years ago.[1] After a few initial hiccups, it worked like a dream. This clinic now sees virtually every patient who becomes jaundiced in Cornwall. The clinic has assessed over three thousand patients with jaundice, ninety-five percent of whom avoided admission to hospital. This is much preferred by most patients and saves many hundreds of hospital bed days per year, with huge associated cost-savings in the process. We also had the good sense to keep a record of

[1] J. Mitchell, S. H. Hussaini, D. P. McGovern, R. Farrow, G. Maskell, H. R. Dalton, et al., "Rapid Assessment of the Jaundiced Patient: the Jaundice Hot-line," *The British Medical Journal* 325 (2002): 213–15.

the patients and the cause of their jaundice, which was to prove very important. We found that for five percent of our patients the cause of their jaundice was unknown, despite full and appropriate investigation. Intriguing.

CHAPTER FIFTEEN

DEBBIE

One of the great privileges of being a medic is meeting and treating people from all walks of life. Patients come in all different shapes and sizes and from differing backgrounds. They have different things on their "hard drive"—different mindsets, different values, different hopes and dreams, different worries. Most are nice, a few are not. Whatever their background, whatever I think of them as an individual, I always strive to ensure I do my best for them. The key to this aspiration is to listen very carefully to what patients say, both verbally and non-verbally—a lesson I learned from Abe and Robin all those years ago.

I soon found that the most important part of a consultation with patients is the beginning. Nearly always, patients have a clear view in their minds of what they would like to say. This is their story of what has happened to them. Some patients tell their story succinctly, with no deviation. Others give a more roundabout account, while a minority are frankly garrulous. Some patients bring a list of points as an aide memoir. Others will come with several pages of a printed account of their story recorded in minute detail, a copy of which I always request for their case file. It is most important to let the patient express their account of their illness in full. No interruptions are allowed. I may nod and say "yes," but apart from these encouragements to explain in full I never ever interrupt their opening story. While most people will finish their account in a couple of minutes, a minority will take much longer. However, experience has taught me that even the most verbose and rambling patients will be unable to continue talking uninterrupted for much more than five minutes. My personal record is twelve minutes.

Many of my colleagues are aghast that I do this. They are keen to get down to the nuts and bolts of the symptoms and what might be wrong with the patient. I disagree. It is at odds with Abe's dictum: "listen to the patient, they are trying to tell you the diagnosis." The above approach gives a mountain of information about the patient: the way they think, their values, what is important to them. Also, it sometimes allows other issues to come out which might well have not done so if the story had been

interrupted. These secondary parts of the patient's history are frequently more important than the main part of the story. I saw an example of this recently, when a man came to see me with symptoms of heartbum—a very common symptom, usually easily dealt with—which were proving troublesome to control. I didn't interrupt. After a few minutes, just as he was finishing his account, he mentioned that he also had trouble with bleeding from his haemorrhoids as well. His heartburn proved easy to fix and was a minor issue. His main problem was that he had cancer of the rectum. The bleeding from his rectum proved not to be due to his haemorrhoids at all.

Most patients I meet I can't cure. They have long-term ailments such as irritable bowel syndrome, ulcerative colitis, and Crohn's disease. I can help these patients, but I can't make their problem go away forever. It is always very rewarding when a patient can be cured for good. This happens in some patients with some cancers. It also happened to Debbie, who had a different problem. I first met Debbie at the end of a ward round. She'd just come in as a day case to have venography of her hepatic veins. My registrar at the time felt it was unnecessary for me to see her. However, I insisted, as hepatic venography (an x-ray study of the veins that drains the blood from the liver into the heart) is a very uncommonly performed procedure, and I was curious. We did not have a diagnosis. I recalled Abe's dictum (the key to medicine is the diagnosis, and the patient is trying to tell you it), so I asked Debbie to give me an account of her illness from the beginning.

Debbie's story was as follows. She was a fifty-four-year-old office worker. She had previously been very fit indeed, and regularly ran. She had not been well for eighteen months. Initially, she had developed diarrhoea. For this she'd had a colonoscopy performed, which was normal. She then had a CT scan of her abdomen. This was also normal. It was noted that her liver blood tests were slightly abnormal. She had a large bank of blood tests performed to work out why, which were all normal. She had a liver ultrasound performed, which was also normal. She had a biopsy of her liver (a tiny piece of liver tissue removed with a fine needle). This was normal, except that it showed some congestion of blood in the veins that drain the blood from the liver back to the heart (hepatic veins). Because of this finding, she was sent for hepatic venography to check that there was nothing blocking the blood flow from the liver to the heart. This test was normal too. I was now very interested in Debbie's case indeed.

The above series of investigations had taken eighteen months and Debbie had seen six different doctors, although I had never seen her before. I went back to the beginning and asked her to tell me what had

happened to her, in her own words. Two things struck me about Debbie's account. Firstly, although one of her initial symptoms was diarrhoea, this had settled. Her most pronounced symptom was severe fatigue. This was a very fit woman who could previously run a marathon. She was now totally exhausted after walking four hundred yards. The second symptom was very unusual, and I have never heard any patient complain of this before or since. Debbie described a problem with her ears. When she bent over, her ears turned blue. This happens to anybody if you bend over for long enough as, due to gravity, the head and ears with fill with venous blood and take on a blue colour due to venous engorgement. However, when Debbie stopped bending over and adopted the upright position again, her ears would remain blue for a minute or more. That was very unusual.

The symptoms of fatigue and blue ears on bending pointed to a cardiac cause for her problems. The liver biopsy findings of congested hepatic veins, which were anatomically normal, pointed in the same direction. I remembered my father's case. I recalled his story of how his diagnosis was made by an examination of his neck veins. I needed to look at Debbie's neck veins. If they were prominent and standing up, this was definitely a cardiac problem and could be the same condition my father had when I was a boy. I took a long, very careful look at Debbie's neck. There was no doubt about it—the neck veins were very prominent indeed. In fact, they were so prominent they made her ears waggle in time with her heartbeat. My bedside clinical diagnosis was constrictive pericarditis.

I rang up the cardiologist and Debbie had a scan of her heart that afternoon, which confirmed the diagnosis. I would not have reached this diagnosis without the help of my father, long since dead. Like my father, Debbie subsequently had cardiac surgery to remove the diseased, thickened membrane around her heart, which had been literally squeezing the life out of her. She made a complete recovery. I was chuffed to bits to get an email from her a year later telling me she had just completed the Great North Run (a half marathon) with her daughter in the very respectable time of one hour forty-five minutes, which is twenty minutes quicker than my best time.

CHAPTER SIXTEEN

PENZANCE, 1999

David Levine is a colleague of mine, a consultant gastroenterologist, just like me. David works at the West Cornwall Hospital in Penzance. We meet occasionally when he comes up to Truro for departmental meetings and seminars. David is of the old school of medicine. He works at an even pace. He likes to think about his medicine, about the problems in front him—a quality that's becoming increasingly scarce, which I admire very much. I sometimes refer to him as the "wise old owl in the west." He always replies, "not so much of the old." Although David has largely retained his youthful good looks, even he will have to admit he is now entering middle age. He retired a few years ago.

David's thoughtful approach has resulted in several stunning diagnoses over the years, although he would be too modest to say so. One such case was a man in his early sixties who presented to him some years ago. The patient, who had recently been widowed, became ill with fever and muscle aches, and generally felt very unwell. He had not been abroad for several years and drank no alcohol. A week into his illness he became jaundiced, which worsened. He was sent to see David, who admitted him to the West Cornwall Hospital in Penzance. As usual, the first step was a scan of the liver to determine if the bile duct was blocked. It was not. Then the patient had a series of blood tests to determine the cause of his liver injury. The blood tests showed that he was suffering from hepatitis, but the cause was uncertain. He tested negative for all the normal causes of viral hepatitis (Hepatitis A, B, C, and D). He also tested negative for the more unusual infectious agents such as the viruses that cause glandular fever, which can also occasionally cause a nasty hepatitis.

David was left with a patient who had a severe hepatitis, but the cause was not certain. What could be wrong with him? When faced with a patient such as this it is always important to go carefully over the drugs and medicines the patient has had in the last few months. The reason for this is that drugs can be toxic to the liver. This includes over-the-counter medicines, herbal/alternative remedies and, in younger patients, illicit drug use (the use of ecstasy is a common cause of liver injury in younger

patients in the United Kingdom). David went over the patient's drug history with a fine toothcomb. Nothing there. By this time, the patient had been in hospital for over a week and thankfully his liver was showing signs of improvement. By the end of the next week the patient's jaundice was settling, and his liver blood tests well on the mend. He was allowed home and made a full recovery within six weeks.

David still puzzled over the cause of his patient's illness. For reasons he has never fully satisfactorily explained to me, he decided to test the patient for hepatitis E infection. Hepatitis E, as you will recall, is an infection that occurs in developing countries, and is only seen in the United Kingdom in travellers returning from endemic areas. This patient had not travelled to any endemic area, ever. He'd not even been abroad for several years. A month later, his blood test results came back from London. The patient had hepatitis E infection.[1]

[1] D. F. Levine, R. P. Bendall, C. G. Teo. "Hepatitis E Acquired in the UK," *Gut* 47 (2000): 740.

CHAPTER SEVENTEEN

MINT IMPERIALS

Another patient who made a lasting impression on me was Eileen. She is the mother of a friend of mine. I was at my friend's house and, over dinner, he told me Eileen had been to Canada, and while there had not been well. After dinner, he gave his mum a ring to see how she was. I did not speak to Eileen but listening to my friend's end of the conversation, I knew there was something seriously amiss. I'm not sure how I knew, but I did. A sixth sense, perhaps. I arranged to see Eileen at my clinic.

Eileen duly turned up to see me shortly afterwards. As soon as she came through the door I knew my initial impression was correct. Although I had never met Eileen before, she looked unwell. She had that drawn, pinched look in her face, slightly sunken shadowed eyes, and her skin looked waxy. I sat her down and asked her to tell me her story. This took a long time, as Eileen could talk for England. I got a blow-by-blow account of her trip to Canada and her symptoms that could only be charitably described as circuitous. She told me about her diet in detail, including her liking for old-fashioned sweets. She had a particular liking for mint imperials and had recently been consuming large quantities. As per usual I did not interrupt Eileen, and what I (eventually) established was that Eileen had had intermittent diarrhoea for several weeks, had lost a stone in weight, and had abdominal swelling.

At the end of a consultation I often ask patients what they think may have caused their symptoms. I do this primarily to determine what their worries are, rather than needing any diagnostic assistance. Having said this, it's surprising to me how frequently patients get the diagnosis correct when I ask them this question. Other patients will simply say they do not know. A small minority reply: "You're the doctor, not me," or something along those lines. At the end of our consultation I asked Eileen what she felt may have caused her symptoms.

"Well, Harry. I was wondering if the mint imperials may have upset me," was the reply.

At that stage, I did not know what was wrong with Eileen, but I did know it wasn't an overdose of mint imperials. I arranged a couple of tests

for her, including a colonoscopy. I also requested a CT scan of her abdomen, as when I had examined Eileen she appeared to have a significant amount of fluid inside the abdominal cavity. This is usually an ominous sign in a patient in her late sixties with significant weight loss. The next week I did Eileen's colonoscopy. For this test, the patient needs to have a bowel clearance to remove all faecal matter from the colon. We use a preparation called Picolax, which I colloquially refer to as "rocket fuel." This term gives the patient a graphic idea of the effect this stuff has on the bowel, not to mention its taste, which is frankly disgusting. Once the bowel is clear patients are given a couple of injections to make them sleepy, and the colon is then inspected with the colonoscope. This is a 1.5-metre-long tube-like instrument that is inserted through the anus and up the colon. In the old days colonoscopes used fibre optics, but these days it's all chip technology. Images of the patient's colon are displayed on a large TV screen.

Eileen turned up with Kandy, an old friend of mine. Kandy is Eileen's daughter in law and an ex-intensive care nurse. I did the colonoscopy and could find no abnormality. However, I noticed that Eileen was a bit breathless before, during, and after the procedure. I was concerned about this. I allowed her to go home, but asked Kandy to give me a ring the following day. She did, and told me that the breathlessness was worse, and that Eileen's legs had started to swell. I was not happy about this at all. I decided to admit her to my ward for further evaluation as I suspected she had had a pulmonary embolus—a clot on the lung.

Eileen had a lung scan. This confirmed that she did have a clot on the lung, a potentially very serious condition. If she had a further clot on the lung it could be fatal. I started her on blood thinning treatment (heparin) to prevent any further clots forming and to allow the existing clot to dissipate. She went on to have a scan of the abdomen. This confirmed that she had a collection of fluid inside the abdominal cavity, the cause of which was uncertain. We removed the fluid from the abdominal cavity by inserting a drain. This was performed by giving Eileen some local anaesthetic into the skin of the abdominal wall. The site chosen was three inches to the left of the belly button and down a bit. Once the skin was numb, a small drain was carefully inserted. The drain itself is a clear plastic tube of about one-centimetre diameter. It is delivered into the abdominal cavity as a sheath over what is essentially a small knitting needle. Once in place, the "knitting needle" core is removed, leaving the drain in place. Fluid from the abdominal cavity then drains into a collection bag. We recovered over one gallon of straw coloured fluid from Eileen's abdominal cavity over twelve hours, which was sent to the

laboratory for analysis. This confirmed that Eileen was suffering from cancer of the ovaries. Oh no. I now had the task of breaking the news to her.

This is difficult at the best of times but was made much more stressful for me knowing that her son and daughter in law, my friends, would be there when I told her. I had already given Eileen what is termed a "warning shot" when I first met her in clinic. At that stage, I told her that I did not know what was wrong with her, but it might be something serious. I broke the news as gently as I could. Bad news is bad news, I couldn't make it good. It was difficult for me. I took a slow, stepwise approach. Towards the end of our conversation, we discussed treatment. She would need some chemotherapy. I advised her about the mental approach to her illness and asked her to consider her current plight as a journey in a car over an uneven road. My job was to help steer the course, avoiding as many bumps as possible. We also had a couple of light-hearted moments, not least when I said: "Eileen, I never thought this was due to the mint imperials." She chuckled and said: "No, I didn't really think it was either."

Eileen was on my ward for a further ten days. We needed to sort out the clot on her lungs. We needed to sort out her chemotherapy. We needed to drain some more fluid from her abdomen, which had re-accumulated within a few days of the initial drainage. Being in hospital is not a bundle of laughs at the best of times. Eileen was mentally in the doldrums. I tried to help by being cheery. I went to see her each day and mostly just talked to her about non-medical things to try to keep her mind off what was wrong with her. I sometimes spent half an hour with her when time permitted. I always finished by giving her a peck on the cheek.

Sometimes, I take an unconventional approach to patient care. I did so in Eileen's case. I decided that I would treat her with mint imperials. I wrote them up on her drug card: "mint imperials T tds, after meals" ("one mint imperial three times a day"), alongside her conventional meds. I got a packet of mint imperials and had the nursing staff put them in the ward drug trolley. The ward pharmacist was not best pleased, but every time Eileen had her prescribed medication the nurse gave her a mint imperial. Every time this happened, Eileen would smile. That's the best medicine I know.

Another case that left an indelible impression on me was Peter. He died from acute viral hepatitis.

CHAPTER EIGHTEEN

REGGIE

I was very interested in David's case of hepatitis E infection when he told me about it. I was conscious of the fact that in five percent of the cases of jaundice we had seen at the hotline clinic we were unable to reach a diagnosis. I wondered. Working with us at that time we had a young doctor known as Reggie. A nice man; intelligent, conscientious, and fun to work with. We asked him to look back through the records of all the patients who had attended the jaundice hotline. He did so, but this took him quite some time as there were many cases to sift through, and he had to do this between a very heavy clinical workload. He found the cases where we did not have a diagnosis.

The next step was to get in touch with the microbiology laboratory. I spoke to a colleague there by the name of Richard Bendall (known by the students and some colleagues as Bendy Boy), a clinical microbiologist—a trained clinical doctor specialising in the diagnosis and management of infections. He was very helpful, as he has proven to be countless times since. He told me that in cases where the diagnosis was not certain the microbiology laboratory routinely hung on to the patients' blood samples for several years. This was done in case any further testing proved to be necessary. The samples were stored in deep freeze at –70°C. He agreed to look out the samples on Reggie's list. A couple of weeks later, Bendy Boy gave me a ring. He'd found some, but not all, of the samples. We discussed what to do with them. In the end, we sent them to the national reference laboratory at the Centre for Infections in the Heath Protection Agency in London.

It took a month or more before the test results came back. Four of the cases of "unexplained" hepatitis turned out to have hepatitis E infection. We all got quite excited about this and set about analysing the cases in detail. The first thing to establish was whether any of the patients travelled abroad in the three months prior to becoming ill. None of them had. All of these patients had acquired their infections in the United Kingdom as the incubation period of hepatitis E is up to eight weeks, and no longer. Since

they hadn't travelled in the previous three months there was no chance that any of these cases were imported infections from the developing world.

The second thing we did was analyse the type of patient affected. The first thing we noticed was that these patients, like David's initial case, were older. They were all in their sixties, seventies, or eighties. Now this was very strange indeed. This virus seemed to have a liking for older people. Certainly, the strain of virus that causes hepatitis E in India (genotype 1) causes an illness primarily in young adults. This strain of hepatitis E virus that we'd encountered appeared to be behaving very differently. There are vanishingly few other viruses currently known that preferentially cause illness in older people. We looked at the outcome of each case. Three of the four patients had a self-limiting illness. They became unwell, jaundiced, and then recovered completely within four to six weeks. The fourth case was different. He was in his eighties and had a number of other medical complaints, including a longstanding heart condition. This patient developed a very severe liver injury due to the hepatitis E virus. He was admitted to hospital and died quite suddenly on day three of his hospital admission.

This was fascinating and worrying. We had uncovered four cases of hepatitis E infection in Cornwall in individuals who were in late middle age or older—five if you include David's case. One patient died. None of them had travelled to an area where hepatitis E is normally caught. From where had they caught this infection? We were not sure and discussed this at length. In the end, we decided to send the blood samples from the patients we had identified with hepatitis E for viral sequencing. This is a technique that is akin to fingerprinting in police work, which takes a detailed looked at the construction of the genetic material in a virus. The sequencing data eventually came back. The viruses in our patients were not the same as found in patients with hepatitis E in developing countries; it was a very distant cousin. In technical terms, the viruses in our patients were genotype (strain) 3; the virus found in Asia and Africa is genotype 1. What was even more interesting is that the virus found in our patients was identical to HEV, which had recently been documented in UK pigs. In pigs, the virus appears to cause no harm; they carry it without symptoms. Somehow, the virus appeared to have "skipped" from pigs to humans—to our patients.

CHAPTER NINETEEN

BLACK HOLE

I have worked hard all my life—some would say too hard. I think I had little choice in the matter, as the work ethic had been placed on my "hard drive" when I was a boy and has proved to be quite impossible to remove. I have taken my professional responsibilities very seriously, and always tried to do my best for the patients I looked after. Most days I would work twelve hours straight, and then of course there would be the emergency on-call work to do in addition. I married when I was twenty-nine years old. Despite four lovely children, all boys, we were unhappy.

Some years ago, I decided to take the family to Australia for a month over Christmas. We stayed with friends in Melbourne and Adelaide and visited the wonderful city of Sydney. When we got back I didn't feel too well at all. I had a kind of extended jet lag. I had no energy at all and had associated profound sleep disturbance. I took a week off work but was still no better. I went to see my doctor. I told him my symptoms. In true general practitioner style, he asked me what I thought was wrong. I told him I thought I was probably depressed. He agreed. My emotional batteries were completely flat. I was prescribed happy pills to boost my neurotransmitters and recharge my batteries. I also went to see a colleague who specialised in looking after sick doctors. I found this very helpful, and as a result came to realise that to make a complete recovery I would need to leave my marriage behind. I'd also have to work less hard. I'd been signed off sick for four months. To get a bit of space, and a suntan, I went to Sri Lanka for a month. The suntan bit was important, as there was a distinct seasonal variation in my symptoms—I have always felt a bit low in winter. The sun would do me good, so I was advised.

One of the reasons I chose to go to Sri Lanka was to watch England play cricket. I have always been keen on the game and play whenever I can. I also go to London to watch the Lord's test match on the Saturday most years, work permitting. I had, however, never seen a test match from start to finish, all five days' worth. Now was an ideal opportunity to do so. I joined the aptly named Barmy army of overseas England cricket fans and watched the whole of the third test at Colombo. What a treat. There were

far more England supporters than Sri Lankan. The Barmy Army were very vocal in their support, fuelled by considerable volumes of the local Lion lager. The Sri Lankans have a unique method of serving beer at a cricket match, which I had never seen before. What they do is get their barmen kitted up "Ghostbuster-style," with tanks of chilled beer on their backs. The beer is served through a wand and nozzle. When one requires refreshment, one merely raises one's hand and shouts "Lion Man!" The barman duly skips over to one's seat and replenishes empty glasses with ice-cold Lion beer. One group of lads in the Barmy Army hired a Lion Man for a day. He stayed with them throughout and was kept pretty busy. England played well and won within three days.

I spent one month in Sri Lanka. When I got back, I left home. I was to stay in the black hole for the best part of eighteen months. I was initially off work for four months. I then went back, but my symptoms recurred, and I had to have another extended period of leave. What was the black hole like? It's impossible to do it justice using the written word: "you had to be there," as the saying goes. What were my symptoms? The most troublesome was difficulty sleeping. I would wake at three am every morning, almost on the dot. I used to listen to the BBC World Service from waking until seven am, when I got up. Ever since then, whenever I hear the 5.20 am shipping forecast—"Viking, North Utsire, South Utsire, Forties, Cromarty ..."—it sends a shiver down my spine. Not surprisingly, I felt completely knackered during the day. I could not concentrate. I had bouts of anxiety and paranoia, which would set my pulse racing and cover me in sweat. I had no appetite. I lost two stone in weight. I became self-absorbed and found talking to other people difficult, if not impossible. I had brief periods of up-swings, as though someone had switched on the black hole's floodlights. They did not last long and were characterised by over-appropriate jollity and recklessness. It was in one of these periods that I bought a Porsche. I could not afford it, and it went back after a couple of months. After I left home, one of my sons asked me the following question:

"Dad? Aren't you lonely?"

How perceptive for a six-year-old. He got it about right. It was bleak, it was bare, it was barren. But above all, it was lonely.

Some of my consultant colleagues at work were supportive, some indifferent, and some openly hostile—I'm not entirely sure what sparked off the latter response. While I was on sick leave some of my colleagues had to cover some of my duties, thus creating extra work for them. This might have been an issue for some. However, I wonder now, looking back, whether the adverse reaction of some of my consultant colleagues related

to the stigma still carried by mental illness. Or maybe it exposed their own potential vulnerabilities, a "there but for the grace of God go I" kind of thing. I'm not sure. What is clear is that quite a few were unhappy that I came back to work with a fantastic Sri Lankan sun tan. I expect they were of the school of thought that if you are too sick to work, you are too sick to travel, not realising that a month in the sun was part of my "treatment." When I eventually got back to work one colleague quipped: "Did you have a nice holiday in Sri Lanka?" Thanks, matey.

This all seems a very long time ago now. What did I learn from this experience? In addition to finding out who my true friends were, I learned that too much work is not a good idea. Cutting back was always going to be difficult, if not impossible, for me but (in the end) I did try to cut back on my NHS work, and eventually stopped my private practice altogether. This was to prove a pivotal point in my career, as it left me with time to think about things. I thought about all sorts of interesting stuff, including, naturally, patients with unexplained hepatitis.

CHAPTER TWENTY

AUCKLAND, 2005

I decided I needed a break from working in the NHS and took a year's career break to live and work in New Zealand. I managed to find a vacant post in Auckland on the North Island. Auckland is a large, vibrant city of more than a million souls. It has the usual set of modern skyscrapers downtown, which back on to the magnificent bay area with the harbour, docks, and marina. It is known as the City of Sails, and one look at the size of the marina and its contents will explain why. It is simply vast. Auckland has seen considerable immigration over the last thirty years, with settlers from all over the world, but particularly from Asia. It is said that over twenty-five percent of the population of Auckland is now of Southeast Asian origin.

New Zealand is a beautiful country, with some stunning scenery. I found the Kiwis to be warm and friendly, and of course totally potty about rugby. Everywhere you travel in New Zealand there are playing fields with rugby posts sticking up. The kids on the beach do not play soccer or cricket, as you might observe in other countries. They chuck a rugby ball about. Most young Kiwi boys' dream is to play for the national side, the All Blacks.

While I was there, the British and Irish Lions rugby side visited on tour. The Lions side played three tests against the All Blacks and got soundly thrashed. The Lions were not a bad side, but the All Blacks were very strong indeed. Despite the results on the field, the hordes of British and Irish supporters certainly impressed off the field. The Kiwis could not understand why so many supporters had come over to follow the team, and with such enthusiasm and good humour. There must have been at least ten thousand or more Lions fans in New Zealand at this time. Most hired camper vans, and in fact hired the whole New Zealand national fleet—you could not get one for love nor money during the tour. The supporters followed their team around New Zealand, watched the rugby, did the sights, and generally had a ball. Between the Wellington and Auckland tests, the convoy of Lions camper vans, all decked out with Lions flags, on the main road north to Auckland is said to have stretched at least ten miles.

The other thing about the Lions supporters, in addition to their phlegmatic attitude to the results on the field and a penchant for camper vans, was that they all wore the Lions "uniform." These were red waterproof jackets with the Lions motif on the breast pocket. I happened to be in Queen Street in the centre of Auckland on the morning of the test match in Auckland. I looked down the street, which is the main shopping area, and all I saw was a sea of red jackets—the Lions fans were in town. They were laughing and joking, with no hint of any trouble, despite their side already being 2-0 down (shortly to be 3-0) in the three-match series. A remarkable sight.

A couple of years later, during the rugby world cup in France, the All Blacks were odds-on favourites. They had the strongest side by far. They were expected to win by the New Zealand nation, all four million of whom to a man and woman were right behind the team. During the initial group stages the All Blacks barely broke sweat—it was like a training exercise for them. However, in the quarter finals they were drawn against France, the home nation and much tougher opposition. The All Blacks lost, and England went on to beat the French in the semi-finals. The Kiwis were grief-stricken. I emailed a Kiwi friend:

Subject: Rugby
Message: "Parlez vous?"

A couple of days later I received the reply:

Subject: Rugby
Message: "Bugger off"

The thing that impressed me most about the Kiwis as a nation is not their ability on the rugby field, prodigious though it is. It is the sense of tolerance. New Zealand has seen considerable immigration over the years from all over the world. To get on as a nation they have welcomed diversity and embraced it as part of their national culture. It was wonderful to work in that kind of environment. The diversity of colleagues I was to work with is a case in point. The nursing staff in the Auckland City Hospital endoscopy unit included Maori, third-generation European Kiwis, Filipinos, a Japanese, a South African, a Tongan, a Samoan, Chinese, and an Indian, among others. The Indian was a forty-year-old nurse who had emigrated from Mumbai three years previously. She was called Lourdes, and used to bring in goat curry for lunch, which she would occasionally share with me. The curry was fantastic. I asked her one day, goat curry sauce dripping down my chin:

"Lourdes, do you consider yourself Indian or a Kiwi?"

"Doccy," she said, "I'm a Kiwi of course, and proud to be one."

Auckland is a lovely city in which to live and work, but there are many other places to visit. I did the usual tourist trips to South Island to see Milford Sound, Queenstown, Christchurch, and of course Kaikoura. The latter is a Maori name and means "to eat [Kai] crayfish [koura]," and relates to the quantity and quality of the local lobster—the Kiwi crayfish. There are endless small outlets along the coast road selling cooked crayfish. A real treat with some mayo and a bag of chips, and best eaten on the beach watching the sunset. Kaikoura is also the home of New Zealand whale watching. There are a bunch of adolescent sperm whales that live a few miles offshore, and spend their time diving down to the bottom of a one-mile deep trench. It's one of the natural wonders of the world watching these huge beasts flip their tail fin in the air and dive off down into the depths.

My favourite place to visit, however, was on the North Island, towards the top. It's a place called the Bay of Islands, which has truly stunning scenery and is historically important in New Zealand history. It was one of first European settlements in the nineteenth century. The sleepy, quaint town of Russell, with its whitewashed clapboard houses and tourist eateries of today, was, in the 1840s and 1850s, a raunchy, rowdy, and bawdy place, with many drunken brawls and several brothels. It was in the Bay of Islands that the Treaty of Waitangi was signed in 1840. This treaty ensured that the Maori and European settlers lived and developed in relative harmony—more or less. This was in stark contrast to the situation in Australia where the indigenous people were treated with contempt and abused and slaughtered in their thousands. Another example of the tolerance of the Kiwis as a nation.

The Bay of Islands is a great place to go fishing. I went several times, always with same guy—Carl. A lovely man in his late thirties, very friendly and with plenty of experience with the rods. The first time I went a friend came along too. It was the first time she had been fishing. She was naturally delighted to get the first bite and hauled up a nice-looking small snapper. Carl expertly de-hooked it and put it up against the ruler, set in the frame of the aft of the boat.

"Nah, mate. He's too small."

He promptly chucked it back in. My friend was aghast. It all happened so fast—her first ever fish, chucked straight back in! What we didn't realise was that, in New Zealand, there are very strict rules about catching undersized fish. If Carl had been caught with a snapper less than twenty-seven centimetres from tail to mouth, he would have received a very hefty

fine and would have his commercial fishing licence removed for good. No arguments considered. I think this is a good rule, and perhaps one the EU might consider adopting in due course. Shortly afterwards, we found out how good the rule was. We landed a boat full of enormous snapper. They were so big the rods nearly snapped when landing them. The largest was over five kilograms—now that's what I call a fish. They tasted good too.

I worked as a gastroenterologist at Auckland City Hospital, which is the largest hospital in New Zealand. The University of Auckland also appointed me honorary associate professor of clinical medicine. I enjoyed my time working with the Kiwis, and I found my colleagues to be knowledgeable, well trained, hardworking, and conscientious. The standard of medicine practised there was of the highest quality. The hospital itself was set high on a hill overlooking the bay. I couldn't help wondering if such a magnificent view helped speed the patients' recovery. I'm sure it must have an influence, although I think this would be very difficult to measure in a proper scientific way. I've been interested in how environment influences healing for some time. Back home in Cornwall, a few years previously, I'd commissioned some local artists to do a "makeover" of the corridor that ran through the endoscopy unit and up to my ward. They painted the whole corridor yellow—a cross between a sand colour and Cornish clotted cream. They then made up a couple of dozen beautiful signs (all copied from local establishments in Cornwall) for things such as "Deep Sea Shark Fishing Tours," "Bed and Breakfast at Gina's," "The Mermaid Arms, fine food and drink," etc., which were displayed against the creamy/sandy backdrop of the walls. The effect was visually stunning. I've seen countless patients walk down this corridor, worried about what may be wrong with them, and their imminent test. Suddenly, they would look up and feel that they were in St Ives or remember that fishing trip they had years ago. It takes their mind off their troubles, albeit fleetingly. It always gives me a kick when I see this happen.

I had wanted to extend the concept into the ward. The idea was to have a sea-blue floor covering. The bog-standard, anonymous bed curtains were to be replaced by ones made up of deckchair-striped material. The partitions between patient bays were to be replaced by floor-to-ceiling fish tanks and filled with tropical fish. The idea was to give the place a holiday feel to it, again to just take the patients' minds off why they were there. Although I'd identified a source of funds to pay for it all, inevitably I met all sorts of NHS red tape that prevented the project being completed. For example, apparently there is only a (very limited) standard range of curtain materials available for NHS use, all of which are totally hideous. Why this is I do not know. Deckchair stripes were simply not available. However,

this is not what really stopped the project. The sister on the ward did not share my vision. She was a formidable woman, and I gave in. A shame.

Inevitably, while working in the New Zealand health service, I drew comparisons with my experience of my years working in the NHS in the United Kingdom. The first thing that struck me was the number of very elderly Kiwis who were very fit indeed. It was not uncommon to meet such individuals in their nineties, on their first hospital admission, with wafer-thin medical notes. Such patients were invariably Caucasian and, more often than not, female. This is in complete contrast to the United Kingdom, where usually elderly patients have several volumes of notes so large that they have to be carted around in a trolley. I am unsure why there is such a difference. Maybe it's the Kiwis' outdoor lifestyle. Maybe it's a question of self-selection, i.e. immigrants to New Zealand are tougher and fitter than those who did not emigrate there. Maybe it's to do with the amount of exercise the Kiwis do. It is not uncommon to see people in their late eighties "power-walking" in tracksuits around the park first thing in the morning. This is a sight rarely seen in the United Kingdom.

I found looking after the indigenous Maori and Pacific Islanders an interesting experience. The Maori have a great sense of family, and family means all the family: children, grandchildren, cousins, aunts, and uncles. When a family member is sick in hospital, they visit, which they do *en masse* and may stay many hours. To accommodate this, and to ease congestion at the bedside, each ward has a massive family room that gets very well used. The family often bring food and treats for their sick relative. They also support them in a very direct way during their stay. On my first day working in Auckland I had my initial experience of this. I was due to colonoscope an elderly Maori woman who had presented with rectal bleeding. Not a problem. The patient was wheeled in on her bed accompanied by six grandchildren who had come to support Grammy during her illness. This meant coming along with her for her procedures and staying with her the whole time. It took me a little while to get used to having a room full of relatives watching Grammy have her colonoscopy, as this rarely (if ever) happens in the United Kingdom. I think we in the UK could learn something from the Maori's sense of family, but maybe not to the extent of watching Grammy's colonoscopy.

The Maori and Pacific Islanders have a number of important health problems and as a consequence their life expectancy is considerably shorter than the Caucasian Kiwis of European extraction. Chief among the Maoris' medical problems is obesity. This really is, quite literally, an enormous problem for them. They eat a diet high in carbohydrate, and as a result they gain weight at a phenomenal rate when they get into their

thirties. The problem with obesity in tum leads to other problems such as diabetes. During my time in New Zealand I met some very big patients indeed. The patients' excessive weight caused a number of logistical issues in terms of their medical care. One of these issues was getting a CT scan on very big patients. Most standard CT scanners have a limit on the size of patient that can actually fit into the machine. This equates to a patient weight of approximately 150 kilograms as the absolute upper limit. In Auckland, there is a specially designed scanner able to accommodate individuals of up to about two hundred kilograms. For the really big guys, there is always the option of sending them to Auckland zoo (I jest not), as they have a scanner there that can scan an elephant.

Another thing that struck me about working in Auckland was the range and very high quality of diagnostic investigations available for the patients, and equally importantly the speed at which they were delivered. I had one patient with a complex bowel problem. She needed a full work-up as an inpatient to determine what was wrong and the treatment she required. I requested a number of tests including blood tests, a colonoscopy, a gastroscopy, a small bowel meal x-ray, and an MRI scan. All done and dusted in just over three days. The patient was getting a bit edgy at the excessive length of time her tests were taking. I smiled at her. I told her that the tests she had done would have taken nearer three weeks in the good old NHS back home.

I was very impressed not only by the quality of my Kiwi medical colleagues, but also by their number. The doctor/patient ratio was incredibly high. This, of course, meant that for the average working doctor there was more time to spend with each patient. For example, I did a couple of outpatient clinics per week. I would see five new patients and two or three follow-up patients per clinic. This meant that I could spend a good half hour with each new patient and fifteen to twenty minutes with the follow-ups. I found this bewildering at first, as when working in the NHS I would commonly see twenty patients in a clinic, and constantly be nagged to slip in additional urgent extra ones. However, I quickly adapted and found the extra time professionally rewarding. The extra time allowed me to get to know the patients properly and in turn deliver high-quality care, individually tailored to each patient's unique set of circumstances. In other words, this was proper, old-fashioned patient care of the highest order. Also, while working in New Zealand, I did not see any queues of old folk on trolleys in the corridor waiting to be seen by a doctor. Such queues simply did not exist.

The above scenario is a million miles away from medicine as increasingly practised in the UK NHS, which is now almost completely

driven by a political imperative related to election promises made by the government to "sort out" the service, taking the physical form of "targets." Targets must have measurable end points, and almost invariably are focussed on waiting times. This has spawned a whole raft of government diktats: patients with suspected cancer should be seen within two weeks, patients should be seen, diagnosed, and treated within eighteen weeks—the list goes on. Every year, the targets become shorter.

Some, but nowhere near enough, money has been pumped in to the NHS to achieve all this. Existing staff have been flogged to death with demands from extra work done quicker and quicker. Staggeringly high salaries have been offered to attract doctors from Eastern Europe and elsewhere to do some of the extra work. Patients are increasingly referred for a specialist opinion by their general practitioner using tick-box charts, in order to obviate delays in the typing up of "old-fashioned" referral letters. I find this latter practice exceptionally offensive professionally, but also particularly poignant in terms of the mess the NHS now finds itself in. The patient's general practitioner may have known the patient all their life. They will also know the patient's previous illnesses and their response to them, their drugs, their social circumstances, their family circumstances, what makes them tick—all of which may have a direct bearing on their current problem. This rich tableau is now being reduced to one tick in a box in order to speed up "processing." I use the latter term with due care, as to my eye the UK's NHS is now moving towards a "sausage factory" mentality. The key imperative is "how quickly can you process the patients?" Where is the quality agenda? The simple answer is—there isn't one of any meaning.

When I returned to the United Kingdom after my year in New Zealand I was struck by what an unhappy place the NHS is to work in. All my colleagues looked harassed and grey. They were all miserable. They were all fed up of being told how to practice medicine "sausage factory" style. This was despite having a considerable wage increase the previous year in order to soften the blow. It may have softened the blow for some, but most consultant staff feel disenfranchised from shaping the way in which healthcare is delivered, and deeply frustrated by their inability to provide patient-centred care for their charges. Considering that New Zealand is on an economic par with Turkey, and that the United Kingdom is the fourth wealthiest nation in the world, how come the Kiwis can produce decent quality healthcare and the NHS can't (no offence to our Turkish colleagues intended)? In my view the NHS, once the envy of the world, is in a complete, and mainly politically driven, shambles.

CHAPTER TWENTY-ONE

CAPTAIN COOKERS[1]

While working in New Zealand, my interest in hepatitis E continued. I started to test patients I came across with unexplained hepatitis. Shortly after doing so, I received a phone call from the head of the microbiology department:

"I see you've sent several requests for hepatitis E tests. What's going on? Have we got an outbreak here in Auckland that I don't know about?" she asked.

"Yes, I think there possibly is. It's just nobody has looked for it before," I replied.

"What do you mean?" she said.

"I think I'd better come around and explain."

Later that same morning I dropped into the lab to meet her. She was a short, wiry, slightly shrivelled woman in her early sixties with a shock of dyed orange hair. She was plain talking, stood no nonsense, and told it exactly as she saw it, and was very intelligent as well. I liked her immediately. I explained what I had been doing in England and about the cases of hepatitis E that we had seen. I also figured that if we found it in England there was no reason to suspect that we would not be able to find it in New Zealand. She was interested. She told me that a few years ago she had been involved in a study with a number of other colleagues looking at the prevalence of the hepatitis E virus in New Zealand pigs. In common with most countries throughout the world, HEV genotype 3 had been previously identified in New Zealand pigs. However, the number of New Zealand pigs infected was enormous—they had identified that ninety percent that were tested for the hepatitis E virus showed evidence of infection, but none had any symptoms.[2] They had wanted to test humans

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[1] Captain Cookers (Oxford dictionary) are wild pigs still commonly found and hunted in the New Zealand bush, and so named as they were introduced to New Zealand by Captain Cook in the eighteenth century.

[2] O. Garkavenko, A. Obriadina, J. Meng, D. A. Anderson, H. J. Benard, B. A. Schroeder, Y. E. Khudyakov, H. A. Fields, M. C. Croxon, et al., "Detection and

for hepatitis E infection but could not get any of the local clinicians in Auckland interested in a collaborative study. Would I like to meet her colleagues who did the initial study?

Yes, I most certainly would, and I duly met up with her colleagues, a Russian and a Kiwi. Both were molecular virologists, and both were bright and enthusiastic. I learned that they had applied for Ethical Committee approval for a human hepatitis E study (every study on human samples needs Ethical Committee approval before it can start) a few years previously. The approval had lapsed due to lack of interest from clinical colleagues, and the study had never actually started. All that needed to happen was to update the study protocol, get the amendment approved, and we were good to go. I did all this in a couple of weeks. I also managed to relieve the Auckland Gastroenterology Department of ten thousand dollars to fund the work. This was no mean feat, as the Kiwi and their cash are sometimes difficult to part.

The study was up and running in next to no time. We tested everybody we came across in Auckland with unexplained hepatitis over a six-month period. This amounted to just over seventy patients. I was impatient for the results. After the end of the recruitment phase of the study, I eventually got a call—we had found four cases out of the seventy or so tested. None of these four patients had travelled to an area traditionally thought of as endemic for hepatitis E. In common with the cases we had discovered in Cornwall, all were in elderly patients over the age of seventy. All had had a self-limiting illness and recovered. All were caused by genotype 3 hepatitis E, the same strain found in New Zealand pigs. I looked at the cases in more detail. One man with hepatitis E had just returned from a trip to Europe, and it seemed almost certain that he picked his infection up there, bearing in mind the incubation period for the virus is two to eight weeks. I rang him up as I wanted to know where he had been. He had spent two weeks staying with friends, visiting the Eden Project and the Lost Gardens of Heligan in Cornwall, England. But that was not all. His wife had accompanied him. A thought crossed my mind, had she become infected too? I rang the patient up.

"Has your wife been unwell too?" I asked.

"No. No, she's been fine" he replied.

"Do you think she would mind if we took a blood sample in case she has picked up the infection, but has no symptoms?"

Characterisation of Swine Hepatitis E Virus in New Zealand," *Journal of Medical Virology* 65 (2001): 525–9.

"No, I'm sure she would be delighted to. She goes up the hospital several times a week as she works as a voluntary worker in reception, so giving a sample will be no problem."

She was tested. Her liver blood tests were normal, but we isolated the genotype 3 hepatitis E virus from her bloodstream. Very, very interesting indeed. Thus, in a few months we proved a number of important points about hepatitis E that were not known before[3]:

(1) It occurs in New Zealand, in patients who have not travelled to endemic areas
(2) In two of the cases it was contracted in New Zealand, as they had no travel history at all
(3) It is caused by the same strain (genotype 3) that we saw in our cases in the United Kingdom
(4) It is caused by the same strain (genotype 3) that is found in New Zealand pigs
(5) It can occur with no symptoms
(6) It can occur with normal liver blood tests

I thought about these findings on the plane back home to the United Kingdom after my year-long stay in New Zealand was sadly over, in between watching a summary of England beating the Aussies in a summary of the thrilling Ashes cricket series of that year (2005) that had just ended. I watched it three times.

[3] H. R. Dalton, H. J. Fellows, E. Gane, P. Wong, S. Gerred, B. Schroeder, M. C. Croxson, O. Garkavenko, et al., "Hepatitis E in New Zealand," *Journal of Gastroenterology & Hepatology* 22 (8) (2007): 1236–40.

CHAPTER TWENTY-TWO

THE SHED

I returned to the United Kingdom in mid-December, via Australia, where I spent a few days in Sydney. What a fabulous city: vibrant, full of young people, brash, but with a good dash of Aussie culture. The highlight for me was a visit to the Sydney Opera House. Champagne cocktails outside on the terrace overlooking the bay and Sydney Harbour Bridge followed a performance of Tosca. Life doesn't get much better than that. After Sydney, it was off up the New South Wales coast to sample the delights of the Hunter Valley, and a week's holiday by the sea.

When I got back to the United Kingdom I was raring to go. My batteries were fully charged and the break from NHS work had been refreshing. However, moving from the Southern Hemisphere summer to the Northern Hemisphere winter did come as a real shock to the system. It was cold, dismal, damp, and dank. There was an overwhelming sense of greyness to everything, including my colleagues at work whom all, to a man and woman, looked thoroughly fed up. While I had been away, two new consultant colleagues had started work as gastroenterologists in Truro. I met them both on my return. They were both friendly and switched on and were to prove excellent working colleagues. Neither had yet been ground down to dust by the NHS treadmill, as so often happens to doctors working for any length of time at consultant level. It's a sad sight to see bright enthusiastic hardworking doctors who really care at the start of their consultant career turn into sad, disillusioned, wrinkled, cynical shells.

There are a number of issues that, in addition to the sausage factory/treadmill nature of current NHS work, are guaranteed to seriously raise the hackles of its beleaguered consultant staff. One of these is the thorny issue of parking. Most NHS hospitals around the United Kingdom have started to charge patients and staff to park on hospital grounds. In some institutions, the level of charging has reached ludicrous levels. For example, I know of one hospital that charges patients and relatives £10 for parking for more than four hours. If there are one thousand patients in the hospital at any one time, over a year that equates to a nice little earner. Not

content with this, the hospital staff are also charged for the privilege of parking their car at work. This can mean in excess of £500 per year. Introducing staff charges for parking was not at all well received. A lead balloon springs to mind.

Another issue that causes serious resentment among consultant staff is that of office accommodation. Thirty years ago, each member of the consultant staff had their own secretary, their own office, and their own dining room where they were provided a "silver service" lunch. Not anymore. As the NHS has expanded it has changed. The consultant dining rooms are long gone, and with them the collegiality and, more pertinently, the opportunity to do business with one's colleagues face to face over luncheon. Many consultants now share a secretary from a typing pool. Most consultants share an office with one or more colleagues, if they are lucky.

While I was away in New Zealand my office had been given to one of my new colleagues. The Aussie who had been doing my work while I was away had been bundled unceremoniously into a portacabin in the car park situated at the back of the hospital. This was his office. It was also mine when I returned to work. The portacabin was truly awful. It dated, I believe, from a period just after the Second World War, an era not renowned for the quality of UK portacabin construction, or many other buildings, for that matter. The portacabin was constructed (this is a rather generous description) from a wooden frame, with walls made from a rendered aggregate. The windows were rotten, as were the pillars that supported it at a height of eighteen inches above the ground. The four corner pillars, however, had not all rotted at the same rate, which meant that the portacabin leaned gently towards the prevailing winds from the southwest. This was rather disconcerting for the unwary, as it resulted in a slightly vertiginous feeling when moving around inside. The walls were, appropriately enough, painted grey, and the rotting wooden frames and windows were finished in peeling blue paint. The portacabin was freezing cold in winter (with a lowest recorded working temperature of –5°C) and baking hot in summer (its highest recorded working temperature was 38°C). It was christened "the shed". Little was I to know that over the next few years the shed was to become an internationally recognised nerve centre for research into hepatitis E infection.

I thought longingly of warm and friendly New Zealand, where I had a huge air-conditioned office to myself overlooking the bay. It would be easy to jump on a plane. No. I decided to stay. I'm an Englishman, I'm a European. I could not emigrate permanently to the Antipodes. Also, I

wanted to take my research work further, and I knew that New Zealand was not the place to do so.

To do my research work properly I needed time to do it. Time in which to ponder, time to consider the possibilities. I also needed time to sit down and design and execute a number of studies that I'd been thinking about while away in New Zealand. What I needed was a day every week away from the NHS sausage factory. I went to see the dean of the medical school and told him what I had been up to, and what I wanted to do. He was very encouraging, and, in the end, arranged for the medical school to generously support me by providing funding for a whole day's research work per week. However, there remained the thorny issue of getting this idea approved by the NHS management, which ran the clinical service in the hospital. Following a vigorous discussion regarding the merits and demerits of me doing one day per week of research, permission was denied. I was pretty cross about this. I reconsidered my decision about returning to New Zealand, but after a period of careful deliberation I decided to stay and resolved to do the research work in my own time.

CHAPTER TWENTY-THREE

PLYMOUTH, 2007

While in New Zealand, I wrote up the cases of the locally-acquired hepatitis E we had found in Cornwall. The article, when completed, was sent to a number of medical journals for consideration. Every single one rejected it as "unsuitable for publication." From memory, we tried at least six different journals. The answer was always the same—rejection. I realised that we needed to find more cases so that colleagues in the medical profession would take the issue seriously. I thought about how to do this. I considered this for a good while, mulling the possibilities over in my mind.

I decided a two-pronged approach would be best. First, we would start testing everybody with hepatitis for evidence of hepatitis E infection. This was a significant step forward, as until then we had only been testing a limited number of patients for hepatitis E infection, i.e. those patients with hepatitis unexplained by another cause. This meant testing a lot more patients but was ultimately to lead to the uncovering of a large number of cases. The other thing I decided to do was to look across into neighbouring Devon and try to enlist the help of colleagues who worked there. As it turned out, colleagues in Plymouth were supportive and very helpful. Plymouth is the largest city in the county of Devon, and has for centuries been a major port, servicing the needs of the Royal Navy. Plymouth is about sixty miles from Truro, is situated in the southwest corner of Devon, and is geographically isolated from Cornwall by the river Tamar.

At the time, the hepatology (liver) unit in Plymouth had a research registrar who was taking a couple of years out from clinical work to do a PhD, much as I had done years before in Oxford. He was delegated the task of collaborating with me on the subject of hepatitis E. My colleagues in Devon had copied our idea for the jaundice hotline clinic and set up a similar clinic in Plymouth a couple of years before. The first thing to do was go through all the patients that had been seen at that clinic to check out all cases with unexplained hepatitis and get them tested for hepatitis E. Also, I asked them to consider testing for hepatitis E in every patient presenting with hepatitis in Plymouth, much as we had started to do. In

very short order, between us we had come up with twenty-three cases of hepatitis E. Now we really had something to work with. We performed a detailed analysis of the cases. Two of the twenty-three cases had travelled to areas endemic for hepatitis E, namely India and China. These were therefore cases of imported hepatitis E in travellers returning to the United Kingdom in line with the, now increasingly outmoded, traditional medical model of this illness in developed countries. We did not consider these cases any further, they had nothing new to teach us. We looked at the remaining twenty-one cases in minute detail.[1] They potentially had a great deal to teach us about hepatitis E that was locally acquired in Cornwall and Devon, and, in due course, the rest of the United Kingdom and the developed world as well.

None of the remaining twenty-one patients had visited an area endemic for hepatitis E infection in the three months prior to becoming ill, so there was no chance that any of these patients caught their infection in the developing world. They had contracted their illness at home in the United Kingdom. The median age of the patients with locally acquired hepatitis E was sixty-seven, with a range from thirty-five to eighty-five. We found that the "attack rate" was approximately three times higher in males, as fifteen of the twenty-one patients were male and only six were female. These were interesting observations, for which we had no explanation.

The clinical symptoms in the twenty-one patients varied from mild flu-like symptoms to a more severe liver injury with jaundice requiring prolonged hospital admission. One patient had no symptoms and never became jaundiced. No patients developed irreversible liver failure. Twenty patients made a full recovery with complete normalisation of liver blood tests, usually within four to six weeks. One patient died. We looked at the lifestyle of each patient in some detail. All the patients were Caucasian. Not surprisingly, given the age of the patients, thirteen of the twenty-one were retired. The remaining patients had the following occupations: retail assistant in a shop (two), publican (one), butcher (one), truck driver (one), care assistant (one), unemployed (one), and unknown (one).

Twenty of the twenty-one cases of hepatitis E presented between the months of March and October. We were puzzled about this observation. Viral infections are frequently seasonally related. However, as viruses do not care for too much heat, the seasonal variation is usually the reverse of what we had observed in our cases of hepatitis E, i.e. the incidence of most viral infections peaks during the winter months. The hepatitis E virus was

[1] H. R. Dalton, P. H. Thurairajah, H. J. Fellows, S. H. Hussaini, J. Mitchell, R. Bendall, M. Banks, S. Ijaz, C. G. Teo, D. F. Levine, et al., "Autochthonous Hepatitis E in Southwest England," *Journal of Viral Hepatitis* 14 (2007): 304–9.

behaving in a most unusual manner. Not only did it seem to prefer middle aged and elderly men, it also liked the heat. It was proving to be a very strange virus indeed.

One of the cases was a holidaymaker who came down to Cornwall from the Southampton area one summer. He was in his late forties and became ill a couple of days after arriving, with fevers, chills, and muscular aching. Not being registered with a local general practitioner in Cornwall, he presented himself to A&E at the hospital in Truro. There was nothing much to find on examination, and there was no evidence of jaundice. This sounded very much like a case of flu. That is until his liver blood test results came back from the lab. These showed him to have a moderate hepatitis. I was rung about his case by a colleague and recommended that he should be tested for all the causes of viral hepatitis, including hepatitis E. Two weeks later we got his hepatitis E results back—they were positive. This was not flu, this was acute hepatitis E.

This case taught me two important lessons. Firstly, patients with hepatitis E infection may not have any symptoms of hepatitis, such as jaundice. It would have been easy to make an erroneous diagnosis of flu in this case had the liver blood tests not been performed. I wondered how many patients there were around the world with a diagnosis of "flu" who in fact had hepatitis E. The second thing was that this case suggested that the twenty-plus cases of locally acquired hepatitis E infection that we had observed in Cornwall and Devon were unlikely to represent a local "outbreak" of this infection in southwest England. The reason for this is that the shortest incubation period is two weeks and is usually more like six or eight weeks. The patient who was on holiday in Cornwall from Southampton became unwell two days after arriving in Cornwall. This made it extraordinarily unlikely that he had contracted his infection in Cornwall. He'd brought it with him from Hampshire, 250 miles away along the southern English coast.

Another very important lesson we learned from these cases was the issue of accuracy of diagnosis. The case from Southampton illustrates how easy it could be to misdiagnose hepatitis E infection as flu, unless liver blood tests are performed in such cases. In addition, a detailed analysis of our twenty-one cases revealed that four had been misdiagnosed as a drug reaction, prior to being tested for hepatitis E infection. When a patient is given a new medication it always comes with a drug data sheet—a folded sheet of paper that is usually tucked inside the box of tablets. Frequently, patients don't bother to read the drug data sheet. However, those patients that take the trouble to do so will know that it contains quite a lot of detail about the medication they are about to take. The data sheet contains

(among other things) a list of active ingredients, and conditions in which the medication should be avoided, together with a list of possible side effects. This list is often very lengthy and almost invariably includes side effects such as nausea, vomiting, diarrhoea, and skin rashes. Not infrequently, however, the side effect of "hepatitis" or "liver injury" will appear on the list.

I have an interest in the effects that drugs can have on the liver. Some years ago, along with three other colleagues, I helped with a study looking at the patients who attended our jaundice hotline clinic who had iatrogenic (an illness caused by a doctor) hepatitis due to taking a prescription medicine issued by a member of the medical or dental profession. We found that a common scenario would be as follows. The patient develops a skin infection and goes to see the doctor. The doctor examines the patient and makes a diagnosis of cellulitis, a commonly occurring infection of the skin, the affected area becoming red, swollen, and painful. The patient is prescribed antibiotics and the skin infection gets better within a week or two. Two or three weeks later, the patient becomes jaundiced. A side effect of the antibiotics has caused an injury to the liver, known as drug-induced liver injury/hepatitis.

Our study showed that the commonest cause of drug-induced liver injury by far was the penicillin-based class of antibiotics.[2] A reaction to this class of drug accounted for approximately fifty percent of the cases of drug-induced liver injury that we observed and appeared particularly common in patients over the age of sixty. That's not to say that liver injury is inevitable after taking penicillin—far from it. Penicillin has been used safely for over seventy years and is a very commonly prescribed and effective drug. Only a tiny minority of patients who take this drug get liver injury as a result. To give an idea of just how uncommonly this occurs following penicillin therapy, our estimate is that significant liver injury occurs with a frequency of three to nine times per one hundred thousand prescriptions.

During the course of planning, performing, and writing up this study, we had to think very carefully about the criteria we used to make an accurate diagnosis of drug-induced liver injury. There are established criteria to make this diagnosis. Naturally, one is a temporal relationship between taking the drug and the subsequent development of liver injury. The timeframe between ingestion of the drug and onset of the liver injury is usually, but not invariably, between five and thirty days. Another very

[2] S. H. Hussaini, C. S. O'Brien, E. J. Despott, H. R. Dalton, et al., "Antibiotic Therapy a Major Cause of Drug Induced Jaundice in Southwest England," *European Journal of Gastroenterology & Hepatology* 19 (1) (2007): 15–20.

important criterion is the exclusion of all other causes of liver injury, including viral hepatitis.

With this in mind, when analysing the twenty-one cases of hepatitis E, I paid particular attention to the patients' list of medications that they were taking and when they had started taking them. As the patients were largely middle aged or elderly, and prescription drugs were those more commonly taken by older people, the list of medications taken by some of the patients was fairly extensive. I also had to nail down exactly when these patients had started each medication. This took up quite a bit of time delving through medical records. We found four patients out of our total of twenty-one with locally acquired hepatitis E who were initially but erroneously thought to have drug-induced liver injury prior to their hepatitis E results being available.

One of these four cases was that of a sixty-eight-year-old retired man. He was perfectly well, and active for his years. He had been noted by his general practitioner as having a high cholesterol level and had this checked reasonably regularly. The patient was started on a low-cholesterol diet. This helped a bit, but not much. The general practitioner decided to treat the patient with a statin, in this case a drug called atorvastatin. This is a very effective drug at lowering the serum cholesterol and is used regularly for this purpose by countless millions of patients worldwide, including myself. Browsing the drug data sheet that came with his first box of atorvastatin, the patient would have observed the following statement: "Very rare side effects (affects fewer than one in ten thousand patients taking the drug): hepatitis (liver inflammation), jaundice (yellowing of the skin and whites of the eyes) …"

The patient's doctor was aware of this also, and when the patient next went to have his cholesterol level checked, he checked the liver blood tests for good measure. Despite the fact that the patient felt absolutely fine with no symptoms whatsoever, the liver blood tests showed he had hepatitis. Of course, the general practitioner thought this was a classic case of drug-induced hepatitis, and immediately asked the patient to stop the offending atorvastatin. He also rang me up. I said that he was probably right, but that we better just check the patient did not have hepatitis E infection before we made the assumption that this was related to the atorvastatin. Two weeks later, the results came back from London. This was not a drug reaction. It was genotype 3 hepatitis E infection, viral RNA having been isolated from the patient's bloodstream. The patient's liver blood tests went back to normal within four weeks. He was restarted on the atorvastatin without a problem and was somewhat bemused by all the fuss being made, as he felt perfectly well and had done throughout.

I found this a fascinating case for two reasons. Firstly, his case established unequivocally that hepatitis E infection could occur without any symptoms at all. The only reason this case was diagnosed as hepatitis E infection was the serendipitous testing of the patient's liver blood tests for another reason, in this case to check the atorvastatin was not upsetting the liver. I wondered how many other patients had this infection but had no symptoms. Secondly, it confirmed, also beyond any reasonable doubt, that hepatitis E infection can be misdiagnosed as drug-induced liver injury. This was interesting. We subsequently looked at a group of patients with criterion-referenced drug-induced liver injury and tested them for hepatitis E. We found that thirteen percent of patients who had been initially labelled as having drug-induced liver injury had an erroneous diagnosis. They did not have drug-induced liver injury, they had locally acquired hepatitis E infection.[3] This added another piece to the jigsaw. Not only can hepatitis E be misdiagnosed as flu, it can also be, and quite commonly is, misdiagnosed as a drug reaction.

The key question to my mind, however, was what was the source of the infection? I spent as much time as I could talking to the patients who had had locally acquired hepatitis E infection. Between my NHS duties and during the evenings and weekends, I pored for hours and hours over the details of their cases, trying to work out common threads. Older men infected in spring, summer, and autumn. Yes, but where from? The strain of the hepatitis E virus isolated from our patients was genotype 3. The virus that we isolated from all our patients was sent to a veterinary virologist in Surrey for further analysis. He found that all the viruses isolated were very, very similar to that found in UK pigs, which carry the virus but have no symptoms. This evidence suggested that the locally acquired hepatitis E we had seen in our patients could possibly be a zoonosis (an infection of humans derived from an animal host). This was puzzling. Although Cornwall and southwest Devon have a large farming community, farming activity is mainly dairy, and there is relatively little pig farming in the area. Close contact with live pigs or their faeces thus appeared unlikely as the source of our patients' infection.

We went back to the patients. One was a butcher, so he came into contact with pig meat every day of his working life. That was a definite risk factor in his case, but the other twenty patients were either retired or had no contact with pigs during the course of their day-to-day work or life.

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[3] H. R. Dalton, H. J. Fellows, W. Stableforth, M. Joseph, P. Thurairajah, U. Warshow, S. Hazeldine, R. Ramnarace, S. Ijaz, S. H. Hussaini, R. Bendall, et al., "The Role of HEV Testing in Drug-induced Liver Injury," *Alimentary Pharmacology & Therapeutics* 26 (2007): 1429–35.

One patient had direct contact with live farm animals as he lived next door to a field with free-range pigs in it. Pigs are friendly animals and he occasionally leaned over his back-garden fence to give them a stroke. A possible risk factor in this case, but what about the other nineteen patients? We took a very detailed dietary history from each. What we found was that all twenty-one regularly ate meat, including pork. None of the patients were vegetarian. Could the source of infection be dietary, e.g. the consumption of infected pork or pork-meat products? We were not at all sure. We were particularly unsure of the relevance of our observation that all of our patients with hepatitis E were pork eaters, as it was unclear what percentage of the population of Cornwall and Devon were vegetarian. In particular, we did not know how many middle-aged/elderly Cornish men, the risk group in question, were vegetarian. We thought that the figure would be low, and so it proved to be, as in a subsequent study we were to show that only 1.2 percent of individuals in Cornwall over the age of sixty are vegetarian.[4] In terms of improving our understanding of the source of infection, the fact that all our patients with hepatitis E were pork-eating non-vegetarians was therefore neither here nor there.

[4] H. R. Dalton, W. Stableforth, N. Hamad, E. Cole, V. Ellis, R. Bendall, et al., "HEV in SW England: Clinical Features, Natural History and Complications and the HEV IgG Seroprevalence in Blood Donors, Patients with Chronic Liver Disease and Individuals Over the Age of 60 Years," *The European Journal of Gastroenterology & Hepatology* 20 (8) (2008): 784–90.

CHAPTER TWENTY-FOUR

PINKY

While we were beavering away trying to work out what was going on with the hepatitis E story, a research group from Toulouse in southwest France was doing the same. They reported very similar findings to our observations in Cornwall and Devon, with a large group of patients affected, predominantly elderly males. Like our cases, these were locally acquired infections from southwest France, as none of their patients had visited an area traditionally thought of as endemic for the disease. The French study also showed that their cases were caused by the same strain of hepatitis E virus as ours (genotype 3), which was also very similar to that found in local French pigs.[1] However, there were subtle differences in the strains of HEV found in French men and French pigs compared to English men and English pigs, although in both countries HEV was genotype 3. The French findings were of great interest as they suggested that the cluster of cases we had seen in Cornwall and Devon was not just a local outbreak in southwest England. There had also been reports of cases from the Netherlands, Spain, and Japan. As colleagues in the United Kingdom began to test patients with unexplained hepatitis, cases were also popping up all over the country. They were always the same—predominantly middle-aged/elderly males, caused by HEV genotype 3.

We were unsure of the source of infection in our cases of hepatitis E in Cornwall and Devon. We were working on the "porcine zoonotic" (transmission of the virus from pigs to humans) theory, as this looked most likely following the information that we and others had discovered. Quite how the virus was getting from pigs to humans remained an open question. However, there was incontrovertible evidence from Japan that the hepatitis E virus could be transmitted by eating contaminated meat. In what is acknowledged as a hallmark study in this area, Tei et al. described an

[1] J. M. Mansuy, J. M. Peron, F. Abravanel, et al., "Hepatitis E in the Southwest of France in Individuals who have Never Visited an Endemic Area," *Journal of Medical Virology* 74 (2004): 419–24

outbreak of hepatitis E in Japan,[2] which was subsequently published in *The Lancet*. A group of Japanese went hunting and shot a Sika deer. They decided to eat the deer's liver as a sushi, i.e. raw. Four out of the eight people who ate the deer's liver became ill with an acute hepatitis. This turned out to be hepatitis E infection, and all the patients who became ill had an identical strain of the virus (genotype 3), indicating that they were infected from a common source. Tei et al. took a detailed dietary history from the patients and quickly came to suspect the deer liver sushi as the source of the outbreak. As luck would have it, the deer's liver had not all been eaten, and some was still in the freezer. The frozen deer's liver was taken for analysis and was found to be teeming with the same strain of hepatitis E virus as that isolated from the patients. This was an important case study as it showed quite clearly that hepatitis E could be transmitted by eating infected meat. Could this be the mode of transmission from pig to human?

Genotype 3 hepatitis E virus is found in pig herds throughout the world. Eighty-five percent of British pigs that have been tested show evidence of infection.[3] In the Netherlands at this time the figure was fifty-five percent,[4] in Canada was sixty percent,[5] and in Australia it varied from seventeen to ninety-five percent.[6] US pigs also show evidence of infection, but the percentage of pigs affected varies from state to state.[7] Pigs become infected with the hepatitis E virus shortly after weaning. The virus can be isolated from their blood and stool for several weeks and it is likely that the weaners are infected from older members of the herd. The virus

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[2] S. Tei, N. Kitajima, K. Takahashi, and S. Mishiro, "Zoonotic Transmission of Hepatitis E from Deer to Human Beings," *The Lancet* 362 (2003): 371–3.

[3] M. Banks, G. S. Heath, S. S. Grierson, et al., "Evidence for the Presence of Hepatitis E Virus in Pigs in the UK," *Veterinary Record* 154 (2004): 223–7.

[4] S. A. Rutjes, W. J. Lodder, M. Bouwknegt, and A. M. de Roda Husman, "Increased Hepatitis E Virus Prevalence on Dutch Pig Farms from 33 to 55% by using Appropriate Internal Quality Controls for RT-PCR," *The Journal of Virological Methods* 143 (1) (2007): 112–6.

[5] P. Ward, P. Müller, A. Letellier, S. Quessy, C. Simard, Y. L. Trottier, A. Houde, and J. Brassard, "Molecular Characterization of Hepatitis E Virus Detected in Swine Farms in the Province of Quebec," *Canadian Journal of Veterinary Research* 72 (1) (2008): 27–31.

[6] J. D. Chandler, M. A. Riddell, F. Li, R. J. Love, and D. A. Anderson, "Serological Evidence for Swine Hepatitis E Virus Infection in Australian Pig Herds," *Veterinary Microbiology* 16 68 (1–2) (1999): 95–105.

[7] X-J. Meng, S. Dea, R. E. Engle, et al., "Prevalence of Antibodies to Hepatitis E Virus in Pigs from Countries where Hepatitis E is Common or is Rare in the Human Population," *Journal of Medical Virology* 59 (1999): 297–302.

appears to cause the pigs no problems at all. Infected pigs are to all intents and purposes happy healthy porkers and bound for the human food chain when they reach their target slaughter weight.

Although pigs commonly and obliviously carry the hepatitis E virus when alive, at this time it was by no means certain that the virus would find its way into the human food chain. Pigs often carry the virus only for a few weeks, and by the age of twelve weeks they spontaneously clear it. Thus, it seemed likely that by the average age of slaughter (between twenty and twenty-four weeks in the United Kingdom) the vast majority of pigs would be virus free. Furthermore, even if a pig was carrying the virus at the time of slaughter, the virus was by no means certain to survive slaughtering and processing to reach the retail shelves contained in some innocent-looking pork chops.

What we needed to do was have a careful look at pork for sale on the butcher's shelves to see if we could find the virus. I needed to think about this carefully. The first thing I thought about was the ethics of doing this. I wondered whether we would require approval from the hospital Ethics Committee. I discussed this with Bendy Boy, my microbiologist colleague and main collaborator. We also discussed the issue with our veterinary virologist colleague in Surrey, who had agreed to do the virological studies on the meat samples. As the study did not involve human subjects and the specimens were from animals that were already dead, we agreed that the hospital Ethics Committee would not be interested in it. There were simply no patient-related ethical issues to consider.

We then went on to discuss the more general ethical issues. Was it ethical for us to buy pork from a butcher's shop and, instead of eating it, test it for the hepatitis E virus? We considered this. We decided that, as the pork was for up for sale, we could do what we liked with it. We could eat it, feed it to a pet cat, throw it away, or test it for hepatitis E. We were, however, conscious of the potential implications for individual butchers should we find any virus in their meat. We decided, therefore, to anonymise all the samples that we purchased. There would be simply no way of telling from which butcher each sample had originated.

We considered the logistics of the exercise. The first thing we needed to think about was what samples would be purchased? We decided that fresh pig's liver would be best and decided to buy half a pound. From this we would take a sliver of approximately twenty grams. The latter would be placed in a sterile tube and placed in a freezer at –70°C. Once sampling was complete they would be sent up to Surrey for analysis in a single batch. We kept the rest of the unused liver sample in the freezer in case we needed to do any further studies. Thinking about our finding that our cases

presented in spring, summer, and autumn, I wanted to avoid obtaining pig liver samples in the winter. We therefore arranged for the sampling to be done in May, June, July, and August. This turned out to cause some bother in sample acquisition. I went to many a butcher during the study period asking for pig's liver, only to be told they did not have any. The butcher's explanation was that there was not much call for pig's liver in the summer, as people did not tend to eat it much. That got me thinking about whether io were on the right track or not.

I wanted to sample as many butchers' shops as I could. There are over sixty dotted around Cornwall. This would mean a huge amount of travelling, as Cornwall is over one hundred miles long from its north-eastern comer to Land's End at the far southwestern tip. I needed a team of helpers, and I persuaded my colleagues to help. Soon, samples started arriving from all over Cornwall. When they arrived they needed cutting up, with a twenty-gram sliver extracted and placed along with the mother sample in separate containers prior to freezing.

The cut up was done under aseptic conditions. I sometimes did the cut up myself, but more often my registrar did it. He wanted to be a hepatologist, a liver specialist, and I could think of no better way of helping him understand the nature of this organ than by getting him to do the cut up on the pig's liver. It seemed an entirely appropriate part of his training. What I didn't realise was that he could not stand the smell of raw pig's liver. It was a sight of comical irony watching him, training to be a liver specialist, handling the pig's liver, and trying not to heave his guts up. When we got to a total of eighty samples we decided it was enough. We'd visited just about every butcher's shop in Cornwall, some more than once, and the enthusiasm of my team of helpers was flagging. We batched the samples up and sent them up to Surrey for analysis to see how many contained the hepatitis E virus. We had a sweepstake on how many samples would contain the hepatitis E virus. We were all hopelessly wrong. The virus was not present in any of them.[8]

We were disappointed. We had felt sure that we would find the virus in the pork. But no, it was not there. Our disappointment was keen edged, as we knew the Japanese had found hepatitis E virus in 1.9 percent of retail pork samples tested.[9] The Dutch were also to go on and isolate hepatitis E

[8] M. Banks, S. Grierson, H. J. Fellows, W. Stableforth, R. Bendall, and H. R. Dalton, "Transmission of Hepatitis E," *Veterinary Record* 160 (6) (2007): 202.

[9] Y. Yazaki, H. Mizuo, M. Takahashi, et al., "Sporadic Acute or Fulminant Hepatitis in Hokkaido Japan, may be Food Borne as Suggested by the Presence of Hepatitis E Virus in Pig Liver as Food," *Journal of General Virology* 84 (9) (2003): 2351 7.

virus from 6.5 percent of retail pig meat samples.[10] Work in the United States took things a stage further. Not only has the hepatitis E virus been isolated from eleven percent of pig's liver for sale in US grocery stores, the virus that has been found has been shown to be viable (i.e. it was not a dead virus, or bits of dead virus) and infectious.[11] Another study from the United States[12] has shown that the hepatitis E virus is able to survive cooking in temperature up to 56°C, and to be sure of killing HEV it needs to be heated to 71°C for twenty minutes.

These data, taken together, provided some evidence that pointed towards the consumption of infected pork as a possible mode of infection. Why we did not find it in our samples was unclear. Perhaps our sample size was too small. Perhaps it was not in any retail pig meat at all in the United Kingdom. I found this a little hard to accept, as there is not that much difference between animal husbandry practices between the United States, the Netherlands, and the United Kingdom. Perhaps there was a mistake in the lab. I find this even harder to accept. Our veterinary virologist is a scientist of the highest quality. If he said the virus wasn't there, then it wasn't. Period. As it turned out, our friends in the vet lab in Surrey were working on improving their laboratory technique. They retested our liver samples some time later and found HEV in one of seventy-two samples tested. This was the first demonstration of HEV in the human food chain in the United Kingdom at the point of sale.[13]

To establish a definite causal relationship between eating contaminated pig meat and hepatitis E infection in humans, we tried chasing the virus up the food chain. As soon as we came across a case we would get on the phone to the team leader of Environmental Health. She would then get one of the environmental health officers to go to the patient's house and interview them. This would include a very detailed dietary history going back some weeks. They also obtained samples of pork from the patient's

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[10] M. Bouwknegt, F. Lodder-Verschoor, W. H. M. Van der Poel, S. A. Rutjes, and A. M. de Roda Husman, "Hepatitis E Virus RNA in Commercially Available Porcine Livers in the Netherlands," *Journal of Food Protection* 70 (2007): 2889 95.

[11] A. R. Feagins, T. Opriessning, D. K. Guenette, P. G. Halbur, and X-J. Meng, "Detection and Characterisation of Infectious Hepatitis E Virus from Commercial Pig's Liver Sold in Local Grocery Stores in the USA," *Journal of General Virology* 88 (2007): 912 17.

[12] S. U. Emerson, V. A. Arankalle, and R. H. Purcell, "Thermal Stability of Hepatitis E Virus," *The Journal of Infectious Diseases* 192 (2005): 939 3.

[13] M. Banks, F. Martelli, H. J. Fellows, S. Grierson, W. Stableforth, R. Bendall, and H. R. Dalton, "Hepatitis E Virus in Retail Pig Livers," *Veterinary Record* 166 (2010): 29.

freezer, if there was any. They also obtained samples of pork from the patient's usual butcher. Then, the pork samples were tested for the virus. The problem with this approach, however, was that by the time the case presented two to eight weeks had elapsed (the normal incubation period of virus). Another couple of weeks delay also occurred before the diagnosis was confirmed, as the patient's blood samples had to be sent up to London for testing. So, by the time we got to the case, the trail was cold. All the food samples tested in this way were negative.

While all this was going on we were busily trying to find more cases. I expanded the net to cover the whole of Devon as well as Plymouth. I enlisted the help of a number of colleagues, including those in Torbay, Exeter, and Barnstaple. My consultant colleagues in Truro also helped a great deal and watched with amusement and bemusement as I ploughed forward. Bendy Boy and I swapped ideas by email and phone. We chased around together, tracking down cases. Once in a while we would have the luxury of a couple of hours to ourselves to knock about some ideas, or go over our latest results in the lab, or write up a paper. These sessions were priceless, intellectually stimulating, and very rewarding. I owe Bendy Boy a lot. We have essentially done all the work together and discussed our latest findings as we went. It's been an absolute pleasure working alongside him.

In summary, we agreed that pigs were the "prime suspect" in terms of the source of the hepatitis E infection seen in our patients. However, we could not prove it unequivocally.

CHAPTER TWENTY-FIVE

VETERINARY MEDICINE

Over the years, friends, family, colleagues, and patients have called me all sorts of names, mostly in jest. I've even been accused of being a vet. While my veterinary surgical colleagues, with whom I have collaborated for over a decade on the HEV story, may regard this as somewhat offensive, I will admit to having practised "veterinary-style" on no more than two occasions.

I was asked to see Mickey by a colleague of mine for a second opinion. Mickey was a local character. A Cornishman by birth and a farm labourer by trade, he had no teeth, smoked like a chimney, and had a raucous laugh topped off by an edentulous grin that spread from ear to ear. When I went to see him for the first time, however, Mickey was not smiling. He had been in hospital for four months. His symptoms were nausea, vomiting, relentless diarrhoea, and weight loss. He had lost half his body weight, and now weighed in at five stone. He looked like a concentration-camp survivor. From the end of the bed you would guess his age at eighty years, but he was in fact only in his mid-forties. Despite an endlessly long list of investigations, it was unclear what was wrong with him. I sat down and talked to him for a very long time. I knew this was going to be a difficult case to unravel. Mickey told me about his symptoms one by one, regularly punctuated by his thick Cornish brogue:

"I'm not having no more tests, docc'er. If I were a dog you'd put me down."

I then spent a couple of hours going through his hospital notes. He was, by that stage, on his second volume. I combed through every detail, every test result. I thought about his symptoms. I thought about the test results. I did not know what was wrong with him either. But what to do? Mickey was not having any more tests done, there was no doubt about that. But without further tests, we might not reach a diagnosis, and without a diagnosis we were on a sticky wicket in terms of giving him the appropriate treatment. I thought about Mickey and mulled his case over.

The next day I went to see him again.

"Mickey, how are you?" I said.

"I'm not having no more tests, docc'er. If I were a dog you'd put me down," was his mantra-like reply.

"OK … if we don't do more tests we might not be able to find out what's wrong with you."

"I'm not having no more tests, docc'er. If I were a dog you'd put me down."

"What are we going to do with you Mickey?"

"If I were a dog you'd put me down."

"Mmm …"

"I'm not having no more tests, docc'er."

"Mickey, I promise I won't ask for any further tests, unless you change your mind."

"I'm not having no more tests, docc'er. If I were a dog you'd put me down."

"Mickey?"

"I'm not having no more tests, docc'er. If I were a dog you'd put me down."

"Mickey. No more tests!"

"I'm not having no more tests …"

"No more tests," I repeated.

"No more tests then docc'er," he replied.

"No more," I said, as reassuringly as possible

"No more?"

"No. None"

"None." He finished.

"Mickey. There will be no more tests, but I can't put you down like a dog, or I'd get sent to prison."

"Oh!"

"What we could think about is treating you like a vet would."

"What do you mean, docc'er?"

"Well, vets will sometimes treat a sick dog without doing any tests. That's the way I would like to treat you, if you would like me to."

"No more tests?"

"No."

"How'r you gonna treat me?"

"Veterinary."

"What, like a dog?"

I smiled, and so did he. I treated him "blind," without a diagnosis. I gave him massive doses of steroids by injection and an extraordinarily expensive drug called octreotide. The latter is a hormonal preparation, also given by injection, which slows the transit of the gut. We waited. A week

later, his symptoms were considerably better. His diarrhoea had stopped, as had his vomiting, but he still felt sick and was eating barely enough to nourish a sparrow. The treatment was continued and he continued to improve, but his weight did not. We needed to get some nourishment into him somehow. After over two weeks of treatment I talked to him again.

"Mickey!"

"Docc'er!"

"How's the veterinary working?" I asked.

"I think he's working just fine, docc'er."

We had an extended conversation about how I would like to change his treatment. The key to his case was to replenish his stores of nourishment. He was eating hardly anything. What I wanted to do was insert a feeding tube (known as a gastrostomy) directly through his abdominal wall and into his stomach. This would allow a nutrient mixture to be fed directly into the stomach twenty-four hours a day and is a very good method of re-nourishing patients who cannot eat enough to maintain their nutritional status. The problem I had is that the placement of the gastric feeding tube is performed with an endoscope. This would mean that Mickey would have to have another endoscopy (he'd already had three diagnostic endoscopies), and I'd promised him no more tests.

Gastrostomy tubes had been used by Pavlov in his famous experiments on dogs in the late nineteenth century. Pavlov was studying the conditioned response and, in particular, the physiological responses in gastric secretion to the stimulus of a bell. I decided to tell Mickey all about Pavlov and his dogs with gastrostomy tubes. Mickey agreed to have a gastrostomy placed on three conditions: (a) it was not a test, (b) he would remember nothing about the procedure, and (c) I placed the gastrostomy for him myself. I did so, and we fed him via the gastrostomy for several months. His weight gradually increased. His appetite eventually returned, and we were able to remove the feeding tube as he could now keep up with his nutritional requirements the normal way. He needed months and months of rehabilitation. One year and a day after he had first been admitted to the ward, he walked out the door and off home.

The only other time I did veterinary medicine I did it properly, i.e. on an animal. Two friends of mine got a young Sussex spaniel by the name of Archie, known as "Arch." Arch was going to be sent to a rescue home. He was the runt of a litter and was found to have a heart murmur. My friends fell in love with Arch. They took him in at the age of ten weeks with the aim of giving him a nice home, for whatever remaining life Arch had left. They had no intention of having his heart murmur investigated or treated, nor could they afford it. I was round at my friends' house one evening

having dinner. Arch introduced himself, tail wagging, nipping at my ankles. They told me the story about his heart murmur. Much against my better judgement, I was badgered into getting my stethoscope out to have a listen to Arch's heart. Arch was having none of this. We chased him round the sitting room, and he thought that was hilarious. He was eventually caught and given a firm cuddle as I slipped my stethoscope on.

I've never listened to any animal's heart, and certainly not a dog's. I knew, however, that physiologically a dog's heart is very similar to a human's. There was nothing to lose, so I pressed the bell of the scope up against Arch's chest wall on the left. Arch's heart was going like the clappers. No great surprise there, as just spent the last five minutes chasing him around the sitting room. I waited a few minutes and tried again. Arch's heart was still going pretty fast. I listened hard for low-frequency murmurs with the bell attachment of the scope, then quickly flicked over to the diaphragm attachment to listen for higher frequency sounds. Then back again to the bell. What did I hear? "Chuckachucka, chuckachucka, chuckachucka, chuckachucka, chuckachucka."

I'd heard that noise before, once, when I was a boy. This was the sound of the weaving machines in the woollen mills in my hometown in Yorkshire. It was also the sound I'd heard through my stethoscope many years ago when a fourth-year medical student. This was in a three-week-old baby who had a patent ductus arteriosus, an abnormal connection between the pulmonary artery and aorta. It causes abnormal blood flow around the heart, producing a characteristic "machinery murmur." In humans, this abnormal connection sometimes closes on its own. It can also be closed surgically. Occasionally, drugs are used to close it. The drug most commonly used is indomethacin.

I told my friends what I thought. I also told them I wasn't a vet. They laughed and said that was not what they'd heard. I told them I had no idea if dogs could get this condition but promised to find out. I emailed a vet friend, a patient of mine. Yes, dogs do get this condition, it can be closed surgically, but would cost a lot. There was not much data on the use of indomethacin in this condition in dogs. I forwarded the vet's email to my friends, then popped around to see them the following week. Naturally, after a good play with Arch, we got around to talking about his heart murmur. Surgery was out of the question. When they took him on it was to look after him as best they could without resorting to vets (present company excepted) and surgery. We discussed it some more and decided to go with the idea of treating Arch with indomethacin tablets, crumbled into his food once a day for a couple of months. In the end, Arch lived for a few years, but died earlier than one would have expected for his breed.

It's not clear if the indomethacin helped, but when I saw him while alive his tail always wagged, and he usually seemed pleased to see me.

CHAPTER TWENTY-SIX

BLOOD DONORS I

In terms of the research work, the next thing we turned our attention to was trying to get an estimate of how common hepatitis E infection is. We looked at this in two ways: firstly by comparing it to the commonest type of acute viral hepatitis, hepatitis A; and secondly by looking at a group of blood donors to see how many of them showed evidence of previous exposure to the virus.

Hepatitis A has for many years been considered the commonest cause of acute viral hepatitis in developed countries. It affects young adults and causes jaundice and a flu-like illness. In the vast majority of cases the illness is self-limiting, and the patient almost invariably recovers without a problem. We decided to test the hypothesis that hepatitis E was more common that locally acquired hepatitis A. With the help of colleagues in Devon, we checked all the tests that had been performed for hepatitis A and hepatitis E in the microbiology labs in the whole of Devon and Cornwall over a two-year period. We found that there had been far more tests performed for hepatitis A (4,503 tests) compared with hepatitis E (838 tests). This was no great surprise. The reason that there were five times fewer hepatitis E tests performed almost certainly related to the fact that we had largely only been testing patients with unexplained hepatitis for hepatitis E. It was only relatively recently that we had started to test "all comers." Another point to make about the number of tests for hepatitis E over this period is that it almost certainly represents the highest number of tests per head of the population performed anywhere in the United Kingdom (and possibly the rest of the world)—a natural reflection of our interest in this virus.

We then checked the number of cases of hepatitis A that had been diagnosed in this period and compared it with the number of hepatitis E cases that had been diagnosed over the same timeframe. We found twenty cases of hepatitis A, compared with twenty-eight cases of locally acquired hepatitis E. These data showed that the commonest cause of acute viral hepatitis in Cornwall and Devon was not hepatitis A, but hepatitis E. We compared the cases and found that, compared with hepatitis A, patients

with hepatitis E were older (by a mean of sixteen years), more likely to be male (by a factor of 2.5), more likely to have complications, and less likely to present in winter.[1] Similar data also emerged from Japan[2] and France.[3]

The other way we tried to get an idea about how common hepatitis E infection is in the United Kingdom was to do what is known in the trade as a "sero-survey." When humans encounter a virus, or any other micro-organism for that matter, human defence mechanisms mount a response to kill the virus. One of these defence mechanisms is the production of antibodies. There are a number of different types of antibodies (or immunoglobulins, to give them their proper name), but one is an antibody named immunoglobulin G (or IgG for short). The thing about this antibody is that, following an infection, it sticks around in the bloodstream for an indefinite period. So, for example, if you had measles as a child you would have a measles-specific IgG antibody present in your blood for the rest of your life. The presence of this antibody confers immunity to measles. It is because of the presence of this antibody that you cannot get measles twice.

The same principle applies to hepatitis E infection. Individuals who have had this infection in the past should have specific antibodies (of the IgG variety) to it circulating in their bloodstream. The idea was simple—we would get hold of some blood samples from blood donors. In the United Kingdom you can only donate blood up to the age of seventy, so we therefore needed to get some blood samples from older patients. The latter group was an important one to test, as we knew the virus seemed to have a predilection for the elderly for some reason. Once we had all the samples together, we would test the lot to see how many had IgG antibodies to the hepatitis E virus.

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[1] H. R. Dalton, W. Stableforth, S. Hazeldine, P. Thurairajah, R. Ramnarace, U. Warshow, S. Ijaz, V. Ellis, R. Bendall, et al., "Autochthonous Hepatitis E in Southwest England: a Comparison with Hepatitis A," *The European Journal of Clinical Microbiology & Infectious Diseases* 27 (7) (2008): 579–85.

[2] T. Mitsui, Y. Tsukamoto, A. Hirose, S. Suzuki, C. Yamazaki, K. Masuko, et al., "Distinct Changing Profiles of Hepatitis A and E Virus Infections among Patients with Acute Hepatitis, Patients on Maintenance Haemodialysis and Healthy Individuals in Japan," *Journal of Medical Virology* 78 (2006): 1015–24.

[3] J. M. Peron, J. M. Mansuy, H. Poirson, C. Bureau, E. Dupuis, L. Alric, J. Izopet. "Hepatitis E is an Autochthonous Disease in Industrialized Countries. Analysis of 23 Patients in Southwest France over a 13-month Period and Comparison with Hepatitis A," *Gastroentérologie clinique et biologique* 30 (5) (2006): 757–62.

Before we could start any of this I had to fill out an Ethical Committee Form, which was seventy-two pages long, and which needed to know everything about the study, the patients, the tests, and the research team. It also needed to be accompanied by endless other documentation, including a good number of signatures from various worthies in the NHS hierarchy. I kept a rough record of how long this process took me from start to finish. I reckon it took me about fifty hours of work

Once the Ethical Committee had approved the study, we needed some cash to pay for the tests. I approached a local charity, Duchy Healthcare Charity. They kindly donated ten thousand pounds, which was much appreciated. One day, I went to get my lunch at the hospital League of Friends shop, which I did on most days. Jean, a lovely lady in her late sixties, and the coffee shop head honcho, always served me my lunch. She'd been a patient of mine and spent quite a bit of her spare time working at the little shop in the hospital. As I was paying her she said to me:

"You're interested in research work, aren't you Doctor?"

"Yes, I am Jean," I replied.

"We have some spare cash and we'd like you to have it."

"Oh, thanks. What would you like me to do?"

"Just give a lay summary of what you would like to do and how much it would cost," she replied.

While eating my cheese and tomato sandwich, I summarised the study on my computer. I printed it out and gave it to Jean on my way to clinic. A month later there was a cheque for five thousand pounds. That made a grand total of fifteen thousand pounds. We did the whole study and many other subsequent projects using this money and plenty of goodwill from colleagues who were pleaded with and cajoled into helping us out. This was guerrilla research on a shoestring budget.

We were now ready to go. We received five hundred blood samples from the Blood Transfusion Service in Bristol. They were meant to charge us for this, but never did, for which I was very grateful. At the appropriate insistence of the Ethics Committee these samples were anonymous, i.e. we did not know the donors' names, age, sex, or anything else about them at all, other than they had recently given blood somewhere in the southwest of England. It took a little longer to get the samples from our older age cohort, which were taken from patients over the age of sixty attending the hospital in Truro. In the end, 336 Cornish men and women generously donated a bit of their blood to enable us to complete the study.

We put the samples through the antibody assay in the lab in Truro. As we had no "research lab" to speak of, this was done out of hours in the

microbiology department by a friendly technician, once the daily NHS work had been completed. I couldn't wait to be called with the results and went around the first thing the next morning to see Bendy Boy poring over a long computer printout. The results showed that sixteen percent of the blood donors had IgG antibodies to hepatitis E. In other words, sixteen percent of the blood donors showed evidence of past infection of this virus. These data allowed us to do a very rough and ready estimate of how commonly this infection might occur. We did not know the age of the blood donors, but if we assume their average age to be forty, and we also assume that the rate of exposure is equal in each year of life, this equates to an annual incidence of 0.4 percent, or four in every one thousand people of the population. Extrapolating these data to the rest of the country suggested that every year in the United Kingdom (population sixty-five million), 260,000 people become infected. This was mindboggling. The results in the over sixties were fascinating as well. The older the patient, the more likely they were to have the antibodies. Over thirty percent of Cornish men and women over the age of eighty had IgG antibodies to the hepatitis E virus. We also noted that men were slightly more likely to have antibodies compared with women, but not by much.[4]

We now had overwhelming evidence that hepatitis E was far more common than had been previously supposed. We had documented a large series of cases. We had shown that it was more common than hepatitis A infection. We had also shown that the antibody seroprevalence was staggeringly high and increased with age. This latter result could only have two explanations: either most infections with the virus cause no symptoms, or most infections are unrecognised in patients who do have symptoms, or a combination of the two. The likeliest source of infection still appeared to be pigs. Given that we really struggled to find it in retail Cornish pig liver, the exact mode of infection remained uncertain.

[4] H. R. Dalton, W. Stableforth, N. Hamad, E. Cole, V. Ellis, and R. Bendall, "HEV in SW England: Clinical Features, Natural History and Complications and the HEV IgG Seroprevalence in Blood Donors, Patients with Chronic Liver Disease and Individuals over the Age of 60 Years," *The European Journal of Gastroenterology & Hepatology* 20 (8) (2008): 784–90.

CHAPTER TWENTY-SEVEN

THE BARBEQUE THEORY

I thought a lot about the seasonal variation of the cases of hepatitis E that we had seen. The cases seemed to cluster in the spring, summer, and autumn. The other striking thing was the age and sex of the patients affected—middle-aged/elderly males. How could we tie these facts together? Did they give us any clues about the origin of this infection? One of the possibilities we considered, originally suggested by a local Cornish general practitioner, was the "barbeque theory." The barbeque theory ran as follows:

(1) Viable hepatitis E virus can be found in retail pork
(2) The virus can be transmitted from eating infected meat, as demonstrated by Tei and colleagues in the sushi outbreak in Japan
(3) The virus can withstand cooking temperatures up to 56°C
(4) Could the route of infection be through poorly cooked barbeque food?

In the United Kingdom, having a barbeque is definitely a seasonal event. It is simply too cold in the winter to have a barbeque outside. This seasonality of UK barbeques seemed to sit nicely with the observation that our cases of hepatitis E infection occurred in the spring, summer, and autumn. Another thing about UK barbeques is that, almost invariably, males perform the cooking. The reason for this is uncertain, but maybe it's a throwback to primeval hunter-gatherer days. Whatever the explanation, what is beyond dispute is that the quality of barbeque cooking by your average UK male can only be described as inconsistent. It is a common experience, as anyone who has attended a barbeque in the United Kingdom will know, to tuck in to a barbequed sausage that on the outside looks well-cooked only to find that the meat on the inside is uncooked or significantly undercooked. The sausage has been flamed, blitzed, and charred on the outside, but is raw in the middle. We started asking our patients with hepatitis E about barbeques.

We found more and more cases. There was a flood from Devon, as well as more from Cornwall. Soon we were up to forty-two cases of locally acquired hepatitis E in Cornwall and Devon. The new cases we had discovered were similar to those we had seen before—predominantly middle-aged and elderly men. However, we noted that a significant minority (fifteen percent) of our patients had sustained complications from their hepatitis E infection.

Patients who get hepatitis E infection have a number of symptoms. These include jaundice, fever, abdominal pain, and flu-like symptoms, including muscular aches. Seven of our forty-two patients had vomiting as a symptom. In some patients, this was a severe and protracted problem. This was the case in an elderly man who vomited persistently for over ten days. In fact, he vomited so much and with such force that he sustained a spontaneous rupture of his oesophagus. This is a very serious condition and carries a high mortality, particularly in the elderly. The tear in the patient's oesophagus had to be treated by surgical repair. The patient required a two-month stay on the intensive care unit and was very fortunate to survive.

Most worryingly, however, was the outcome in patients who caught hepatitis E infection who had pre-existing liver trouble. The first patient we came across was a seventy-year-old man who had longstanding cirrhosis (scarring) of the liver of unknown cause. When he developed hepatitis E on top of this he became desperately sick. He showed signs of liver failure, his conscious level deteriorated, and he became semi-comatose. He survived, but only just. The second patient was a seventy-six-year-old man on holiday in Devon. He was not known to have any problems with his liver prior to becoming ill. He had been a reasonably heavy drinker all his life. While on holiday he developed hepatitis, subsequently diagnosed as hepatitis E infection. He was very sick indeed. During the course of his hospital admission it was clear that, in addition to his hepatitis E infection, this man also had a damaged and scarred liver (cirrhosis) from years of over-indulgence with alcohol. He showed signs of liver failure. He was transferred to a hospital near his home some four hundred miles away, but his liver never recovered, and he died from liver failure five months later. These two cases showed that patients with existing liver disease had an adverse outcome when they developed hepatitis E infection in addition.[1] We might have guessed that this would

[1] H. R. Dalton, S. Hazeldine, M. Banks, S. Ijaz, and R. Bendall, "Locally acquired Hepatitis E in Chronic Liver Disease," *The Lancet* 369 (2007): 1260.

be the case, as there had been a couple of reports from India[2] suggesting that the mortality rate in patients with existing liver disease was about seventy percent when infected with genotype 1 hepatitis E.[3] And then there was Peter.

As the cases came in we plotted them on a graph, indicating in which month of the year the case presented. As the cases mounted up, a clearer picture of the seasonality emerged, which cast significant doubt on the barbeque theory. Firstly, there were a number of cases in January and February—barbequing at this time of year is very much a minority sport in the United Kingdom, as it's just too cold and wet outside. Secondly, a specific enquiry regarding consumption of barbeque food by the affected patients showed that only a minority of cases could recall attending a barbeque in the eight weeks prior to becoming ill. Finally, one of our patients was a bed-bound eighty-six-year-old nursing-home resident. She had not been to a barbeque for many years. Thus, although undercooked barbeque food could account for some of our cases, it certainly did not account for all of them.

During the course of my studies on hepatitis E infection, I enlisted the help of my patients attending my clinic who had other medical problems. For example, many of my older patients were approached to help with the antibody study by donating a sample of their blood. Such patients were always given a patient information sheet that described the nature of the study and what the background to it was. They were given the opportunity to read this sheet before being asked if they would donate a bit of their blood for the study. They did so with great generosity of spirit, for which I thank them. One such patient was a very intelligent man, a retired pharmacist, and a patient of mine for the best part of twenty years. I see him every six months or so, and as his medical condition has been stable for a long time we nearly always have the chance for a quick chat about one thing or another. He was interested in the hepatitis E antibody study, and happily gave us some of his blood for the project. He wanted to know a little more about the background, so I filled him in. I told him about the seasonal distribution of cases. I also told him about the barbeque theory, and the doubts we had about it.

A couple of weeks later the patient sent me an email. He had clearly been giving the matter some thought. He sent me over some data from the

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[2] S. S. Hamid, M. Atiq, F. Shehzad, et al., "Hepatitis E Virus Superinfection in Patients with Chronic Liver Disease," *Hepatology* 36 (2002): 474–8.

[3] J. Ramachandran, C. Eapen, G. Kang, et al., "Hepatitis E Superinfection Produces Severe Decompensation in Patients with Chronic Liver Disease," *Journal of Gastroenterology and Hepatology* 19 (2004): 134–8.

British Pig Executive that proved to be quite thought provoking. What this data showed was that, in common with all other meat consumption, pork consumption in the United Kingdom is seasonal. When the weather is warm in the summer, pork consumption goes down by twenty percent. I also recalled my conversations with many a Cornish butcher during the course of the pig-liver study that indicated that this was particularly so for the consumption of pig liver, which tailed off drastically in the summer. I put the data for UK monthly pork consumption together with our cases by month of presentation and compared them. The two graphs did not match up. These data not only threw serious doubt on the barbeque theory but questioned the whole notion that hepatitis E was being transmitted by eating contaminated pork meat. In terms of understanding the route of infection, we were nearly back to square one.

It was time to visit a pig farm. I wanted to know if there were any major seasonal differences in pig husbandry that might give us a clue.

CHAPTER TWENTY-EIGHT

HEROES

There are several colleagues within the profession who I have never had the opportunity to meet (some of whom are dead), but who I have admired from a distance. The first one that springs to mind is Christiaan Barnard. He performed the first heart transplant in South Africa in the late 1960s, a brave, courageous, and pivotal pioneer in twentieth-century medicine. I remember when I was a boy in the late 1960s, seeing grainy black-and-white images on the television of his first heart transplant recipient, Louis Washkansky. I was awestruck. Barnard got quite a bit of stick from religious groups at the time but changed the face of modern medicine forever. There are now hundreds of thousands of organ recipients around the world enjoying happy, healthy lives, thanks, in part, to Barnard's single-mindedness and determination.

In my own field of gastroenterology, with whom would I most like to sit down and have dinner? It's got to be Barry Marshall. Marshall is an Australian and did his training in Perth. As a young doctor, he teamed up with Robin Warren in the Department of Pathology in Perth to study the stomach. They were particularly interested in the causes of peptic ulceration, a very common affliction throughout the world. It had been known for generations that when you look at the lining of the stomach under the microscope it is possible to see, in a minority of individuals, some spiral-shaped bacteria. The received wisdom for the previous one hundred years was they were "commensal organisms," i.e. these bugs just lived there quite happily but did not cause the human host any problems. This notion was to prove utterly inaccurate.

What Marshall did was to look at patients with peptic ulcers, both gastric and duodenal. He found that patients with peptic ulcers were far more likely have the commensal spiral bacteria in the lining of their stomach. He proposed that the cause of peptic ulcers was an infection caused by the bacteria. I never personally heard any of Marshall's lectures on this hypothesis at the many international conferences at which they were presented, as it was before my time. I understand, however, that the medical establishment's response to this brash young Aussie with

"ridiculous" notions was less than complimentary. His reception from big pharma, with billions and billions in financial interests in patented conventional ulcer-healing drugs on the market, was openly hostile. Marshall got a roasting.

Marshall took no notice. He eventually managed to culture the bacteria (known now as *Helicobacter pylori*) from a human stomach on a plate in the lab, then swallowed the lot and became very ill indeed.[1] He got a colleague to endoscope him and the bacteria were recovered from his stomach lining, which by that time was red-raw. He had pictures taken of what his stomach looked like through the endoscope and under the microscope. He then gave himself a prolonged course of antibiotics to kill the bacteria in his stomach. He recovered completely, the bacteria were killed, and his stomach returned to normal. He presented these findings, and although there remained some hostility from some quarters, colleagues started to listen to what he had to say, and ask themselves the question "what if Marshall is right?"

Marshall was right.[2] The vast majority of peptic ulcers can now be treated with a simple one-week course of antibiotics to clear the *Helicobacter pylori* bacteria. This cures the problem once and for all. This has saved countless lives and improved the quality of millions of patients' lives worldwide. Also, and even more remarkably, there are some rare cancers of the stomach called MALTomas. These are relatively aggressive cancers in the stomach which appear to be driven by the *Helicobacter pylori* bacteria, as when patients are given appropriate antibiotic therapy to clear the bacteria the cancer shrinks and sometimes disappears altogether.

Barry Marshall was awarded the Nobel Prize for his work in 2005, along with his colleague Robin Warren. Some of my colleagues feel that Marshall should not have been given the prize as his discovery was rather opportunistic, and intellectually and scientifically his work may not have been quite of the same quality as some previous winners. I would disagree with this point of view. To my mind, he challenged medical orthodoxy, and in doing so stuck his head well above the parapet. He helped cure millions of people worldwide from peptic ulcers with a one-week course of antibiotics, whereas previously they had symptoms for years and years, with only partial relief from ulcer-healing medication such as Zantac. Brilliant. Well done, Barry!

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[1] The early 1980s appears to have been a popular time for self-experimentation. It was at about the same time Balayan was experimenting on himself with HEV.

[2] B. J. Marshall and J. R. Warren, "Unidentified Curved Bacilli in the Stomach Patients with Gastritis and Peptic Ulceration," *The Lancet* 1 (8390) (1984): 1311 15.

However, Marshall's laureate does give me some pause for thought. It illustrates that, in medicine, there is a fine line between being the discoverer of an amazing new idea or treatment and being showered with accolades and awards, and being branded a mischievous, self-seeking charlatan or crackpot, and being pilloried. The latter was the fate of Ignác Semmelweis. Semmelweis was a Hungarian obstetrician in the mid-nineteenth century who was interested in a condition known as puerperal fever. This condition (also known as "childbed fever") is characterised by high swinging fever, pelvic discharge, and septicaemia following childbirth. In those days, nearly one hundred years before antibiotics were introduced into clinical practice, it was a very serious condition with a mortality of up to thirty-five percent. It was also a very common condition, affecting up to one woman in five following childbirth.

By a series of meticulous observations at the General Hospital in Vienna in the late 1840s, Semmelweis showed that by ensuring that medical and nursing staff washed their hands in a chlorinated lime solution before touching a patient, the rate of puerperal fever could be cut from twenty percent to one percent. He postulated that puerperal fever was caused by "particles" transferred from the attending clinician's hands to the patient. This ran completely against the medical thinking at the time and none of the medical establishment believed him. By all accounts, Semmelweis was pretty vociferous, so much so that he was sacked from his job. He was subsequently appointed professor of obstetrics at the University of Pest in Hungary, where he replicated his work on the beneficial effects of handwashing on the incidence of puerperal fever.[3] Still nobody listened to him. He became even more vociferous and possibly mentally "unhinged." He died in 1865, shortly after being admitted to a mental asylum.

What is so tragic about Semmelweis is that he was correct, but nobody listened to him. They thought, quite simply, that he was a "nutter." He may or may not have been, but what is incontrovertible is that had the medical profession listened to him, hundreds of thousands of young women worldwide might have been spared an unnecessary death during childbirth. It wasn't until the 1860s and 70s when Joseph Lister (who was influenced by Semmelweis's earlier work) successfully introduced antiseptics to surgical practice and Louis Pasteur invented the germ theory of infectious disease that the rate of puerperal fever declined. It subsequently emerged that puerperal fever is caused by bacterial infection

[3] I. F. Semmelweis, *Die Ätiologie, der Begriff und die Prophylaxis des Kindbettfiebers* (1861).

of the pelvis, often following delivery. This was several decades after Semmelweis's original discovery, and several decades too late for the countless women who had died in childbirth in the interim. The next time you walk round an old graveyard, check out the ages of the women buried in the eighteenth and nineteenth centuries. What you will see is a large number who died in their early twenties. The chances are that a good proportion of these will have died during childbirth, many of puerperal fever. The gravestones of women in their twenties with a date of death from 1850–70 may well mark the final resting place of those who died needlessly, had Semmelweis been taken seriously at the time.

If the Nobel Prize could be awarded retrospectively, Semmelweis would certainly be on my shortlist. However, the doctor I hold in the highest regard is John Snow. Most non-medics will have never heard of him, but he was a brilliant nineteenth century physician working in London. Some years ago, he came top of a British Medical Association poll for the UK "top-doc" of all time. Snow was born in York in 1813 and qualified as a doctor at the medical school at the university of Newcastle upon Tyne, in the far northeast of England. He eventually made his way to London, which is where he made his name. His seminal work founded not one but two separate disciplines of medicine: epidemiology (the study of the distribution, occurrence, cause, and spread of disease) and anaesthesiology. A fertile and prodigious effort, if ever there was one.

In nineteenth-century Britain cholera was a common problem, as it was in many other industrialising countries, including the United States. It occurred in outbreaks in big cities such as Chicago, Glasgow, Manchester, and London. Cholera causes torrential progressive and unstoppable diarrhoea, with a high case fatality rate. In those days, diseases were thought to be transmitted by "miasma," i.e. by smell. Based on previous observations of an outbreak of cholera in Newcastle upon Tyne in the early 1830s, Snow's thesis was that cholera was not transmitted by smell but by water. This view was rubbished in the medical journals of the time:

> There is, in our view, an entire failure of proof that the occurrence of any one case could be clearly and unambiguously assigned to water.[4]

In late August 1854 there was a large outbreak of cholera in Soho, London, and eighty-nine people died. Snow decided to study the cases to see if he could prove what might have caused the outbreak. He carefully recorded each case and, more importantly, kept an open mind regarding the cause. For each individual with cholera in the outbreak, Snow

[4] *London Medical Gazette* (1849).

meticulously marked their place of habitation on a map. He studied the map, and after doing so noted that the cases centred around the public water pump in Broad Street.[5] Snow arranged for the pump handle to be removed, and the outbreak stopped. Snow's observations fundamentally undermined the received wisdom of the time that diseases were transmitted by smell. Within a couple of decades, building on the work of Semmelweis, Pasteur proved that infections were transmitted by microbes. In the Broad Street cholera outbreak, the bacteria (*Vibrio cholera*) were in the pump water. Moreover, Snow's work founded the discipline of epidemiology that revolutionised the medical approach to understanding diseases. It was, for example, epidemiologists who established the link between smoking and lung cancer[6] in the 1950s.

One hundred and fifty years after first been employed, Snow's basic methodology is still in use. The Centers for Disease Control and Prevention (CDC) is a US government institution with a very long international track record of identification and control of new infections afflicting the human race. Over the last forty years, the CDC has identified and controlled countless infections with previously unrecognised micro-organisms.[7] These include the outbreak of Lassa fever in Nigeria (1969–74), the Ebola virus (Zaire and southern Sudan, late 1970s), and Legionnaire's disease (Philadelphia, United States, 1976), to name but three. The CDC also played an important role in nailing down the cause, extent, and control in the AIDS epidemic (1980s onwards), in conjunction with the two main research centres: the Pasteur Institute, Paris, and the National Institute of Health, Bethesda, Maryland. What is the first thing the CDC guys do when investigating an outbreak with a brand-new bug? They draw a map, à la Snow, of all the suspected cases. There are vanishingly few other methodologies in medicine that have stood the test of a century and a half's use.

Snow did not finish there, as he was also interested in anaesthetics. This had been introduced in the United States in the 1840s but was treated with disdain in the United Kingdom. He became more interested in the subject and, as time went by, introduced it to his practice. He showed by example how effective it was, and it soon became accepted by his peers. Snow had the honour of administering the first anaesthesia for a royal childbirth when Queen Victoria gave birth to Prince Leopold in 1853.

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[5] J. Snow, *On the Mode of Communication of Cholera* (London: John Churchill, New Burlington St, England, 1855).

[6] R. Doll and A. B. Hill, "Smoking and Carcinoma of the Lung," *The British Medical Journal* 2 (4682) (1950): 739–48.

[7] L. Garrett, *The Coming Plague* (London: Penguin, 1995).

Thus Snow, almost single handed, founded the discipline of anaesthesia on this side of the pond.

There is now a John Snow Society, established to commemorate his life and labour, mainly (but not exclusively) his epidemiological work. It has thousands of members throughout the world, including myself. Each year there is a Pumphandle Lecture held in London at the beginning of September, as near to the anniversary of the pump-handle removal as possible. Although the John Snow Society is regarded by some as a quaint and rather quirky English club, with its traditions such as the presentation of the pump-handle to invited speakers, the Pumphandle Lectures are serious affairs and attract world-class speakers from all over the globe who lecture on the latest thinking in communicable/waterborne diseases. Inevitably, perhaps, after the lecture, attendees are encouraged to repair to the John Snow public house on Broadwick Street in Soho for refreshments. This pub was named after Snow in the 1950s, has various Snow/cholera memorabilia that can be viewed, and a visitor's book that can be signed. The site of the original pump is just outside the front door. It's worth a visit if you are in London.

CHAPTER TWENTY-NINE

NORFOLK, 2008

I pondered long and hard about the source of hepatitis E infection in the patients we had seen. We'd plotted them out on a Snow-type map but, at this stage, there appeared to be no discernible pattern. I had doubts about the barbeque theory. I needed to visit a pig farm, as I wanted to learn about pig husbandry. I needed to check if there were any seasonal differences in pig farming which might help unravel the seasonality of the cases of hepatitis E that we had seen.

I rang up a friend of mine, a farmer in Norfolk, which is one of the most important pig-rearing areas in England. His youngest brother is a pig farmer. After a couple more calls I arranged to go to the pig farm. The farmer took me around and introduced me to the three thousand pigs and piglets in his charge. What a great way to spend a Sunday morning! It was a free-range pig farm, an increasingly common sight in the English countryside. In contrast to the majority of pigs in the United Kingdom (and also elsewhere) that are raised entirely indoors, the pigs on a free-range pig farm are raised outdoors. The farm was quite a sight. Each set of thirty or so pigs had a shelter consisting of a horseshoe-shaped stack of straw bales, on top of which was a corrugated iron roof. This was very cosy and cleaned out on a regular basis. The pigs had plenty of room to roam and wallow in the mud. I learned this was an essential part of good husbandry, as pigs are very sensitive to the sun. Pigs suffer from sunburn if they do not have shelter, as would be found in their normal woodland habitat, or a good coating of mud from wallowing. The pigs had access to clean drinking water and were fed on pig nuts twice each day. Each pig run was bounded by a knee-high electrified fence, which appeared to contain the pigs without difficulty. The farm was spread over several acres and consisted of approximately one hundred pig dwellings with their individual pig runs.

The breeding sows are fertilised by artificial insemination. Not a pleasant task, but apparently far more reliable than allowing the breeding boar free rein. The pregnant sows are isolated from the rest of the herd when it gets to around the time of labour. The pregnant sows get a bit

territorial and crotchety and are each given their own farrowing shed to facilitate the birth and immediate aftercare of their youngsters. Each sow gives birth to a variable number of piglets. The average is approximately eight or ten, but twelve or thirteen would not be uncommon.

The piglets stay with their mum for a few weeks and are weaned by about six weeks. They are then given their own pig run with their brothers and sisters, together with the offspring of a couple of other sows. There they grow steadily and happily in the great outdoors. The warmth of their straw-lined pig house awaits them if they want a snooze or to escape inclement weather. When they reach their target weight of one hundred kilograms, they are sent off to the local abattoir for slaughter. Every year, the fields used for raising the pigs are cleared of the straw-lined shelters, ploughed, and used for the cultivation of (well-manured) vegetables. The pigs are moved to fresh fields for the following year. This is no great problem as the deconstruction and reconstruction of the pig shelters is simple and they are easily transportable to adjacent free land.

I was particularly interested to learn of any differences in animal husbandry in the winter. I questioned the farmer about this quite closely. The process of artificial insemination, farrowing, and growing pigs is a year-round activity. The only seasonal difference I could identify from talking to the farmer was that the practice of "finishing off" is often done indoors in the winter. The target weight for a pig to be brought to slaughter in the United Kingdom is one hundred kilograms, as this gives the best quality meat at the most economical cost of raising it. When a pig is grown outdoors, its growth rate tails off in the winter as the temperature drops. Presumably, the animals have to expend more energy keeping themselves warm, and therefore less is available for growth. This has led to the common practice of finishing off indoors during the winter months. What this means in practice is that in the winter the pigs are brought indoors to large warm pig sheds. This optimises their growth and enables them to reach their target weight four weeks earlier than they would have done if they had been raised completely outside.

I could not figure out how this would influence the potential transmission of the hepatitis E virus from pigs to humans, but I'd spent a very pleasant few hours with the farmer and his pigs. I'd learned a great deal about pigs and pig farms, but I was not really any further forward. It was a cold February morning, and my questions were now exhausted. It was time for some refreshments. We went to the local pub and had a delicious lunch of mouth-watering, home-prepared ham (well cooked), free-range eggs, and chips. It wasn't until we finished our meal that the

farmer asked me why I wanted to know all about pigs. I told him. He was completely unfazed by my explanation. What a nice man.

CHAPTER THIRTY

LIVER AND ONIONS

Over the next few weeks, I turned over in my mind what I had learned from the farmer about pigs. I considered the seasonal variation of the cases of hepatitis E that I had seen in light of my new knowledge. I could not see the journey of the virus from pigs to humans, no matter how hard I tried. I talked to my colleagues about it; I talked to my friends about it; I talked to my students about it. I have a colleague who is a dyslexic doctor, and, like many dyslexics, she has an unusual way of thinking about things. Often when presented with a problem she will come up with an idea of tackling it that at first seems way off beam. In psycho-babble this is termed "knight's-move thinking." It describes the process quite well, as it involves an indirect and unique approach, similar to the move a knight makes on a chessboard.

"What if it's not the pig meat?" She said.

"What do you mean?" I replied.

"You've made the assumption that the route of infection is by eating infected pig meat, haven't you?"

"Yes, I have," I said.

"What if that assumption is incorrect?"

"I'm not sure how else the virus could be transmitted," I countered.

"What about pig manure?" She asked.

"Mmm ...?"

"Can the virus survive in pig manure?"

"I don't know," I answered.

"If it can survive in manure, might it be able to contaminate the crops that the manure is fertilising?" She asked.

"I don't know the answer to that either, but it's worth considering."

During the course of my studies on locally acquired hepatitis E, I kept up to date with developments in other parts of the world. One way I did this was by regularly visiting the PubMed database on the internet. PubMed is a free, publicly available database of all peer-reviewed scientific papers that have been published in the medical literature and is updated on a very regular basis. One day, I was browsing through the

Medline database when my attention was drawn to an article with an interesting title: "Green onions: potential mechanism for hepatitis A contamination." I obtained the full article and found that it described some experiments that were performed in the wake of the biggest outbreak of hepatitis A in the United States in living memory. In 2003 there was an outbreak of hepatitis A in Pennsylvania in which 601 individuals were affected, and 124 hospitalised. The outbreak was investigated by, among others, the Epidemic Intelligence Service of the Centers for Disease Control and Prevention, Atlanta, Georgia. The outbreak was traced back to some spring onions served at a hotel restaurant in an onion salsa. Individuals who had eaten at the restaurant and had the onion salsa became infected. The onions originated from Mexico.[1]

Following this outbreak, some researchers from Pittsburgh were interested in how the offending onions might have become contaminated with the hepatitis A virus. What they did was grow spring onions under controlled conditions, then sprinkled them with live hepatitis A virus. They also fed the growing onions with a culture medium containing live hepatitis A virus. Not surprisingly, they found the hepatitis A virus on the outside of the onions at the end of their experiment. However, they also found that the growing onions had **internalised** the hepatitis A virus, presumably via their root system. No amount of washing or cleaning of the infected onions could remove the virus contained inside.[2] These experiments are frightening, but at the same time I found them of interest in the context of the hepatitis E infection. They showed quite clearly that, under the right conditions, a virus can be internalised by growing vegetables. I wondered if this could be the route of infection for the cases of hepatitis E infection that we had seen. I went back to my data on the seasonal variation of cases of hepatitis E. After adding the new cases, the data now showed that there were no cases of hepatitis E in November and December. I reflected on this overnight. The next day I rang up my farmer friend in Norfolk.

"Harry. What's up?" he asked.

"I've got a technical farming question for you."

"OK. Fire away."

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[1] C. Wheeler, T. M. Vogt, G. L. Armstrong, et al., "An Outbreak of Hepatitis A Associated with Green Onions," *The New England Journal of Medicine* 353 (9) (2005): 890–7.

[2] D. D. Chancellor, S. Tyagi, M. C. Bazaco, et al., "Green Onions: Potential Mechanism for Hepatitis A Contamination," *Journal of Food Protection* 69 (6) (2006): 1468–72.

"Can you name a vegetable crop that is impossible to bring to market in the UK in the months of November and December?" I asked.

"Well," he replied, "it's possible to bring virtually any crop to market at any time of the year if you use artificial means such as heated greenhouses and poly-tunnels."

"Okay. Let's concentrate on vegetables grown outdoors."

"Right. I'll need to think about this," he said. After a few moments thought he went on: "The only outdoor crop that I've grown that I would really struggle to get ready for market in November and December is spring onions."

"Are there any other crops that you can think of?" I asked.

"No."

"That's very interesting," I said. "Have you grown spring onions?"

"Yes, I have," he replied.

"Could you tell me how you grow them?"

"Well, the first thing I generally do is to give the field a good covering of organic material."

"Could you explain exactly what you use?"

"I tend to use chicken manure, but any farm manure would do just as well."

"What about pig manure?" I asked.

"Yes. That would be fine."

"What do you do next?"

"I'd drill the onions in as soon as possible after spreading the manure. Next day if possible," he said.

This was getting me very interested indeed. The next day, I popped over to have a chat with Bendy Boy and told him the story. We gave our veterinary virologist colleague a ring at his lab in Surrey and talked to him about whether it was biologically feasible for the hepatitis E virus to survive in pig manure and be internalised into the manured growing vegetables. We discussed whether the virus could conceivably survive in the vegetables until it reached the human food chain and decided that the theory was plausible and possible. How should we go about testing the theory?

After much discussion we came up with two studies that would help confirm or refute the pig manure/veggie theory of transmission. First up, we needed to repeat the experiments done in Pittsburgh, but use the hepatitis E virus to try to infect the onions instead of the hepatitis A virus. This would tell us if the hepatitis E virus, like it's very distant cousin the hepatitis A virus, could be internalised by growing vegetables. The second study was a repeat of the sero-survey study that we had done the previous

year. However, this time we would check for hepatitis E antibodies in a group of vegetarians/vegans and compare with the hepatitis E antibody prevalence in age and sex-matched onmivores. If there was no difference in the prevalence of hepatitis E antibodies between the two groups, this would support the theory that hepatitis E is not transmitted by eating contaminated pork, but might be explained by eating contaminated vegetables such as spring onions.

After a certain amount of deliberation and discussion, I decided to do the first study myself. It was, somewhat inevitably, dubbed the "Great Back Garden Experiment." Great it did not prove to be, but I did do it in the back garden of my house. I have an interest in gardening and grow a lot of my own vegetables. They taste good. I like to pick them and cook them immediately. They taste so much better than vegetables on sale at UK supermarkets. A good example of this is carrots. Carrots on sale in the United Kingdom are largely been picked six months earlier and chilled prior to being put on sale. They are straight, unblemished, but taste like cardboard. My own carrots are not straight, not unblemished, but are cooked within one hour of harvesting. They are sweet, delicious, and good to eat. Growing a bunch of spring onions should prove no problem. The idea was to grow a set of spring onions in some pots. Half of these would be supplemented with pig manure containing the hepatitis E virus. The other half would have no pig manure supplementation and serve as controls. I bought some spring-onion seeds and started them off in the greenhouse. As they matured, I transplanted the seedlings into larger pots outside. Now all I needed to do was get hold of some pig manure with the hepatitis E virus in it.

I rang up a colleague who keeps pigs as a hobby. I told him what the plan was, and could he help us find some pig manure? He was very helpful, and in no time at all produced samples originating from four different sets of pigs. We sent them up to Surrey for testing to determine which of the samples contained the virus. A week later I got a telephone call. Three of the samples had no virus in them at all. The fourth sample did contain the hepatitis E virus, but only in very small concentrations. I thought about this for a while. I needed to be certain that my growing veggies received a decent dose of the virus, and I thought that the fourth sample was not good enough for that purpose. After further discussion and a number of telephone calls, I solved the problem. I decided to try to infect my spring-onion seedlings with neat virus, rather than mess about with pig shit of dubious quality, at least as far as my experiments were concerned. I managed to obtain a supply of the genotype 3 virus from a reliable source.

The sample arrived deep-frozen and contained in fifty tiny test tubes. Right, game on!

I realised I had to be careful with this stuff and I took the biohazard issue very seriously indeed. When preparing to infect my seedlings I decked myself in full protective gear, gloves, and a mask. I used liberal amounts of piping-hot soapy water and bleach to sterilise the working area both before and after infecting the seedlings. The whole process took much longer to complete than I had anticipated. One of the things that slowed me down a lot was that I had to defrost the samples containing the virus. They had been stored at -70°C, and this took quite some time. Each of the fifty tiny test tubes was emptied with great care. All equipment that was used was treated as a potential biohazard and incinerated at an appropriate facility.

After sprinkling the virus on the soil in the pots in which half the spring onions were growing, everything was washed down with hot soapy bleach to kill any virus that may have inadvertently escaped despite the great care I had taken when handling it. In addition, I made the infected area completely animal and bird proof, with a Heath Robinson affair that was constructed from timber and a good deal of chicken wire. I did not want garden animals or birds to become infected. More importantly, I did not want there to be any chance of my control seedlings becoming cross-contaminated. This would ruin the experiment completely.

Following the application of the virus, every week or so I sampled a spring onion that I had infected with HEV. I also took a six-inch soil core from the infected growing pots. These were carefully bagged and labelled, and frozen as soon as possible. In addition, I took control samples from the seedlings that had not been treated with the virus. These were also frozen. I usually did the sampling first thing in the morning wearing the full kit. The experiment went on for five months. At the end of this time the samples were sent for analysis. The growing pots and their remaining contents were bagged up for incineration. The whole area was completely disinfected with hot soapy water and bleach and a good scrub. I waited a long time for the results.

The second study we had in mind proved much more difficult. What we wanted to do was look at how many vegetarians had been exposed to the virus and compare this figure to how many pork eaters had been exposed. The idea was to get blood samples from both groups and see how many in each group had hepatitis E antibodies. If there was no difference between the vegetarians and the pork eaters, this would blow the infected pork consumption theory of transmission out of the water once and for all. When designing a study like this, one of the first things that needs to be

done is what is known as a "power calculation." What this means is that one needs to ensure that there are enough individuals in each group to be certain that any difference might be detected between the two groups is a true difference, and not merely an aberrant result due to insufficient observations. To pass muster, in statistical terms, our power calculation indicated that we needed blood samples from over one thousand vegetarians and over thousand pork eaters. This was a logistical nightmare. Where were we going to find one thousand vegetarians willing to help us with a sample of their blood? I tussled with this problem. I could not see a way of doing this without going to enormous, time-consuming effort. When faced with a problem like this I often ask others for their views. In this case, I decided to ask my students how they would tackle the problem. We all met up in the Shed one afternoon and did a bit of brainstorming. It was to prove a fruitful hour, in terms of the ideas that were generated.

One student came up with the idea of attending a vegan event. Every year, there are a number of such events in the United Kingdom. They attract all manner of people from health-conscious old fogies to the animal liberation extremists. I decided to run with the idea and applied to have a stall at the Bristol Vegan Fayre. The idea was to set up a stall and get the vegan punters to give us a bit of their blood. It wasn't that simple—the organisers were not happy at the prospect of us taking blood from the people attending the event as they were concerned about health and safety regulations. They also felt that taking blood from the attendees would detract somewhat from the family-day-out nature of the event. They had a point. In the end, the students and I all went along. It was an interesting if slightly surreal way to spend a Sunday afternoon. The attendees ranged from sprightly, kindly grannies to scary young guys with a fairly extreme outlook. Two things struck me about the people who attended this event. Firstly, there were a lot of very fit looking elderly vegan folk, none of whom appeared to smoke. Secondly, it appeared to be quite impossible to purchase an alcoholic beverage, despite there being over thirty vegan food and drink stalls. Maybe they had no licence to sell alcohol at the event, or maybe vegans don't drink alcohol. Whatever, we got the email addresses of 180 vegans who would potentially be interested in helping with our project. This was not enough—not by a long chalk.

Another idea that one of the students came up with was to approach the WHO-sponsored EPIC project.[3] The EPIC project is a long-term European

[3] "European Prospective Investigation into Cancer and Nutrition (EPIC)," http://epic.iarc.fr.

study looking at health outcomes relating to diet. Each EU country has one or more centres with a very large database of individuals with an accurate dietary history. The EPIC project has studied, among other things, the incidence of cancer in vegetarians compared to meat eaters. We were particularly interested in the ●xford database. Not only did they have a very large number of vegetarians on their books, they also had blood samples on them. The question was, would they collaborate with us and let us have a tiny portion of their existing samples, so we could test them for hepatitis E antibodies? I emailed the guy in charge in ●xford, explaining what the theory was and that we would like to do a collaborative study. Could he let us have a tiny portion of the blood samples from the vegetarians, and also the pork eaters, please? He was interested. However, he needed to talk to his colleagues about it. A couple of weeks later, he rang me to say that, after discussion with his colleagues, they would not be able to help after all. The blood samples they had were simply too precious. All the samples we needed were sitting in a freezer in ●xford. We could not have them. I was gutted.

I was even more upset when I eventually got the results back from the Great Back Garden Experiment. None of the spring onions were infected with the virus. How disappointing. What was curious, though, was that all of the soil samples were negative too. I wondered if we had made a mistake by doing the experiments outdoors in my back garden. Shortly after the vegetables were dosed with the virus it rained solidly for two weeks; it was a very wet summer that year, even by UK standards. Maybe it rained so hard it just flushed all the virus away? I should have done the experiments in the greenhouse after all.

We never published the results of the above experiment. I kept badgering my lab colleague. In the end, I got a call from him.

"Harry. You know the virus you used in the Great Garden Experiment?"

"Yes?"

"We just got our HEV culture system working, and we tested it. I'm afraid the virus you used was all dead."

"●h, bollocks!" I then burst out laughing, recalling all the quite unnecessary precautions and viral angst the Great Back Garden Experiment had engendered. ●nwards and upwards.

CHAPTER THIRTY-ONE

PETER

Apart from mild diabetes and a high cholesterol, for which he took tablets, Peter was otherwise fit. He was fifty-nine-years-old and had been working at a local concrete factory for a number of years as a labourer. He didn't like the job that much, but it paid the bills. A few days before I met him for the first time, he started to feel unwell. He went off his food. This was unusual for him. He felt listless and lost a bit of weight. One night he became feverish. It felt as though he had the flu, but when he woke up he noticed that the whites of his eyes looked a little yellow. Like most men, Peter was not keen on going to the see the doctor. His eyes became more yellow and his skin started to look a little yellow too. With some "gentle" persuasion from Jackie, he eventually went to see his doctor. His doctor took one look at him, picked up the phone, and phoned the jaundice hotline.

The next day I met Peter at my clinic. He was a livid lemon colour, and his blood tests showed that he had a severe hepatitis. He was the right age, the right sex, and this was in April, the right time of year. The most likely clinical diagnosis to my mind was hepatitis E infection. At the same visit, he had a liver scan. This showed that Peter's liver was coarse, irregular, and scarred, and his spleen was big too. These findings suggested that he had cirrhosis of the liver, probably due to alcohol excess in his formative days. This was very concerning. If my diagnosis of hepatitis E was correct, Peter was in deep trouble.

We took the blood tests for hepatitis E and sent them up to London for urgent analysis. While we were waiting for the results we arranged for Peter to have a liver biopsy. This is a procedure to take a sliver of liver with a tiny needle, which is done after first injecting the skin over the liver on a spot below the right nipple on the right lower ribcage with local anaesthetic. The sample of liver was sent to the lab for analysis. A couple of days later we got the result back. Peter had cirrhosis of the liver due to his previous alcohol use. In addition, the liver was very inflamed. A week later we got the result of his hepatitis E blood test from London. It was positive—hepatitis E genotype 3. Peter was in very deep trouble indeed.

Whenever I'm really worried about a case or I'm struggling with the diagnosis, or I'm not sure what to do next, at the end of the day I often go and sit and talk to the patient. The conversation is not necessarily medical, and frequently isn't. I generally do this when I've finished all my other work. It gives me the time I need. When I've spent half an hour or so with the patient, I put on my coat and drive home. More often than not, by the time I get home I know what needs to be done. Sometimes, in more difficult cases, I sleep on it and the next morning when I wake up the case is crystal clear. I went to see Peter and Jackie nearly every evening for over a week. Peter and I talked about all sorts of stuff. We talked about his life, his wife, and his family. We talked soccer. Liverpudlians are either blue or red, and Peter was a true-blue "toffee"—an Everton fan. He bemoaned the current state of his team. He was highly amused to learn I was a Leeds United fan. After a good deal of good-natured jousting, we agreed that Everton's problems on the field of play were nothing compared to Leeds', who at that time were plummeting down the English Leagues and were over fifty million pounds in debt. Every time Leeds lost, which was every week, he would gently take the piss.

One of the things I needed to establish was Peter's relationship with pigs. Peter never came into contact with pigs. He did not do much cooking. He ate pork, but only occasionally. I wondered from where he might have contracted his hepatitis E infection. I asked Jackie about Peter's diet, and if they had any pork in the freezer. They didn't. What butcher did they use?

They were visited, and a couple of samples were sent to the lab in very short order. I asked about his job. Peter worked at a concrete factory and spent a lot of his time in a forklift truck moving concrete slabs about. Was there anything that might give us a clue here? He told me there was a sewerage manhole cover that sometimes overflowed. That interested me. I rang up Bendy Boy, and we agreed that the environmental-health team should pay his place of employment a visit, and so they did.

The manhole cover proved to be a "red herring." However, the sharp-witted environmental-health officer found something much more interesting. One of the Peter's responsibilities at work was to wash down dirty containers with a high-pressure hose. This resulted in him being heavily splashed with the water used for cleaning the skips, which was abstracted from a pond adjoining the yard. The pond was filled by a stream that ran adjacent to a free-range pig farm. The environmental health officer managed to get several samples of pig stool and water from the stream and pond. We sent them to be tested for hepatitis E virus. It was to be quite a long time before the results came back.

Meanwhile, Peter's condition deteriorated. His liver was slowly failing, and he became more and more yellow. Fluid started to accumulate in his abdominal cavity. We had to take some off and removed over five litres. His conscious level fluctuated, and there were periods when he was a little confused. His liver tests deteriorated further. I rang up an old colleague at the Birmingham Liver Transplant Centre. We discussed Peter's case at length.

We decided to treat Peter with drugs and injections to help his liver. Over the next couple of weeks, the rate of deterioration of his liver blood test slowed, but the trend was inexorably downwards. Peter was now over six weeks into his hospital stay. I rang my colleague in Birmingham again, and we agreed that Peter should go up to Birmingham for a liver transplant assessment. Peter was in Birmingham for over a week. While he was there his liver blood tests had started to improve, and it was decided that he was not a candidate for a liver transplant. He came back down to Cornwall, and his liver continued to slowly improve. By this time, he had been in hospital for nearly nine weeks and was going stir crazy. He wanted to go home, and I could see that nobody was going to persuade him otherwise.

Shortly afterwards I went on my annual two-week holiday. At the end of my holiday I developed shingles. I was surprised how painful shingles was, and I was off work for a further ten days. When I got back to work I heard that Peter had not been well. He was more jaundiced, and his liver was failing. The fluid in his abdominal cavity had re-accumulated and had to be drained off again. He then developed very severe pains in his shoulder and hip. He was readmitted to hospital and both joints required a washout. This showed that they were infected with the "superbug" methicillin-resistant *Staphylococcus aureus* (MRSA). MRSA was also grown from his blood stream. Peter was now critically ill with MRSA septicaemia (infection of the blood stream). Patients with liver failure are very susceptible to infections of all kinds. Just about the worse infection he could have got was the superbug MRSA. This bacterium is resistant to nearly every antibiotic known. When it causes septicaemia, it carries a high mortality, particularly (as in Peter's case), when the patient has other serious ongoing medical problems.

We tried everything we could to save his life. Despite all we did, his condition got worse and worse. He was in a great deal of pain. It was distressing for me to see him deteriorate like this and suffer so much. Jackie and their son were beside themselves. After about two weeks of intensive treatment I went to see him one day. He was much worse and very distressed. We had lost the battle. After talking to Peter, Jackie, and their son we decided to withdraw treatment and let nature take its course.

Continuing to treat him would only have prolonged his agony. We could not save him, and he died shortly afterwards. The staff on the ward were upset that we lost him. My house physician at the time burst into tears. I gave her a big hug. She wanted to know where we had gone wrong and who was to blame. We had not gone wrong. We had done everything we possibly could to save him, but we couldn't. It was as simple as that. I rarely go to my patient's funerals, but I made an exception in Peter's case. Jackie asked me to say a few words during the service. I was honoured to do so.

A few weeks after Peter's funeral we got the results of the samples the environmental health officer had collected from the pigs, the stream, and the pond adjacent to Peter's place of employment. The stool samples from the pigs in the field next door to the factory were found to contain the hepatitis E virus. The stream and pond samples were negative. The fact that we found hepatitis E virus in the pigs' stool was not in itself a surprising finding, as we already knew that the majority of UK pigs that have been tested show evidence of asymptomatic HEV infection. We needed more information regarding the virus found in the pig-stool samples. Part of the RNA from the virus isolated from the pigs' stools was sequenced and compared to a similar part of the RNA of the hepatitis E virus that we isolated from Peter. They were different. The hepatitis E virus we had isolated from the pigs had not caused Peter's illness. The pork samples from Peter's butcher were also negative for hepatitis E virus. We had not found the cause of Peter's illness and death, despite trying very hard.

After Peter died, I occasionally spoke to Jackie on the phone. I promised Peter I would keep an eye on her if anything happened, and I kept my word. I explained to her the results of the samples that we had taken from Peter's work. I asked her if she would mind if we wrote up Peter's case to be published in a medical journal. She said she would like us to. My house physician and I sat down and went through every detail of Peter's case with a fine toothcomb and then wrote it all down. One evening after work we went to Jackie's house. It was nice to see her. We had a chat and a cup of tea. We talked about "the old git," as she sometimes refers to him. We showed her what we had written and explained the technical parts in a way in which she could understand. She agreed to it being submitted for publication, on the grounds that it might help someone else in the future.[1]

[1] G. L. Lockwood, S. Fernandez, R. Bendall, M. Banks, S. Ijaz, and H. R. Dalton, "Hepatitis E Autochthonous Infection in Chronic Liver Disease," *The European Journal of Gastroenterology & Hepatology* 20 (8) (2008): 800–3.

CHAPTER THIRTY-TWO

ACADEMIA

There are two types of consultant working in the NHS in the United Kingdom. The vast majority, myself included, have full-time clinical jobs. What this means is we look after patients five days a week and have, in addition, out-of-office hours on-call duties and responsibilities. The other type of consultant is what is known as an "academic" clinician. Doctors on academic contracts are employed by the universities and medical schools. Their university work includes teaching the medical students and research. This typically takes up about half the week. In addition to their main university contract they have an honorary NHS contract and spend the rest of their time seeing NHS patients.

The main focus for any self-respecting academic clinician is research. The key reason for this is that promotion up the academic ladder and pay scale are driven by the quality of the research each individual does. This is measured on a regular basis by the universities, on a national scale, by the Research Excellence Framework (REF). Each university and medical school is given an REF rating based on the quality of peer-reviewed papers published and the number, source, and quantity of research grants obtained. The REF rating determines the quantum of government funding that each university and medical school receives. Thus, most academics are completely driven by the need to publish. They are very much less interested in teaching students as this usually carries little or no academic kudos and is unlikely to significantly impinge on the climb up the greasy academic pole. This accounts for my observation when a medical student that some of the teaching I received was of poorer quality than I would have expected, as academics have little incentive to provide high-quality teaching.

In contrast, for full-time NHS clinicians like myself there is little or no encouragement to do research work. It does not carry any prospect of promotion and little in the way of financial remuneration. It is time consuming and has to be fitted around the edges of an already over-full clinical diary. It appears to be frowned upon by NHS managers who believe it distracts clinicians from their main task of government-driven

"sausage factory" targets. Research funding is difficult to obtain, and the grant applications take hours and hours of form filling. Then, to top it all off, there are the ethics forms to complete. More hours and hours of wading through red tape. It is little wonder that very few full-time NHS consultants engage in research in a serious way. It is simply not worth their effort.

When a research project has been completed it needs to be published, to communicate the findings to the rest of the profession. Such articles are published in one of the many medical journals available. Some journals are of a general nature and publish articles from any specialty. The most well-known of these are *The New England Journal of Medicine* in the United States and *The Lancet* here in the United Kingdom. These journals are published weekly and are what are known as "high-impact" journals. They have an enormous circulation, their research papers are the most quoted in the medical literature as a whole, and their content is not infrequently deemed newsworthy by the world's press. Not surprisingly, it's every researcher's ambition to be published in one of these. This is rather easier said than done. They reject well over ninety-five percent of the research papers submitted for consideration. On the upside, when they do reject your paper it's generally done in a very timely fashion—at least it's a quick death.

In addition to the general medical journals there are a plethora of other more specialised journals. Such journals are generally published monthly and concentrate on research papers pertaining to a particular medical specialty. There are no prizes for guessing to which specialties the journals *Gut*, *Brain*, and *Thorax* pertain to. Specialist journals vary in terms of kudos from very high-impact journals that are widely quoted to low-impact journals that barely anybody bothers to read. Most specialist journals take months and months to let you know if they would like to publish your research work. It's extraordinarily frustrating to wait for six months or more for a reply, just to be told "no we don't want to publish this, and by the way we think it's a load of old rubbish."

When a research article is submitted to a medical journal for consideration it undergoes a process of peer review, which has for generations been the accepted way of externally validating medical research work. The paper is sent to two or more colleagues in the same specialty for a view on its quality and originality. On the basis of these anonymous referees' reports, the journal will generally take one of the following three actions:

(1) Rejection—far and away the most common response, particularly from the "top-end" journals
(2) Request minor or major revision, followed by resubmission and reconsideration
(3) Accept the paper as it stands—a surprisingly uncommon response

Over the last few years, I have submitted papers for peer review to medical journals on countless occasions. I have kept a record of some of the responses.

I thought this was a charming way of saying that they were not interested and originated from *The Lancet* in 2007:

> Several editors have read your paper. After careful thought and deliberation, we think this paper is best placed with another journal. We are sorry to disappoint you but due to the large number of papers submitted for consideration, we have to decline over ninety percent

A rather less charming response from *Gut* in 2007:

> The aims were clear but naïve

Another rather terse rejection from a leading hepatology journal from 2008:

> The article is too long and rambling. The results are all over the place and the discussion unfocussed.

This response was received from an (anonymous) reviewer for a leading microbiology journal in 2008:

> It is unbelievable that the authors claim that some patients appear not to mount an immunological response to HEV.

What is actually the truth is that the reviewer in question clearly knows next to nothing about locally acquired hepatitis E infection. This illustrates an important limitation in the peer-review process. This reviewer demonstrates not only that he or she has limited knowledge of the subject they have been asked to make a judgement on, it also shows that their thinking is constrained by the limits of the existing medical model. Intellectually, they are "boxed in." They have "tunnel vision." As far as the reviewer is concerned, if we (the authors of the said paper) are correct then pigs might fly.

For the most part, these academic constraints are of little importance as most research work sits well within accepted medical scientific thinking. However, when the subject demands a step outside perceived conventional wisdom, the process of peer review is dependent on individual reviewers who are on the one hand prepared to think "outside the box," yet on the other maintain high scientific standards. It's a question of intellectual balance. They need to discern the "slightly whacky but scientifically plausible" from the "totally whacky and scientifically implausible." From first-hand experience of submitting my hepatitis E work, such individuals are a relatively rare breed.

I sent one of our best early articles at the start of the hepatitis E story to *The British Medical Journal*. The following response was received ten days later:

> This article is of insufficient interest to our readers ...

I was really quite cross about this. A couple of weeks before they published an article that clearly was of interest to their readers—a paper describing the treatment of obstructive sleep apnoea by getting patients to learn to play the didgeridoo,[1] from a group of Swiss researchers. What possible practical use is that? Also, what do the Swiss know about playing the didgeridoo? I was incandescent. I get *The British Medical Journal* every week, as I am a member of the British Medical Association, which is the UK doctors' trade union. *The British Medical Journal* comes free to members. In years long gone by, *The British Medical Journal* was one of the world's leading medical journals. It used to publish papers that were of outstanding international importance, an example of which in my field is Sidney Truelove's 1955 paper on the treatment of ulcerative colitis.[2] Dissemination of this paper throughout the world's medical community saved tens of thousands of lives. These days, *The British Medical Journal* is reduced to a cross between *The Sunday Times* magazine and *The Sun*. In true "tabloid" style on one of the front inside covers we now have: "The week in numbers ..." Research papers are scant, and of "didgeridoo" quality and substance. Like many of my colleagues, I now only read the obituaries. Sidney will be turning in his grave.

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[1] M. A. Puhan, A. Suarez, C. L. Cascio, A. Zahn, M. Heitz, and G. Braendli, "Didgeridoo Playing as an Alternative Treatment for Obstructive Sleep Apnoea: Randomised Controlled Trial," *The British Medical Journal* 332 (2006): 266–70.

[2] S. C. Truelove and L. J. Witts, "Cortisone in Ulcerative Colitis: Final Report on a Therapeutic Trial," *The British Medical Journal* 2 (4947) (1955): 1041–8

After countless rejections from journals in the early phase of my research on locally acquired hepatitis E, things started to change. I decided that the correct approach was to first express my scientific thinking in small, digestible, bite-sized chunks. Second, I decided a thick skin was necessary—some of the reviewers' comments were complete tosh. Third, and above all, persistence was required. Acceptances started to trickle in, and then the floodgates opened. I was particularly pleased with my papers in *The Lancet*.[3][4][5] In fact, I was chuffed to bits.

Another way of communicating research findings to the rest of the medical community is presentation at national and international medical conferences. I nearly always enjoy going to such conferences here in the United Kingdom and abroad. It's a chance to catch up with old friends and colleagues, and a good way of finding out what the latest thinking is. In my case, it was a good way of finding out what is happening in the field of hepatitis E research. This latter exercise was initially usually brief, as very few of my colleagues were doing much work in this area at that time in the United Kingdom, although recently this has started to change. On the international scene, the main players were initially from Toulouse in southwest France and ourselves. Interest in HEV is now much more widespread across Europe and beyond.

When giving a research paper what happens is that the presenter is allocated ten minutes to present their findings and their relevance. There are then five minutes for questions from the audience, which may vary from fifty to several hundred of one's peers. I enjoy the questions most, and during the course of my work have had many gentle and good-natured jousting sessions with my colleagues. However, the real reason I like the question sessions is that often a question or comment will make me think critically about the work I have done. I find this really helpful. Also, in contrast to the anonymous referees of the journal peer-reviewing process, it's a face-to-face exchange. This is important, as comments or queries from some colleagues I will take very seriously; comments from others, less so.

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[3] Dalton et al., "Locally acquired Hepatitis E in Chronic Liver Disease," *The Lancet* 369 (2007): 1260.

[4] H. R. Dalton, R. P. Bendall, S. Ijaz, and M. Banks, "Hepatitis E: an Emerging Infection in Developed Countries," *The Lancet Infectious Diseases* 8 (11) (2008): 698–709.

[5] N. Kamar, R. Bendall, F. Abravanel, N. Xia, S. Ijaz, J. Izopet, and H. R. Dalton, "Hepatitis E," *The Lancet* 379 (2012): 2477–88.

CHAPTER THIRTY-THREE

TOULOUSE, 2008

France has an enviable history and tradition in the field of infectious diseases. Not least among the French infectious disease glitterati is Louis Pasteur. It was Pasteur who developed the microbial theory of infectious diseases in the nineteenth century,[1] [2] [3]in parallel with but independently from Robert Koch and colleagues in Germany. Pasteur was not a medical doctor but trained as a chemist. His ground-breaking work was not with humans, it was the study of fermentation in beer and milk. Through a series of meticulously planned, executed, and observed studies, Pasteur proved that the miasmic theory (the existing notion that said that infectious diseases were spread by smell) was incorrect. It was during this time he developed the technique, still used today, of pasteurisation of milk to prevent it going off due to microbial fermentation. Pasteur was also asked for help by the Carlsberg brewery in Copenhagen, Denmark. Their beer was going off and the Carlsberg guys did not know what to do. In stepped Pasteur, and in no time at all he had it sorted. Whenever I have a Carlsberg beer, which is not often, I raise my glass to Louis Pasteur. Salut, maestro! If you ever take the Carlsberg brewery trip in Copenhagen, you will meet a statue of Louis just outside the front doors.

Pasteur's work on fermentation was eventually replaced by the study of diseases in animals and humans. He developed a vaccine for anthrax, a disease in sheep and cattle. It caused deaths in the animals, and occasional human cases, and was the scourge of the French farmers at the time. Pasteur was vocal, spoke his mind and, at times, a bit of a showman. When he developed the anthrax vaccine he decided to invite a group of French worthies, including politicians and the press, to observe. What he did was as follows. He used two flocks of sheep; one flock was given the

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[1] S. J. Holmes, *Louis Pasteur* (New York: Harcourt, Brace, 1924).

[2] G. L. Geison, "Pasteur, Roux, and Rabies: Scientific Clinical Mentalities," *Journal of the History of Medicine and Allied Sciences* 45 (3) (1990): 341–65

[3] M. Schwartz, "The Life and Works of Louis Pasteur," *Journal of Applied Microbiology* 91 (4) (2001): 597–601.

new anthrax vaccine, the other was not. They were then placed in adjacent fields, both of which had been infected with anthrax spores. At the inaugural meeting there was not much action, just two flocks of sheep being placed in adjacent fields happily grazing. A few weeks later, the press, politicians, and farmers were invited back. Now there was something to see—all the non-vaccinated sheep lay dead in their field, and the vaccinated ones next door were happy as Larry. Pasteur's vaccine was subsequently taken up by the French farming industry. They were very grateful as he saved them millions of Francs in lost income, and almost certainly prevented many human cases into the bargain.

Pasteur now turned his attention to rabies, a disease in animals including dogs, wolves, and bats. Infection is transmitted to humans by the bite of an infected animal. The rabies virus then enters the nervous system adjacent to the bite and slowly, usually over several weeks or months, works its way to the brain. Prior to reaching the brain, the infected human has few, if any, symptoms. When the rabies virus enters the brain, the patient develops a catastrophic and almost invariably fatal illness characterised by fever, hydrophobia (fear of water), confusion, coma, and death. Pasteur started working on a vaccine which he hoped would improve the outcome of this terrible disease in humans.

The first step was to obtain a dog with rabies. He enlisted the help of the Parisian dog catchers, who quite speedily (rabies was surprisingly common in those days) came up with an infected dog. The French word for rabies is "la rage", which describes in part the symptoms the infected dog exhibited. It was wild, snarling, foaming at the mouth with saliva stuffed full of the rabies virus, and attempted to bite anything in sight. Pasteur needed to obtain some saliva from the infected dog. For obvious reasons this was not without risk and was logistically challenging. The dog died soon after and, in addition to the saliva, Pasteur now obtained tissue from the brain of the dead animal. Pasteur took the infected samples from the dog and injected them into the brain of a healthy rabbit. The rabbit soon died. Pasteur then removed the rabbit's brain and strung it up to dry in the lab for a while. He then mashed up the brain in a mortar and pestle, and injected it into another healthy rabbit, which again promptly died. He repeated the above cycle numerous times, and as he did so he noticed the infected animals were taking longer to die. Finally, after over a dozen cycles of this experiment, the rabbit injected with mushed-up brain from the previous experimental animal did not die. Pasteur's experiments had attenuated the virus; i.e. it was no longer infectious. He had discovered a potential new vaccine.

Pasteur's work was drawing considerable attention in France. One day, a young shepherd boy from Alsace was brought to Pasteur by his parents. The young boy had been severely bitten by a rabid animal. The parent's asked for Pasteur's help, but the new vaccine had never been tried on humans. Pasteur thought about it overnight. This was not without risk. The next morning Pasteur agreed, and the young shepherd boy was given a series of injections of mashed-up rabbit brain collected from the final experimental animal. Then they waited. They waited for weeks on end. This must have been sheer torture for the young shepherd and his parents and enormously anxiety-provoking for Pasteur and colleagues. The injections of mashed-up rabbit brain worked, and the boy eventually returned home to Alsace none the worse for his ordeal. Word spread about this remarkable achievement. Soon, human victims of bites from rabid animals were coming to Paris from all over France, Europe, and beyond to seek Pasteur's new treatment. This included a bunch of Cossacks from Russia bitten by a rabid wolf and a group "bitees" who sailed across the Atlantic from the United States.

Shortly before Pasteur's death, the French Government commissioned a national centre for the treatment of rabies and other infectious diseases. It was named the Pasteur Institute, and since then branches have been established widely across the French-speaking world, including several countries in Africa. The headquarters is still in France. Some years ago, I somewhat belatedly took the trouble to visit the museum at the Pasteur Institute, situated in Paris south of the River Seine. What I found most thought provoking about Pasteur's work was that it was all achieved with meticulous observation—he only had very basic equipment, at least by today's standards. His lab tools consisted of a mortar and pestle, glass flasks, a Bunsen Burner and a low-resolution light microscope. Through the latter he could observe the bacteria which were the cause of some infectious diseases, but it was not powerful enough to see viruses, which are an order of magnitude smaller than bacteria. Pasteur simply imputed the existence of the rabies virus. He knew it was there, he just could not see it.

The French track record in infectious disease in general and viral discovery in particular has continued to the current day, and there are numerous world-class French experts in this subject. In the field of HEV the French have made key contributions, led by Jacques Izopet from Toulouse and Phillipe Colson from Marseilles, both Professors of Virology. A few years ago, there were reports from southern France of cases of hepatitis E where the patient failed to clear the virus. The technical term for this is "chronic" infection and is commonly seen in

patients infected with hepatitis B and C, who also fail to clear these viruses. The importance of infection with HEV as a significant human pathogen was changed forever by two papers that appeared back-to-back in *The New England Journal of Medicine* (the most influential "general" journal in medicine worldwide) in 2008. One paper was authored by colleagues from Toulouse,[4] and the other was penned by colleagues from Marseilles.[5] What these and subsequent papers showed was that, in organ transplant recipients who were taking drugs to suppress their immune system to prevent rejection, when exposed to HEV, sixty percent fail to clear the virus. The virus just sits in the liver and quietly "grumbles."

Patients infected in this way usually have no symptoms. The only clue to the diagnosis is that the liver blood tests are slightly abnormal, but not by much. Such a finding in a transplant recipient is very common and easily ascribed to some other cause, for example one of many anti-rejection drugs these patients have to take on a daily basis. The abnormality in the liver blood test is often so slight it is simply, and hitherto quite commonly, ignored altogether. In the meantime, HEV genotype 3 ("the piggy virus") grumbles away in the liver and silently, and quite quickly, the patient develops serious scarring of liver; they become cirrhotic. Chronic infection with HEV occurs in all types of transplant recipients (liver, kidney, heart, lung, pancreas, bone marrow) and at all ages, including children. A number of such patients have required a liver transplant as a consequence of chronic infection with HEV, and some have died.[6]

Subsequent studies showed that, on average, one to two percent of transplant recipients in Europe have "silent" chronic infection with HEV. However, this varies considerably by geographical location. For reasons we do not understand, the numbers of organ recipients infected in this way in southern France are much higher. In contrast, at least until quite recently, not a single Scottish liver-transplant recipient was infected in this way. This is most certainly not the case now. Happily, and mainly thanks to the detailed work from our colleagues in Toulouse, it is now possible to

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[4] N. Kamar, J. Selves, J. M. Mansuy, L. Ouezzani, J. M. Peron, J. Guitard, et al., "Hepatitis E Virus and Chronic Hepatitis in Organ-transplant Recipients," *The New England Journal of Medicine* 358 (8) (2008): 811–7.

[5] R. Gerolami, V. Moal, and P. Colson, "Chronic Hepatitis E with Cirrhosis in a Kidney-transplant Recipient," *The New England Journal of Medicine* 358 (2008): 859–60.

[6] N. Kamar, H. R. Dalton, F. Abravanel, and J. Izopet, "Hepatitis E," *Clinical Microbiology Reviews* 27 (2014): 116–38.

diagnose and successfully treat patients with chronic infection with HEV. The treatment is as follows[7]:

(1) If a transplant recipient has abnormal liver blood tests, they should be tested for HEV
(2) If the blood tests show the patient has HEV in the blood stream they should be retested after an interval of three months
(3) If the patient still has HEV in their blood at three months there is little chance they will clear it spontaneously; their body's immune system is partially paralysed by the anti-rejection drugs they have to take. These patients have a chronic infection
(4) In some transplant recipients, it is possible to slightly reduce the amount of anti-rejection drugs they take without causing rejection. Obviously, this needs to be done very carefully and thoughtfully with constant monitoring of blood tests. In patients where a safe reduction of anti-rejection drugs is possible then about thirty percent will clear the virus themselves. Their immune system is just strong enough to achieve viral clearance but not strong enough to cause rejection of their transplanted organ(s). This is a tricky balancing act and usually not a good idea in kidney transplant patients who need quite a high dose of anti-rejection drugs to keep their transplant in good shape
(5) In patients where this manoeuvre fails or is not possible then antiviral drugs can be used. We use a very old-fashioned drug called ribavirin, which has been around for over thirty years. It's pretty effective at clearing the virus and does so in eighty-five to ninety percent of cases following three to six months of treatment. What about the ten percent of patients who do not respond to this ribavirin? Unfortunately, these patients are currently untreatable, and HEV continues to grumble away in the liver

How long has HEV been causing problems in our transplant recipients? Nobody knows for sure. In view of its "silent" clinical course and the difficulties in either considering and/or establishing the diagnosis, it is possible that HEV has been in the transplant population for quite some time. Although the "piggy virus" (HEV genotype 3) was only discovered in pigs in 1997 and has been labelled an "emerging infection" by some authors (including myself), it is beyond doubt that the origins of the virus

[7] H. R. Dalton and N. Kamar, "Treatment of Hepatitis E Virus," *Current Opinion in Infectious Diseases* 29 (6) (2016): 639–44.

date back many, many years. Biological time-clock studies (the equivalent of carbon dating in virology) suggest that HEV split into its four main genotypes several hundred years ago. HEV genotype 3 has been living quite happily in pigs since this time, causing no problem for its porcine primary host. Occasionally it skips across to us homo sapiens, until recently unseen by blinkered human eyes. My guess[8] is that HEV has been in our transplant recipients since transplantation was introduced into clinical practice in the early 1970s, on the back of Barnard's pioneering work in South Africa in the late 1960s. We just did not spot it.

[8] H. R. Dalton, "Hepatitis E: 'the New Kid on the Block, or an Old Friend?'" *Transfusion Medicine and Hemotherapy* 41 (2014): 6–9.

[9] H. R. Dalton, and J. Seghatchian, "Hepatitis E Virus: Emerging from the Shadows in Developed Countries," *Transfusion and Apheresis Science* 55 (3) (2016): 271–74.

CHAPTER THIRTY-FOUR

THE BUCKET

In 2008 the discovery that hepatitis E causes chronic infection in the immunosuppressed transplant recipients changed the field forever. Almost overnight, HEV appeared on the radar of a range of clinicians including hepatologists, haematologists, transplant and infectious disease physicians, and virologists. I wondered about other groups of patients who had damaged immune systems. Could they also develop chronic infection with HEV? The first thing that sprung to my mind was patients infected with HIV.

As luck would have it, just as these thoughts were germinating in my brain I was asked to see a patient called Wayne who had HIV. He also had slightly abnormal liver blood tests. He had been diagnosed with HIV some years previously when living in Southeast Asia. He'd also had tuberculosis, an AIDS-defining illness, which had been successfully treated. More recently, he had been complaining of terrible pains in both legs. This was particularly bad in his feet, to such an extent that sometimes he struggled to walk. He had been on antiviral therapy for his HIV, but despite this his immune system was still in very poor shape. In technical jargon, his CD4 count was less than 200/mm^3. CD4 cells are T lymphocytes; white blood cells, which are the "good guys" attacking infections. Wayne had very few of them in his blood, and so was particularly vulnerable to a range of infectious agents.

Naturally, I was intrigued with this case. I wondered if he could be chronically infected with HEV. His blood samples were sent off to London; he had HEV genotype 3. The lab in London had received a number of previous samples from this patient over the previous two years sent by my HIV physician colleagues. The guys in the lab in London rooted around in their freezer. They found quite a few of Wayne's frozen blood samples and tested them all. All of them contained HEV. Wayne had been chronically infected with the piggy virus for at least two years. Now I was really interested.

I subjected Wayne to a range of tests. He had a liver biopsy, which showed that HEV had caused quite severe inflammation and scarring in

his liver. He was already cirrhotic. He also had nerve conduction studies. These are extraordinarily uncomfortable for the patient, as they involved been jabbed with sharp needles followed by a discharge of electricity down them. The nerve conduction studies showed that Wayne had significant damage to the nerves supplying both legs, a condition known as peripheral neuropathy. We wondered if HEV was the cause. To determine this, we subjected him to a lumbar puncture. Again, this is an unpleasant experience for patients as it involves having a large needle inserted through the spine to remove some fluid (known as cerebrospinal fluid, or CSF) adjacent to the spinal cord. The CSF was clear and colourless; it looked normal to the naked eye. We analysed the CSF in the lab—the protein content was just a little higher than it should have been. The CSF was sent to London for virological analysis. As usual, it took a couple of weeks to get the result. Wayne had the piggy virus in his CSF. This raised the question of whether HEV was the cause of his peripheral neuropathy.

Once all Wayne's results were back I needed to consider how to treat him. I was not sure, as this case was complex and completely unique. I gave my colleagues in Toulouse a call and asked them for advice. I spoke with Bendy Boy my friend, colleague, and fellow virus hunter. I rang the guys in the lab in London. After doing all this, it was my call. I thought about it some more; I had to get this right. In the end, I treated him with PEGinterferon-α given by injection three times a week for six months. PEGinterferon-α is an antiviral agent previously very commonly used to treat hepatitis C but superseded by other more effective treatments since. I saw Wayne very regularly as a joint consult with my HIV-physician colleague. His liver blood tests started to improve, and then they normalised. The amount of virus in his blood stream steadily declined, and at the same time the pains in his legs started to improve. He could now walk normally.

By the end of six-months' treatment the amount of HEV in Wayne's blood was miniscule, but still detectable. I was unsure how to proceed, so another round of international phone calls followed. My colleagues in Toulouse suggested adding in ribavirin for three months, and at the same time continue with the PEGinterferon-α injections. I followed their advice, and at the end of this further three-month course of treatment the virus was no longer detectable in his blood or CSF and the painful symptoms in his legs had completely gone. I subjected Wayne to a second liver biopsy. All the inflammation had disappeared, and the amount of scarring in his liver was also significantly improved: his cirrhosis had regressed. The patient

was delighted with the outcome, and so was I. His case taught me three things I did not know before:

(1) HEV can cause chronic infection in patients with damaged immune systems caused by HIV
(2) HEV can be found in the CSF, as well as blood samples, and appeared to be associated with neurological damage
(3) Both the liver and neurological damage caused by chronic HEV infection can be improved/cured by antiviral therapy and viral clearance

Wayne agreed that his case should be written up and published.[1] [2] It was accepted by *The New England Journal of Medicine*, and is the one and only time this august journal has accepted my work.

During the course of the above events I received a phone call from Bob Purcell. Bob is one of the leading virologists in the United States, and over the years, together with his partner and co-virologist Su Emerson, had produced seminal work on hepatitis A, B, and C from his lab at the National Institutes of Health in Washington DC. I'd met him previously at a number of meetings and I knew he was now turning his considerable intellect and technical expertise to HEV. We had the usual polite chit chat to start with. Following this I asked:

"What's up Bob?"

"Harry, I wonder if you can help me please? I'm trying to locate a decent sample of HEV genotype 3. I'm finding this impossible here in the US because, as you know, we currently diagnose very few cases here."

"Bob, tell me exactly what type of sample you'd prefer," I replied

"I'd very much prefer a stool sample, as the amount of virus that we can retrieve from stool is an order of magnitude higher than we can isolate from blood samples," he continued.

"What volume of sample do you want Bob?"

"Well, as large as possible, please," he answered.

"I have a patient I think will be perfect for this. I need to talk to him and I'll get back to you."

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[1] H. R. Dalton, R. Bendall, F. Keane, R. Tedder, and S. Ijaz, "Persistent Carriage of Hepatitis E Virus in Patients with HIV Infection," *The New England Journal of Medicine* 361 (2009): 1025–7.

[2] H. R. Dalton, F. E. Keane, R. Bendall, J. Mathew, and S. Ijaz, "Treatment of Chronic Hepatitis E in a HIV Positive Patient," *Annals of Internal Medicine* 155 (7) (2011): 479–80.

We were just about to start Wayne's antiviral treatment, so if we were going to help Bob and Su with a sample it needed to be taken as soon as possible, before we started him on therapy. I rang him up.

"Wayne. How are you?"

"No different since you saw me last week, Doc."

"OK. We're going to start your treatment in a couple of days' time, so hopefully it will kill the virus. Then you'll feel better." I was not one hundred percent sure of this, as we were treating a unique case and there was no knowing for sure how he would respond. I paused, then asked:

"Hey Wayne, I have had some big-knob Yanks on the phone. They want to study your virus. What do you reckon?"

"If you trust them, I don't mind," he replied. "What kind of sample are they after?" he added.

"They want you to shit in a large bucket."

"No problem," was the reply.

I put the phone down and I then took the stairs to the second floor of the hospital and went to see my colleagues in the Department of Histopathology. This department, among other things, is responsible for the microscopic examination of tissue samples taken in various places in the hospital, including the operating theatres. Tissue samples come in all shapes and sizes and are transferred to histopathology in appropriately sized containers. I needed an extra-large one for Wayne so he could perch comfortably and do the "business." I accosted one of the lab technicians, whom I had known for many years.

"Could I borrow one of your extra-large tissue containers, please?"

"No problem," was the reply. He opened the cupboard behind him and pulled out a white container the size of a large bucket together with a snap-on lid.

"What do you want it for Harry?"

"You really don't want to know."

The white bucket was already clean, but I decided I would sterilise it as much as possible prior to sample acquisition. I filled it with hot soapy water, added some bleach, and gave it a good scrub. I then dried it off, put it in a yellow biohazard bag, and went back to the shed where I put it under my desk. Thursday came, and Wayne reported to the outpatient department to start his treatment, which was weekly PEGylated-interferon injections. I turned up with yellow bag in hand. I took formal written consent from him then gave him the bucket. He disappeared for a while and returned with a wry smile.

"Hey Harry, here it is! Let's see what the Yanks think of that beauty!"

I took the bucket in the yellow bag, with its lid firmly clipped on, straight round to microbiology. There I met the lab technician, who was quite used to me bringing all manner of non-standard samples during the course of my virus hunting. I explained this needed to go straight in the freezer and was bound for the NIH in the United States. The paperwork took months, but eventually the sample was despatched by special delivery. However, before we sent it I thought it would be a good idea if we retained a small sample in our freezer, just in case anything went awry with the "mother" sample's journey across the pond. We discussed the best way to do this. We did not want to defrost it, as this may impact on the viability of the HEV it contained. The lab technician was a resourceful man and came up with the idea of leaving the sample frozen but breaking a bit off the end with a toffee hammer. There were no volunteers for this task, which was duly completed. We kept a small bit of the stool sample while the rest was sent to Bob and Su. It took a couple of days for the sample to arrive at Bob and Su's lab in Bethesda. I then got the following email:

"Harry, the sample has arrived and looks in good shape. It can only be described as magnificent!"

Su and Bob beavered away on the Wayne's sample in their lab at NIH. We heard nothing for six months or so. Then I received a detailed email from Su. They had isolated huge quantities of HEV from Wayne's stool, which was simply teaming with virus. They cultured the virus on various culture media and found on the sixth round of culture (passage is the technical name) a unique strain of HEV. This mutant strain had purloined a very short part of the host's (i.e. Wayne's) genetic material and incorporated it into its own genetic material. The important thing about this mutant strain is that it appeared to be able to grow on just about any culture system, and on a range of cell lines of different cellular origin. This was a very major breakthrough, as HEV had previously been almost impossible to culture in the lab, and this had significantly hindered the basic biological understanding of how the virus interacts with its human host.

A few weeks later I got a call from Su.

"Harry, we need to think of an appropriate name for this strain of HEV."

I was rather taken aback. I had not expected to be asked this question. "Oh!" I said. "I have no idea what we should call it! What's the usual form in this situation?"

"Well, new viruses are named after the place they were discovered. So, the name should have some relationship to Cornwall."

"Maybe I should ring the patient and ask him his view," I replied.

I spoke with Wayne on the phone and asked him. After a pretty brief discussion, we decided on the term "Kernow virus." Kernow is the name of Cornwall in the ancient Cornish language, which has not been spoken by Cornish people as their mother tongue for over two hundred years and is now only spoken by a small number of Cornish enthusiasts. Su agreed to this, and so in the paper that was published in the *Proceedings of the National Academy of Sciences of the United States of America* our new virus was described in detail and was named "Kernow C1p6."[3] Kernow C1p6 is now used in many labs across the globe who are studying HEV. It grows on liver cell lines, kidney cell lines, cancer cell lines, placental cell lines, and neurological cell lines. At the time, the latter observation did not strike me as of particularly significant importance. How wrong I was later proven to be.

[3] P. Shukla, H. T. Nguyen, U. Torian, R. E. Engle, K. N. Faulk, H. R. Dalton, R. P. Bendall, F. E. Keane, R. H. Purcell, and S. U. Emerson, "Cross-Species Infections of Cultured Cells by Hepatitis E Virus and Discovery of a Novel Virus-host Recombinant," *Proceedings of the National Academy of Sciences of the United States of America* 108 (6) (2011): 2438–43.

CHAPTER THIRTY-FIVE

WINSTON AND NOBBY

Within medicine and outside of it, there are a number of people I greatly admire. In the non-medical field the list includes Albert Einstein, Field Marshall Lord Montgomery of Alamein, Martin Luther King, Nelson Mandela, Margaret Thatcher, Edmund Hilary, and Sherpa Tensing. Winston Churchill is also up there. These individuals share some common characteristics. They all have vision, single-mindedness, and a drive to succeed against all odds.

I admire the resolve shown by Churchill during the Second World War and, just as importantly, his repeated prophetic warnings (almost universally ignored until it was nearly too late) regarding the rise of fascism in Germany issued from his semi-self-imposed exile between the two world wars. In the 1930s he had left mainstream British politics and spent most of his time in the political wilderness on his Chartwell estate in Kent. There he painted. He also built a new ten-foot high wall around his estate that stretched many miles—an allegorical statement indicating what Britain would have to (eventually) do to defeat the Nazis.

When Churchill was asked what his favourite animal was, he said: "a pig". When asked why, he said: "dogs look up to you; cats look down at you; but a pig treats you as an equal."

Churchill knew that pigs are friendly, sociable, and very intelligent beasts. I often use the above quote when giving a lecture and have a lovely image of a Gloucester Old Spot pig nuzzling his snout over a fence which I use by way of illustration. Inevitably, he's been nicknamed Winston.

There are a number of colleagues within medicine I also admire. Many are historical figures, others are (or were) my contemporaries and colleagues. One such is Simon Noble (known as Nobby) whom I first met when I was a young consultant. I was doing a ward round, and Simon had joined it; it was his first day on my team. I instantly recognised his tie. It was plain green and carried the letters "CCCC" in an embossed square on the front. This was the tie of the infamous Charing Cross Country Club. The "country club" is a gentleman's drinking club made up of primarily medical undergraduates (but also attended by qualified members) from

Charing Cross Hospital Medical School London, my alma mater. The country club is run along masonic lines and shrouded in secrecy. What is not secret is the enormous volumes of booze knocked back on a country club "run" (a glorified pub crawl). Membership is by invite only. Details of how members are selected are unclear, but any potential member thought unsuitable by any existing member can be "blackballed" in true masonic style. I knew I was in for an interesting few months.

Nobby proved himself to be a remarkable colleague in a number of ways. Despite the slightly demonic reputation gained by some members of the country club, Nobby did not at all fit the mould of the beer-swilling rugby player. First, he did not play rugby, and never had. Second, while he would occasionally have a night out, he was teetotal for very extended periods of time. Another thing about Nobby was the way he dressed. Like some of our consultant mentors at medical school, he had taken to wearing morning dress (black penguin jacket with tails, waistcoat, and striped trousers) to work. Wearing this kit in a London teaching hospital is one thing, but it took great presence to carry this off in sleepy old rural Cornwall—and carry it off Nobby certainly did. That is until a few years later, when he decided on a career in palliative medicine (the art of looking after people who are dying). Once he started doing this work the tails were left in his wardrobe, never to be seen again. I asked about this some years later:

"Nobby, why have you stopped wearing morning dress to work?"

"I had to," he replied.

"Why?"

"A number of my patients mistook me for the undertaker and thought I had come to measure them up!" said Nobby, chuckling to himself.

I'm still not absolutely sure if this is the complete truth, or if he simply got bored with wearing it.

Why is Nobby the best I've doctor I've ever had the privilege to work with? Well, he certainly developed into a first-rate diagnostician. He is also a very, very good clinical teacher. However, it is skill at communicating with patients and his humanity towards his charges that set him aside from the rest. I witnessed this first hand shortly after he joined my team. I was looking after Elsie, a patient with primary biliary cirrhosis. This is a curious and relatively uncommon condition where the patient develops antibodies in her (the condition is very rare in men, for some unknown reason) bloodstream directed against the patient's own liver. The cause of this disease is unknown. Over many years the liver becomes inflamed, scarred, and cirrhotic. In the end, the liver often fails completely. The only treatment is liver transplantation, which is considered in patients who have

an extensively damaged liver. Elsie was in her late eighties and too old for a liver transplant. She was dying, and she knew she was dying. There was nothing I could do to prevent it. One day, when I knew she only had a week or two left to live, I went to her bedside for a chat.

"Elsie?" I said.

"Yes, doctor?" she replied.

"Is there anything I can do to make things easier for you?"

Elsie thought a while and then said: "Yes, there is. Could you please ask Simon Noble to come and see me every day until I die?"

I thought about this for a moment, then I asked the attending nurse for Elsie's prescription chart. I wrote down the following, alongside her regular meds: "Medication: Dr Simon Noble. Frequency: od (once per day). Route of Administration: in person."

Nobby saw and comforted Elsie every day until she died. She died a contented woman. Nobby had always wanted to be a palliative care doctor. He was always going to be brilliant at it, from what I knew of him. One day many years ago he developed a lump in his neck. This turned out to be due to a cancer of the lymph nodes known as lymphoma. He underwent extensive chemotherapy, which in the end cured him completely. Such an experience at a young age is life changing, and I think this may have helped make Nobby quite unique in his chosen field.

I remember some years later he was seeing a patient on my ward who had terminal cancer. I was doing my ward round and the patient was due to be transferred to the hospice the following day, under the care of Nobby and his colleagues. I knocked very quietly on the patient's door (she was in a single room) and opened it slightly with the intention of saying goodbye. There was Nobby talking to the patient. He continued talking to as though I was not there, not a flinch, not a sideways glance, maintaining eye contact with the patient at all times. He was "in the zone," and could not be distracted. He was communicating to her that, as far as he was concerned, she was very special; that he had all the time in the world for her; that she was his only patient; that she could tell him her fears if she wanted to; that things would be okay. I watched in silence for five seconds. I was very humbled. I quietly closed the door knowing she was getting the best care I had ever witnessed.

Nobby and I worked well together. I helped him whenever I could. When he was recovering from his cancer, after he had finished his chemo, I arranged for him to have a part-time job in the undergraduate office teaching the medical students for a couple of days a week. He did this for a year or so before coming back to work full time. I told him he had carte blanche. I encouraged him to express his personality in the way he taught

and, whatever else he did, to enjoy himself. He did so with considerable gusto. He got into "gaming," a method of teaching by getting the students to play a game. One session I witnessed him deliver was a teaching game called "Tubes up Ginger." This was a variant of "pin the tail on the donkey," and involved getting the students to insert various medical devices into a life-sized cardboard cut-out of Spice Girl Geri Halliwell—"Ginger Spice." Absolutely hilarious to watch. And absolutely politically incorrect, but the students who were taught by him will never forget the experience.

A couple of years later Nobby and I, together with some other colleagues, sat down and wrote a couple of undergraduate textbooks together. It was a pleasure working with him in this way. One book was an examination crammer—a book of multiple-choice questions with extended answers. It sells very well and is highly regarded in its field.[1] This is slightly ironic as Nobby, by his own admission, is hopeless at doing multiple-choice questions in the examination setting, and as a result he had to take his exams for the Membership of the Royal College of Physicians (UK) on a number of occasions before he passed. I was so pleased for him when he eventually did pass, after all he had been through, I arranged for the Union Jack flag to be run up the hospital flagpole (this runs strictly against etiquette, as the Union Jack may only be flown from public buildings in the United Kingdom on certain days). The other book we wrote (Nobby did the lion's share of work) is about communicating with patients. It won the British Medical Association undergraduate book of the year prize in 2006.[2] Well done Nobs.

Nobby now has a consultancy in South Wales. Lucky old Welsh, I say. He has distinguished himself in many ways in a short few years. He has developed a large research programme with grants totalling millions of pounds from the Medical Research Council in the United Kingdom and the pharmaceutical industry (this is almost unheard of in the field of palliative care), and now has a well-deserved international reputation in his field. He has presented a paper to the Welsh National Assembly. He also featured in a documentary on a UK national TV network about dying a good death:

> People think that Palliative Care (the care of the dying) is all about syringe drivers (a method of delivering continuous low-dose morphine and other

[1] H. J. Fellows, S. I. R. Noble, and H. R. Dalton, *Best of Five for MRCP* (London: Elsevier, 2005).

[2] H. R. Dalton and S. I. R. Noble, *Communication Skills for Final MB* (London: Elsevier, 2005).

symptom-relieving drugs in patients with end-stage cancer, in order to alleviate pain) and chucking nuns at patients. Well it's not …

I knew it wasn't, and now so did the rest of the country. Nobby was made a professor of palliative care last year.

CHAPTER THIRTY-SIX

TOULOUSE, 2009

Professor Dame Sheila Sherlock was one of the most important women in twentieth-century medicine. She founded the discipline of hepatology in the 1940s and 50s and trained a whole generation of hepatologists worldwide from her Department of Medicine at the Royal Free Hospital in London. Dame Sheila was the first female professor of medicine in the United Kingdom. She was short, driven, did not suffer fools, and was loved in equal measure by her patients and faculty. I never had the good fortune to meet her, but I can feel her intellect around me in the many colleagues she trained and influenced over the years.

By all accounts, Dame Sheila was a sensational teacher and used a distinctive and very direct style, which is not completely congruent with modern received wisdom on how one should facilitate learning in adults—it was perhaps, to some extent, Skinnerian in style and substance. I'd have loved to have been taught by Dame Sheila, but less enthusiastic about being examined by her. Dame Sheila was an examiner for the Royal College of Physicians in London, and it was the dread of every aspiring physician to get "the Dame" as an examiner in the postgraduate MRCP examination, especially the "short cases." During this process, the doctors being examined were taken to a series of patients and asked to do a physical examination and come up with the diagnosis in five minutes, maximum. Quite tricky at the best of times, but with Dame Sheila on your shoulder, able young doctors not infrequently morphed into blithering idiots.

I heard a story many years ago about the Dame, and I am not sure if it is apocryphal or not. Some young doctors taking the exam resorted to pharmacological manipulation to calm their nerves on exam day. The most popular choice was beta blockers. Such drugs do steady the nerves, but they also slow the heart rate. Any astute physician, and Dame Sheila was certainly that, can judge a patient's (or in this case a candidate's) heart rate by a quick glance at the veins in the neck. It is said, and I do not know if this is true, that Dame Sheila would fail a candidate whose heart rate was less than fifty beats per minute, irrespective of the quality of their answers,

as they were almost certainly taking beta blockers. The examination these days has changed and is aligned with the "principles of adult education," and is "softer" on the young doctors taking it. In my view, this has a very major disadvantage—if you could get past Dame Sheila on the short cases you were more than capable of dealing with anything that comes through the hospital door when you are in charge of the medical emergencies.

After we had done the HEV IgG seroprevalence study in blood donors that showed that sixteen percent of blood donors from southwest England had been previously exposed to HEV, we had some antibody kits left over. They had been kindly donated for free by the Chinese manufacturer, as we had no money. Bendy Boy started tinkering with them in the lab, and he compared the Chinese antibody kits to a very expensive, and commonly used at that time, American HEV antibody kit. This was done by studying serial samples from PCR-proven cases of hepatitis E that we had seen taken up to seven years after infection. We got a surprise with the result. What Bendy Boy found is that the Chinese kit was extremely accurate, and ninety-eight percent of the samples tested contained the HEV-specific IgG antibody. However, when we came to look at the American kit it was absolutely hopeless and underestimated the seroprevalence by a factor of four.[1] We knew that our colleagues in southwest France had just published a seroprevalence study in blood donors from Toulouse. They found exactly the same result as us—sixteen percent, but they had used the crappy American kit.[2] If our observations about the quality of the kit used by our colleagues in Toulouse were correct, then the amount of circulating HEV in southwest France was enormous.

Bendy Boy and I sat down and discussed the results at length. We decided that we needed to go and talk to our colleagues in Toulouse and share our new unpublished data with them. A phone call and/or email would not cut it—it needed to be face-to-face. We agreed we should go to Toulouse to see them rather than invite them for discussions in the Shed. I was also conscious that our meeting would need to be approached carefully, thoughtfully, and with humility. We were going to tell one of the leading virology teams in the whole of France that they had got it quite

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[1] R. P. Bendall, V. Ellis, S. Ijaz, R. J. Ali, and H. R. Dalton, "A Comparison of Two Commercially Available Anti-HEV IgG Kits and a Re-evaluation of Anti-HEV IgG Seroprevalence Data in Developed Countries," *Journal of Medical Virology* 82 (5) (2010): 799–805.

[2] J. M. Mansuy, F. Legrand-Abravanel, J. P. Calot, J. M. Peron, L. Alric, S. Agudo, H. Rech, F. Destruel, and J. Izopet, "High Prevalence of Anti-hepatitis E Virus Antibodies in Blood Donors from South West France," *Journal of Medical Virology* 80 (2) (2008): 289–93.

badly wrong. Bendy Boy and I were just two country bumpkin doctors from sleepy old Cornwall, and although we had by this stage written a few papers on HEV, including a rather provocative and subsequently very well cited review paper in the leading infectious diseases journal,[3] in terms of HEV we were just also-rans. Another issue was money—we had none. I was quite prepared to dip into my own pocket, which I have done on countless occasions since, to fund the trip. However, before doing so, I decided to hunt around to see if anybody had some spare cash to help us.

After she died in 2002, Dame Sheila left the Royal College of Physicians in London, of which she was the first ever female vice president, a legacy. This was to be used as the Dame Sheila Sherlock Travelling Bursary to fund clinician researchers for overseas travel to help foster and develop international research collaborations. This legacy reflects the international perspective of Dame Sheila's life, work, and outlook. I decided to apply for the travelling fellowship. After submitting the relevant forms, including a summary of our research intentions, I received an email a couple of months later. It informed me that the travelling fellowship for that year had already been awarded, but the registrar's travelling fellowship had not. Would I like to take the registrar's fellowship, amounting to five hundred pounds? I was delighted by this, as this sum would just about cover our travel and hotel costs, and there would perhaps be enough left over to take our new friends out to dinner. I was also amused, as registrars are usually in their twenties or early thirties, and although I have retained some youthful mental vitality, by this time even I had to admit I was getting well into middle age.

We emailed our colleagues in Toulouse and basically invited ourselves over to share our unpublished data. After a delicious dinner in the central square in the "pink city" (named after the colour of the local stone from which many important buildings are constructed in Toulouse) and a restless night in a cheap hotel, Bendy Boy and I set off for Toulouse University Hospital the next morning by taxi. We were greeted by Jacques Izopet, head of department and one of France's leading virologists, and, as is customary on such occasions, we were given a tour of the faculty. This took quite some time, as the clinical labs covered five floors, as did the separate research faculty next door—all state of the art. This institution housed seventy-six virologists and associated labs and technicians. We got by with one microbiologist (Bendy Boy gets a bit upset when I call him a

[3] H. R. Dalton, R. P. Bendall, S. Ijaz, M. Banks. "Hepatitis E: an Emerging Infection in Developed Countries." Lancet Infectious Diseases 8(11) (2008) 698-709.

virologist, because he says he isn't; his previous interest was in parasitology) and occasional brief use of NHS clinical lab facilities when otherwise not in use. During our day-long stay at the Toulouse University Hospital, I failed to spot anything that even came close to resembling a shed. Nor did I see French patients waiting on trolleys in the corridor.

Bendy Boy and I presented our data to our Toulouse colleagues as a team. I did the clinical presentation, and Bendy Boy spoke afterwards about the lab stuff, including our blood-donor data and findings about the very poor performance of the assay that the Toulouse guys had used in their blood donor seroprevalence study. We asked them, very politely, if it might be worthwhile repeating their study with the very accurate Chinese assay that we had used? They asked for a pause and retired next door to discuss our proposal in private. After about an hour they returned with smiles on their faces—the answer was "oui" from Jacques. Bendy Boy and I were delighted. To make it a bit of fun we had a bet on the result. The French guys bets ranged from twenty to twenty-five percent; Bendy Boy's bet was thirty percent; my bet was that forty-eight percent of their blood donors would have been exposed to HEV and turn out to have anti-HEV specific antibodies. To give an additional edge, the winners were to get a bottle of high-quality champagne.[4]

Champagne always tastes nicer when bought by a Frenchman, as we learned a couple of months later that the accurate seroprevalence data in Toulouse blood donors was fifty-two percent.[5] The email was shortly followed by two bottles of Veuve Clicquot. While toasting our friends from France, Bendy Boy and I discussed the implications of the new data from Toulouse. We agreed that most of the previously published data on HEV seroprevalence, nearly all of which used hopelessly insensitive assays, were wrong. By and large, they mostly showed seroprevalence rates of less than five percent in developed countries, and this is one key reason why we "missed" the silent epidemic of HEV occurring right in front of our noses. We also agreed that HEV, for some unknown reason, was hyperendemic in the Toulouse (Midi-Pyrénées) region, from where the blood donors were drawn. The number of exposed human Toulouseans was of a similar order, or even higher, than one would find in an urban population in Delhi, India. However, in Delhi there are frequent outbreaks

[4] I sometimes use the story of this bet and the outcome to illustrate my lectures. It usually gets a laugh.

[5] J. M. Mansuy, R. Bendall, F. Legrand-Abravanel, J. P. Calot, N. Kamar, M. Miedouge, V. Ellis, H. Rech, F. Destruel, H. R. Dalton, and J. Izopet, "Hepatitis E Virus Antibodies in Blood Donors, France," *Emerging Infectious Diseases* 17 (12) (2011): 2309–12.

of hepatitis E in humans caused by water supplies getting infected with HEV genotype 1. In contrast, there have been no large overt outbreaks of hepatitis in Toulouse where HEV genotype 3 is the dominant circulating virus. It would appear that HEV genotype 3 has been hiding from human scrutiny.

Dame Sheila—thank you, from the bottom of my heart.

CHAPTER THIRTY-SEVEN

PACIFIC OCEAN, 2009

As more reliable tools became available to diagnose current and past exposure to HEV, the incidence of hepatitis E started to become clearer. Incidence is defined as the number of cases of a condition (in this case HEV infection) per year, expressed as a percentage of the population. For example, if the incidence of condition X in England (population fifty million) is one percent, then the number of new cases of condition X in England is five hundred thousand per year.

An incidence estimate from Public Health England suggested that the incidence of HEV infection in England was 0.2 percent.[1] In the United States, the incidence was found to be 0.7 percent[2]; the Netherlands 1.1 percent[3]; and in southwest France a whopping three percent.[4] These figures are mindboggling and suggest that there are a minimum of one hundred thousand cases of HEV in England alone. However, there is a major mismatch between these estimates, based on seroprevalence data, and actual laboratory-confirmed cases. For example, in 2015 in England and Wales there were only 861 human cases of HEV confirmed by Public Health England.[5] The reason for this mismatch can only have two explanations (it is possible that both these hypotheses are concurrently

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[1] S. Ijaz, A. J. Vyse, D. Morgan, R. G. Pebody, R. S. Tedder, and D. Brown, "Indigenous Hepatitis E Virus Infection in England: More Common Than It Seems," *Journal of Clinical Virology* 44 (4) (2009): 272–6.

[2] M. F. Faramawi, E. Johnson, S. Chen, and P. R. Pannala, "The Incidence of Hepatitis E Virus Infection in the General Population of the USA," *Epidemiology and Infection* 139 (8) (2011): 1145–50.

[3] E. Slot, B. Hogema, A. Riezebos-Brilman, T. Kok, M. Molier, and H. Zaaijer, "Silent Hepatitis E Virus Infection in Dutch Blood Donors, 2011 to 2012," Euro Surveillance (2013):18.

[4] J. M. Mansuy, P. Gallian, C. Dimeglio, K. Saune, C. Arnaud, B. Pelletier, et al., "A Nationwide Survey of Hepatitis E Viral Infection in French Blood Donors," *Hepatology* 63 (2016): 1145–54.

[5] Public Health England, "Hepatitis E: Symptoms, Transmission, Treatment and Prevention" (May 2016).

operative): (1) most infections in humans have no symptoms, or; (2) patients with HEV infection who do have symptoms are not currently recognised.

In 2008, the good ship Aurora set sail from Southampton, United Kingdom, on a round-the-world cruise. It had a full complement of passengers, mainly older people/retirees. Aurora sailed across the Atlantic, cruised around the Caribbean, then squeezed her way through the Panama Canal and off into the Pacific Ocean. When she neared Fiji, the holiday atmosphere on board changed—there was an outbreak of hepatitis on board. Overnight, the Aurora changed from an ocean-going cruise liner to a floating *in vivo* human virology laboratory. One of the passengers disembarked at Auckland and went to see one of my old Kiwi colleagues. He made a diagnosis of hepatitis E and gave me a call for some advice; the patient recovered within a few weeks. On return to Southampton the outbreak was investigated by the UK Health Protection Agency based in London. This was no mean task, as there were several thousand passengers and crew aboard during the outbreak of hepatitis E. The investigation included a very detailed inventory of symptoms and diet and a set of blood tests from as many people on board as possible, irrespective of whether they had been ill—a gargantuan task. Following this, cases of HEV confirmed by blood testing were compared to those without HEV, with subsequent cross-referencing to their symptoms and diet. A classic example of a "case-control" study.

The investigation took several months, and Bendy Boy and I were invited up to London to review and comment on the initial findings. Thirty-three cases of HEV infection were identified on blood testing, and in all of whom viral RNA was recovered from the patients' blood samples it was HEV genotype 3. However, two-thirds of patients had no symptoms whatsoever. This provided excellent evidence to support the notion that most human infections with HEV genotype 3 result in no symptoms. What was just as intriguing was the analysis of the dietary history between cases and controls. The cases of HEV infection were much more likely to have eaten shellfish, and there was no difference between cases and controls in pork consumption.[6] I asked if the remaining food had been stored when the Aurora finally docked on her return to Southampton, so maybe any remaining shellfish could be tested. No, it had all been thrown away.

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[6] B. Said, S. Ijaz, G. Kafatos, L. Booth, H. L. Thomas, A. Walsh, M. Ramsay, and D. Morgan, "Hepatitis E Incident Investigation Team," *Emerging Infectious Diseases* 15 (11) (2009): 1738–44.

Studies have shown that pigs worldwide excrete huge quantities of viable HEV genotype 3 in their faeces.[7] HEV has been found in slurry lagoons, streams receiving "run-off" water from adjacent pig farms, rivers, human sewerage, and the sea.[8] It came as no surprise to me that HEV was eventually found in mussels, often in high titre, as these bi-valves are filter feeders. They act as biological hoovers and have clearly hoovered up and concentrated HEV floating around in the sea. Data from the West of Scotland showed that the majority of mussels tested for HEV were infected,[9] and a very recent study showed that a minority of Scottish shellfish were contaminated with HEV at the point of sale[10]—best cook them well, I think. Finally, HEV genotype 3 has found its way to the top of the aquatic food chain, as has recently been found in bottlenose dolphins in Cuba.[11] At the current time, it is unknown if dolphins are unwell in any way when infected with this virus.

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[7] S. Fernandez-Barredo, C. Galiana, A. Garcia, et al., "Detection of Hepatitis E Virus Shedding in Feces of Pigs at Different Stages of Production Using Reverse Transcription-polymerase Chain Reaction," *The Journal of Veterinary Diagnostic Investigation* 18 (2008): 462–5.

[8] S. Ishida, S. Yoshizumi, T. Ikeda, et al., "Detection and Molecular Characterization of Hepatitis E Virus in Clinical, Environmental and Putative Animal Sources," *Archives of Virology* 157 (2012): 2363–8.

[9] C. Crossan, P. J. Baker, J. Craft, Y. Takeuchi, H. R. Dalton, and L. Scobie, "Hepatitis E Virus Genotype 3 in Shellfish, United Kingdom," *Emerging Infectious Diseases* 18 (12) (2012): 2085–7.

[10] Z. O'Hara, C. Crossan, J. Craft, and L. Scobie, "First Report of the Presence of Hepatitis E Virus in Scottish-harvested Shellfish Purchased at Retail Level," *Food and Environmental Virology* 10(2) (2018): 217-221.

[11] M. C. Montalvo Villalba, D. Cruz Martinez, I. Ahmad, L. A. Rodriguez Lay, M. Bello Corredor, C. Guevara March, et al., "Hepatitis E Virus in Bottlenose Dolphins *Tursiops truncates*," *Diseases of Aquatic Organisms* 123 (2017): 13–18.

CHAPTER THIRTY-EIGHT

CORSICA, 2009

Corsicans know how to work hard—it is part of their history, nature, and culture. Like many Corsicans, as a young man René's father had gone to work in nearby Marseilles, a relatively short trip over the Mediterranean Sea. Although René was born in Marseilles, where he has worked for many years, he has retained his Corsican heritage. Whenever he gets the chance, usually in the French month for holidays in August, he takes some time off and hops on the ferry with his family back to Corsica to see his extended network of relations and friends. Family is very important to the French, but particularly so for the Corsicans. There were many gatherings, and all were accompanied by generous amounts of local food and wine—it was a *bon vacances*.

On his return to Marseilles, René did not feel so well. He had flu-like symptoms, some abdominal discomfort, and then developed jaundice. René was well aware of the diagnostic possibilities of his illness, as he was (and still is) professor of hepatology at the Centre Hospitalo-Universitaire Timone, Marseilles. He went straight to his colleagues in the Department of Virology, a world-leading institution, and had himself tested. He had acute HEV infection, genotype 3. So, it turned out, did a number of other people who had attended the same family luncheon in Corsica.

I had wanted to meet René and colleagues in Marseilles for some time, as they have made key contributions to the unfolding HEV story. For example, they described a case of chronic infection in a transplant recipient at the same time as colleagues in Toulouse, which appeared in the same issue of *The New England Journal of Medicine*.[1] This was really important, because at that time the notion that HEV can cause chronic infection was a major paradigm shift in scientific thinking. It would have been relatively easy for narrow-minded conservative peer reviewers to

[1] R. Gerolami, V. Moal, and P. Colson, "Chronic Hepatitis E with Cirrhosis in a Kidney-transplant Recipient," *The New England Journal of Medicine* 358 (2008): 859–60.

label data from a single centre as "impossible," or criticise some aspect of the applied methodology and reject the paper. However, it would have been much more difficult to ignore or denigrate identical data from two different world-class centres that both show the same observation—when a patient is taking powerful drugs to suppress the immune system, they often fail to clear the virus.

I increasingly frequently get invited to give talks and seminars in France and have done so on several occasions in Marseilles. Some years ago, I was invited to dinner with René and his virologist colleague Phillipe Colson in a smart restaurant overlooking the Mediterranean. The food was excellent—bouillabaisse prepared in true Marseilles style—and the conversation was inspiring. Although I had seen many patients with HEV infection, I had never heard an account from a colleague of René's Hepatological stature who had got so up close and personal with the virus. I got a blow-by-blow account of his illness, the most prominent symptom being profound fatigue. He was off work for several weeks and it took another month or so to recover completely. However, what really took my interest was the subsequent virological investigation, which was, of course, thorough and detailed given the cases involved.

I learned that eighteen people from three families attended the lunch in Corsica, and three individuals (including René) developed symptomatic HEV infection. All eighteen attendees were tested for HEV, which showed that a further four people who ate lunch that day had also developed HEV infection but had no symptoms. Thus, seven out of eighteen were infected by HEV genotype 3, and sequencing showed a complete match—they had become infected with identical HEV, presumably from a common source. All eighteen who had attended the lunch were then quizzed in minute detail about what they had eaten during the gathering. Suspicion fell on a local Corsican delicacy called figatellu, an air-dried or smoked sausage containing pig liver. Of the eighteen diners, thirteen ate the figatellu, of whom seven developed HEV infection. Five diners did not consume the figatellu on offer, none of whom became infected. Subsequent investigation showed that figatellu bought from the same Corsican retailer contained large amounts of HEV genotype 3, almost identical to that found in the humans who had been infected.

René and colleagues published their findings in a landmark paper in *The Journal of Infectious Diseases*.[2] It caused a bit of a media frenzy in

[2] P. Colson, P. Borentain, B. Queyriaux, M. Kaba, V. Moal, P. Gallian, L. Heyries, D. Raoult, and R. Gerolami, "Pig Liver Sausage as a Source of Hepatitis E Virus Transmission to Humans," *The Journal of Infectious Diseases* 15 202 (6) (2010): 825 34.

France at the time, and the Corsicans did not uniformly take kindly to having their national dish disrespected, especially by a Corsican. Subsequently, figatellu on sale to the public is now obliged to carry the label "cuit à coeur" ("cook to the heart," i.e. thoroughly). These directions are not completely congruent with many French people's concept of culinary culture, particularly from the south of the country. Some continue to eat figatellu uncooked; some continue to get infected with HEV as a result. Later work was to show that thirty percent of figatelli were infected with HEV genotype 3. However, it is not just Corsican figatellu that pose a health risk to the French public and beyond, as quite a number of French pork-based delicacies have been found to be infected with HEV, often in huge amounts.[3] The list of potentially infected products includes: Toulouse pig liver sausage, dried salted liver, quenelle (pork meatballs) and quenelle paste, and air-dried and fresh liver sausage. Many of these foods are commonly eaten without cooking, and it would appear that HEV may well survive the air-drying process.[4]

But it is not just a French problem, as HEV has been found to contaminate a very wide range of pork products on sale to the public from across the globe, including the United Kingdom.[5] [6] *Bon Appetit!*

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[3] C. Renou, A. M. Roque-Afonso, and N. Pavio, "Foodborne Transmission of Hepatitis E Virus from Raw Pork Liver Sausage, France," *Emerging Infectious Diseases* 20 (2014): 1945–7.

[4] V. Doceul, E. Bagdassarian, A. Demange, and N. Pavio, "Zoonotic Hepatitis E Virus: Classification, Animal Reservoirs and Transmission Routes," *Viruses* 8 (10) (2016): pii: E270.

[5] A. Berto, F. Martelli, S. Grierson, and M. Banks, "Hepatitis E Virus in Pork Food Chain, United Kingdom, 2009–2010," *Emerging Infectious Diseases* 18 (2012): 1358–60;

[6] I. Di Bartolo, M. Diez-Valcarce, P. Vasickova, P. Kralik, M. Hernandez, G. Angeloni, F. Ostanello, M. Bouwknegt, D. Rodríguez-Lázaro, I. Pavlik, and F. Maria Ruggeri, "Hepatitis E virus in pork production chain in Czech Republic, Italy, and Spain," *Emerging Infectious Diseases* 18 (2012): 1282–9.

CHAPTER THIRTY-NINE

TYPHOID MARY

Every doctor has just a few patients who are the bane of their professional life. These are known by some in the trade as "heart-sink" patients. I'm unsure why they have been named as such, but I am familiar with the sinking feeling when a five-volume set of notes is placed on my desk in my clinic. I try my hardest not to think "oh no, not Mrs X again." Heart-sink patients are not patients who are medically complex, angry, distressed, or just have "awkward" personalities—such patients are simply just part of the spectrum of humanity that is an integral part of every doctor's working life. No, heart-sink patients are something entirely different.

In my experience of this type of case, so-called heart-sink patients are more commonly female. They usually have a complex set of symptoms stretching back for years that do not fit any textbook description of any disease currently recognised. Often, they have had numerous investigations and have seen a good number of different doctors, to no avail. The patients that I commonly encounter have frequently been given the unhelpful diagnostic label of irritable bowel syndrome. Sometimes, patients are very angry with the individual doctors they have previously seen. Sometimes they are bemused by the fact that modern medical science has been unable to identify and cure their problem. Their hospital notes are frequently voluminous in the extreme.

A significant proportion of such patients that I see have physical symptoms due to underlying psychological problems or psychological trauma in the past, or due to domestic or working stress. This does not mean their symptoms are not real, or in some way fabricated. This is not the case at all. It is just the way that the patient's body has reacted to stress or psychological injury; the symptoms themselves are real enough and can be very severe. There are important neuronal connections from the brain to the gut. In patients like this, the brain starts firing off all sorts of distress signals. Some end up in the gut and cause the symptoms. I find a careful explanation along these lines often helps the patient understand what is happening to them and why. Before I do so, however, I have to be

absolutely sure there is nothing physically wrong with their gut as, occasionally, some of these patients do turn out to have a problem here. Some illnesses can produce an unusual set of symptoms and can be difficult to diagnose. An example of this type of illness is patients who have furred up arteries supplying the gut. Another example is cancer of the tail of the pancreas, a horrible disease. Once I am absolutely sure there is nothing physically wrong, the most important thing is to tell the patient this as clearly as possible. Afterwards, for many patients their symptoms, although not cured, are somehow less troublesome.

In other patients, it may take a number of years for the disease to become fully manifest to a stage where it can be diagnosed. I recall seeing a woman some years ago who had had symptoms of diarrhoea and abdominal pain for fifteen years. During this time, she had seen several excellent colleagues who had done all the appropriate tests, which were all normal. Her symptoms continued and worsened. She came to see me. I repeated her tests. These showed that she had Crohn's disease. It wasn't that my colleagues were hopelessly incompetent, or that I am brilliant—they were not, and I am not. It just took the disease a good many years to manifest itself sufficiently to a stage where it could be diagnosed.

In some of these cases there is undoubtedly something physically amiss, but current medical thinking and technology are quite unable to make a diagnosis. Maybe our colleagues in the future will have a better understanding of such cases. When I was at school, I dropped history as a subject of study. I had the choice of either learning about geography or history, and I chose the former. As I got older I began to regret that decision, and now read historical texts on a regular basis. I am not sure why that should be—maybe it's to do with my increasing sense of mortality, which was noticeably absent in my more formative years. As a result, I am increasingly aware of the "march of history," with particular respect to medicine.

I have quite a collection of old medical textbooks dating from the eighteenth and nineteenth centuries. When I read these books, I recognise many of the descriptions of the diseases under consideration from my current medical practice. What I do not recognise is the diagnostic processes, received wisdom of mechanism(s) of disease causality, nor any of the therapeutic manoeuvres that were employed by my medical forbears, all of which are completely nonsensical to the modem medical eye. The latter include such things as electric shock treatment for abdominal pain, painting silver nitrate paste on a goitre (thyroid swelling) and sitting out in the sun with the neck extended, and the use of leeches. Although leeches have made a recent comeback for the treatment of

infected wounds, the others seem ludicrous to the modern eye, and underscore the enormity of change in medical science, particularly in recent years. The other thing that strikes me when reading these old and dusty tomes is the style in which they are written—they are stiff, stilted, and pompous. An example of what I mean was written by Richard Mead (President of the Royal College of Physicians and personal Physician to King George II) in the leading medical textbook of the eighteenth century[1]: "We have unequivocally demonstrated that diabetes is not a disease that emanates from the kidney ... rather it is certain that it is an affliction of the liver."

This assertion has not stood the test of time and is totally inaccurate to the modern way of medical thinking. However, what strikes me is the absolute certainty in how it was expressed. This makes me think of the things I write, and how I write them. It is beyond any doubt that in two hundred years times (and, almost inevitably, well before this) some of my future colleagues will read my notes, papers, and books and think to themselves: "What on earth was Dalton thinking about? He got that hopelessly wrong!" (I suspect some of my colleagues may already have this point of view). I try to keep this thought at the back of my mind when writing in the hope that it might temper and humble some of my more non-conformist notions.

Although many patients, often labelled as "irritable bowel syndrome," are very challenging to look after, the difficulties of such cases pale into complete insignificance compared to the case of Typhoid Mary.[2] Mary did not like doctors at all. She did not believe what they said; she did not trust them; she did not follow their advice.[3] She, perhaps at first unwittingly, and later knowingly, caused the deaths of an unknown number (possibly hundreds) of her fellow Americans. Typhoid Mary has to be one of the worst patients of all time.

Typhoid fever is an infection of the gut caused by the bacteria *Salmonella typhimurium*. Typhoid fever is still common in some developing countries. It causes high fever, abdominal pain, septicaemia, and organ failure. Untreated, it carries a mortality of ten to fifteen percent. It is transmitted by the oral-faecal route and a common mode of transmission is by consuming infected drinking water or eating foods such as salads that have been washed with infected water. These days typhoid fever is very uncommon in developed countries such as the United

[1] R. Meade, *Monita et Præcepta Medica* (London, 1751).

[2] J. W. Leavitt, *Typhoid Mary* (Boston: Beacon Press, 1996).

[3] As this was the beginning of the twentieth century, this could perhaps more accurately be described as "doctor's orders" rather than advice.

Kingdom and the United States. It is only seen in patients who have returned from travelling to an endemic area who respond well to antibiotic therapy. Travellers to certain countries are advised to be immunised against typhoid fever. The vaccine offers considerable but not one hundred percent protection. However, in the nineteenth century and early parts of the twentieth, outbreaks of typhoid fever were not uncommon in large urban conurbations in industrialised countries and, as it was the pre-antibiotic era, caused significant mortality. For example, in Chicago in the month of January 1892 there were 311 deaths from typhoid fever.[4]

As recently as 1964 there was a large outbreak of typhoid fever in Aberdeen, Scotland[5] in which over four hundred people were affected. The source of this outbreak was traced to a batch of corned beef that had been imported from Argentina. The canning process was done with infected water drawn from the River Parana at Rosario, Argentina, that had contaminated the tinned meat. The bacteria managed to survive inside the tins despite the lengthy transatlantic crossing and a brief stay at Wapping docks in London. A number of famous people succumbed to typhoid fever in the nineteenth century. Two of the most well-known typhoid victims were Prince Albert (Queen Victoria's husband), who died at the age of forty-two in 1861, and, in the United States, Abigail Adams (1744–1818), the wife of President John Adams.

Typhoid Mary's real name was Mary Mallon.[6] She was born in Ireland in the 1860s and, like many of her fellow country people of that era, emigrated to America in search of a better life. She became a cook and had numerous positions in that role in wealthy New York households at the turn of the twentieth century. She first came to medical attention in 1906 following an outbreak of typhoid fever in the Long Island household of a wealthy banker. Mary was suspected, and an investigation of her employment history over the previous six years showed that there had been outbreaks of typhoid fever in several of the households where she had worked, also as a cook. When Mary was approached, she had none of this. She refused to give any stool samples for analysis and refused to talk to the doctors and health officials involved. Instead, she "did a runner."

In 1907 she was eventually found, again working as a cook in yet another household. She was arrested and taken to hospital. Samples of her stool showed that it contained the typhoid bacteria—Mary was a typhoid carrier. Although she had no symptoms she continued to excrete the bacteria in her faeces. In her role as a cook she was a walking biological

[4] *The New York Times* (February 14, 1892), 4.

[5] Report of the Departmental Committee of Enquiry (1964) H.M.S.O. Edinburgh.

[6] J. W. Leavitt, *Typhoid Mary* (Boston: Beacon Press, 1996).

weapon. She was taken, without trial, and isolated on North Brother Island. She sued for her freedom and lost, spending three years in enforced isolation. In 1910 she was allowed to go free on the strict understanding that she would agree never to work as a cook again.

Typhoid Mary resurfaced five years later. There was another outbreak of typhoid fever, this time at Sloane Maternity Hospital in Manhattan. The cook was Typhoid Mary, working there under a pseudonym. Mary was captured and isolated for the rest of her life. No one knows for sure how many people she infected with typhoid fever during her lifetime. The following extract describing her apprehension gives an impression of what it was like to have Mary as a patient[7]:

> She came out fighting and swearing, both of which she could do with appalling efficiency and vigor. I made another effort to talk to her sensibly and asked her again to let me have the specimens, but it was of no use. By that time, she was convinced that the law was wantonly persecuting her, when she had done nothing wrong. She knew she had never had typhoid fever; she was maniacal in her integrity. There was nothing I could do but take her with us. The policemen lifted her into the ambulance and I literally sat on her all the way to the hospital; it was like being in a cage with an angry lion.

Now that's what I call a difficult patient.

[7] Ibid.

CHAPTER FORTY

GULVAL, 2010

Cognisant of Snow's work in nineteenth-century London, I started putting our cases of HEV on a map of Cornwall pinned on the wall in the Shed. I studied this for hours and hours but could detect no discernible pattern. I asked my colleagues and students to do the same. They could not work out any obvious geographical relationships either. That was until we had the Gulval "mini-outbreak."

Gulval is a small Cornish village of around two thousand souls adjacent to Penzance at the far southwestern tip of the Cornish peninsula. It is set back slightly from the sea and has arguably the best cricket pitch I have ever played on. It overlooks Mounts Bay, in which is situated St Michael's Mount. Previously in private ownership, it is a smallish UK version of Mont St Michel in France, now owned and run by the UK's National Trust. As in the French version, you can access St Michael's Mount by a tidal walkway, but it's quite easy to get cut off unless you keep a wary eye on the state of the sea. I've played cricket on the Gulval pitch many times. When I get bored when fielding on the boundary, I just turn around and look. There she is, St Michael's Mount, magnificent in the calm, glittering waters of Mounts Bay.

Within a two-year period, we had three cases of HEV infection from Gulval. As usual, once I realised this I discussed it at length with Bendy Boy. We both agreed that the geographical and temporal clustering of these three cases was probably coincidental. However, we were not sure, and we had both stopped making such assumptions about HEV long before, as nearly every single piece of "received wisdom" about HEV had so far proven hopelessly inaccurate once we had the correct tools to study it properly. In the end, we decided a site visit would be in order. We both cleared our diaries for the following Wednesday morning, jumped in the car and drove the 25 miles down the A30 to Gulval. The first thing we did was look for the pigs—there weren't any. We discovered there used to be a pig farm in Gulval, but it had closed down some years previously. We noted a fast-flowing stream that was immediately adjacent the places of residence of two of our three cases. We interviewed the cases, trying to

determine if there were any common threads, any common means of potential exposure. The only thing in common the three cases had was that all shopped at the same supermarket. We were oblivious to the importance of this at the time. All were meat eaters, but only one of the three ate shellfish. This took us not much further forward.

One of the cases was a retired engineer, a very intelligent man. He had quite a nasty bout of hepatitis when infected which laid him very low for a couple of months, but he recovered in the end. He was interested in our investigation and asked me what I thought. I told him I was not sure, and from what we had seen that we not really much the wiser. I asked him to think about the issues of these infections in a Gulval-specific context. His wife made us a nice cup of tea, and we sat chatting for a while. Just as we were about to leave he came up with the following: "Harry, I've had a thought. In Gulval we have a feral flock of peacocks. There are literally hundreds of them. They come and go as they please, and nobody can recall how they came to be here. Most times they are away in the adjacent countryside, but when they come into the village, although a magnificent site, they shit everywhere. Do you think this might be important?"

I said I was not sure. A HEV-like virus had previously been found in chickens and poultry, but it was a distant fourth cousin to HEV genotype 3 and had not been found to be the cause of illness in humans. Bendy Boy and I took our leave and repaired to the Coldstreamer pub in Gulval (worth a visit—the food is excellent) for a Cornish Pasty lunch and a discussion. Based on what we knew about HEV, we thought the chance of the peacocks being the vehicle of transmission in the Gulval outbreak was low, but not zero. We decided to do a further investigation, and in no time at all had environmental health officers in bio-haz suits chasing around the village trying to catch peacocks—a bizarre sight to say the least. Multiple samples of fresh peacock poop were sent to the lab in Surrey. This time, the results came back quickly. There was no HEV in any of the samples; the peacocks were out of the frame.

Although we found no virus in the peacocks, HEV has subsequently been found in a bewildering array of other animals, including: pigs, wild boar, deer, rabbits, camels, rats, ferrets, mink, foxes, moose, mongoose, Mongolian gerbils, cut-throat trout, bats, song thrush, little owl, feral pigeon, kestrel, and the common buzzard.[1] Although the list of species in which HEV is found appears to be expanding on almost a weekly basis, most of these animal reservoirs have probably very limited or no role in

[1] V. Doceul, E. Bagdassarian, A. Demange, N. Pavio. "Zoonotic Hepatitis E Virus: Classification, Animal Reservoirs and Transmission Routes". Viruses 8(10): pii: 270.

human disease. The reason for this is that genetic sequencing (fingerprinting) data show that the HEV RNA in these animals is very different to that recovered from human cases. The prime exception to this, of course, is the pig. In true veterinary terms, it is considered the primary host for HEV genotype 3 in relation to human infection.[2] Other animals carrying HEV that cause disease in humans are wild boar, deer, rabbits, and most recently camels.[3] [4] These latter animal reservoirs are probably of secondary importance in terms of human disease. Certainly, Bendy Boy and I spotted no camels during the pleasant morning we spent in Gulval.

The widespread contamination with HEV of many animals which are used as food for humans might, perhaps, engender a certain sense of self-satisfaction among vegetarians and vegans. Unfortunately, I am afraid that this would be, at least partially, misplaced. The reason for this is that HEV genotype 3 has now also been found in strawberries and other soft fruit,[5] salad leaves, and green vegetables.[6] Presumably, these foodstuffs have been infected by the use of HEV-contaminated irrigation water and/or materials used as manure. Having said all this, the risk of exposure to HEV in vegetarians and vegans is probably less than in omnivores, but it is not zero.[7]

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[2] Kamar et al., "Hepatitis E" (2012).

[3] G. H. Lee, B. H. Tan, E. C. Teo, S. G. Lim, Y. Y. Dan, A. Wee, et al., "Chronic Infection with Camelid Hepatitis E Virus in a Liver Transplant Recipient Who Regularly Consumes Camel Meat and Milk," *Gastroenterology* 150 (2016): 355–7.

[4] A. Rasche, M. Saqib, A. M. Liljander, S. Bornstein, A. Zohaib, S. Renneker, et al., "Hepatitis E Virus Infection in Dromedaries, North and East Africa, United Arab Emirates, and Pakistan, 1983–2015," *Emerging Infectious Diseases* 22 (2016): 1249–52.

[5] L. Maunula, A. Kaupke, P. Vasickova, K. Söderberg, I. Kozyra, S. Lazic, et al., "Tracing Enteric Viruses in the European Berry Fruit Supply Chain," *International Journal of Food Microbiolgy* 167 (2013): 177–85.

[6] P. Kokkinos, I. Kozyra, S. Lazic, M. Bouwknegt, S. Rutjes, K. Willems, et al., "Harmonised Investigation of the Occurrence of Human Enteric Viruses in the Leafy Green Vegetable Supply Chain in Three European Countries," *Food and Environmental Virology* 4 (4) (2012): 179–91.

[7] E. Slot, H. L. Zaaijer, M. Molier, K. Van den Hurk, F. Prinsze, B. M. Hogema, "Meat Consumption is a Major Risk Factor for Hepatitis E Virus Infection," *PLoS One* 12 (4) (2017): e0176414.

CHAPTER FORTY-ONE

XIAMEN, 2011

In the aftermath of the biggest outbreak of HEV in human history in northwest China in the late 1980s, the Chinese government decided to establish a world-class vaccine institute. The location chosen was at the University of Xiamen in southern China. Investment was substantial in this project, which was led by a group of senior US-trained virologists who returned home to supervise and direct. The first vaccine chosen for development was to prevent HEV. One of the reasons this vaccine was chosen was the previous outbreak of HEV infection in northwest China, which involved 120,000 cases and the deaths of many pregnant women.[1]

Developing a safe and effective vaccine cannot be done overnight. The basic science needs to be understood, appropriate target antigens chosen, and animal studies need to be performed, followed by studies in humans to determine the immunogenicity and safety. Finally, the effectiveness needs to be determined. The latter was achieved by one of the largest studies in Vaccinology history. Over one hundred thousand people were involved in the trial in eastern China, in which half received the full vaccine and half received a placebo. This study established that the vaccine against HEV was safe and effective.[2] It was licensed for use in China but is currently not licensed for use elsewhere.

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[1] Teo, "Fatal Outbreaks of Jaundice in Pregnancy."

[2] F-C. Zhu, J. Zhang, X. F. Zhang, C. Zhou, Z. Z. Wang, S. J. Huang, et al., "Efficacy and Safety of a Recombinant Hepatitis E Vaccine in Healthy Adults: a Large-scale, Randomised, Double-blind Placebo-controlled, Phase 3 Trial," *The Lancet* 376 (2010): 895–902.

CHAPTER FORTY-TWO

ROME, 2011

HEV genotype 3 has an ●riental first cousin named HEV genotype 4. HEV genotype 4 is found in Japan and eastern China and behaves in a very similar way to HEV genotype 3 in Europe. HEV genotype 4 is found in Japanese and Chinese pigs, causes hepatitis in older Japanese and Chinese men, occasionally causes chronic infection in transplant recipients, and is the east Asian version of HEV genotype 3.

In 2●11, in Rome, Italy, there was a cluster of cases of hepatitis in humans caused by HEV genotype 4. In France and Denmark there have been further cases in humans, again caused by HEV genotype 4.[1] Pigs in Europe are not normally infected with HEV genotype 4, except a few pigs in Belgium who were found to carry this strain some years ago. How did our ●riental HEV cousin get from East Asia to Europe? Nobody knows. Maybe live pigs have been shipped from Japan or China to Europe. That's an awfully long journey, which would take about six weeks and seems very improbable—what's the point? ●r maybe the pigs were flown over in an aeroplane? The journey would be considerably shorter at about twelve hours, but very expensive. Again, what's the point? It makes no sense—pigs don't fly! ●r do they?

[1] Y. ●ouamra, ●. Ger●lami, J. P. Arz●uni, J. C. Grimaud, P. Laff●rgue, M. Nelli, et al., "Emergence ●f Aut●chth●n●us Infecti●ns with Hepatitis E Virus ●f Gen●type 4 in Eur●pe," *Intervirology* 57 (2●14): 43–8.

CHAPTER FORTY-THREE

GLASGOW

I regularly visit Scotland as I have collaborative research links with my colleagues at the Edinburgh Royal Infirmary, Glasgow Royal Infirmary, and a group of veterinary scientists at the Glasgow Caledonian University. Also, the British Society of Gastroenterology, of which I am a member, sometimes has its national conference at the Scottish Conference Centre. This is modern purpose-built complex on the fringes of the city centre of Glasgow. Architecturally, I suppose it's a Scottish equivalent of the Sydney Opera House, with overlapping domes, but not quite as elegant in substance or backdrop. Designed by Norman Foster in 1997, it has eight distinctive overlapping aluminium-clad shell roofs. It is hated and loved by Glaswegians in about equal measure and is known locally as "the armadillo."

I've met a number of people from Scotland over the years (including a Glaswegian who had the dubious pleasure of sharing the Shed with me for many years) and, contrary to most stereotypes, I've generally found them to be warm, generous, and good conversationalists. Almost to a man and woman they have been characterised by a dry, self-deprecating, and at times rather black sense of humour. This is particularly so in the Glaswegians I've met. I'm a great fan of the comedian Billy Connolly and, although I've never met him, he is a good illustration of what I mean in terms of personality and wit.

Whenever I visit Glasgow, I always get talking to the cabbies. I find them straightforward, knowledgeable, and often hilarious. Many years ago, a friend of mine was studying for some postgraduate examinations. He wanted to become a surgeon, but before beginning his surgical training in earnest he had to pass a very difficult examination to become a fellow of the Royal College of Surgeons, the pass rate of which was only about fifteen percent. The examination could be sat in London, Edinburgh, and Glasgow. As the pass rate was so low, it was common practice for would-be surgeons to sit the examination at all three sites to increase the chances of passing. My friend arrived in Glasgow Central station on the overnight sleeper to take his examination at the Royal College of Surgeons. He

queued for a taxi. One duly arrived, the nearside front window descending as it pulled up.

"Do you know where the Royal College of Surgeons is?" asked my friend.

"Are you a doctor, are you?" Came the reply

Slightly taken aback, my friend responded:

"Yes"

"Do you know where the gallbladder is son?" came the riposte, a grin on the cabbie's face.

On one of my trips to Glasgow I found myself with a couple of hours to spare. I decided to take a walk around the famous Glasgow Necropolis, which is a unique cemetery situated on top of a hill adjacent to the Royal Infirmary, with stunning views over the city. Somewhat fittingly, it was a rather bleak day with dark grey clouds and squalls of wind and rain. I was interested to see if I could locate the mass graves used for the burials of the hundreds and thousands of Scots who had perished from outbreaks of cholera, which I knew had affected Glasgow particularly badly in Victorian times. I had been told that the mass graves were there by a Glaswegian colleague. I soon suspected that the Necropolis was unlikely to be the site of the mass pauper's graves. Although bleak and depressing, the black and weatherworn tombstones were magnificent, many of which included ornate carvings and sculptures. The cemetery grounds were kept immaculately. This was not the burial ground of the poor, but of wealthy gentry and merchants of Glasgow. As I was leaving I came across a couple of cemetery groundsmen and asked them where the mass graves were. They confirmed that they were not in the Necropolis. It was some years later that I discovered where they had buried the cholera victims—five hundred yards to the northwest. The Glasgow Royal Infirmary had been built on top of some of them.

In the mid-nineteenth century, infectious diseases were believed to be spread by miasma. The miasmic theory held that it was putrid smells and odours that were the route of infection for communicable diseases. In the 1860s, the Surgical Department at the Glasgow Royal Infirmary was in crisis. The surgical ward was situated on the ground floor and had horrendously high mortality rates—most patients were dying because of infected wounds. The hospital governors decided to take decisive action to tackle the problem and removed the mass graves which were situated immediately under the floor of the surgical ward. They were convinced that the rising "miasma" from the previously buried cholera victims under the floor were the cause of the infected wounds on the ward. The floor of the ward was dismantled, and the burial ground excavated. Of course, this

made not a jot of difference to the outcome of the patients on the ward. However, the arrival of Joseph Lister, newly appointed professor of surgery in Glasgow, did.

Lister did not believe the miasmic theory. He thought that infections in general, and wound infections in particular, were caused by particulate contamination, a view that was heavily influenced by his contemporary, Louis Pasteur. He started using carbolic acid to cleanse the wounds of his surgical patients.[1 2 3] It seemed promising. He then started taking on cases that almost universally carried a death sentence due to wound infection. One of his first cases was that of a young boy who had been run over by a cart and sustained a compound fracture of his leg. Compound fractures are when a bone breaks, with an associated break in the skin. In the mid-nineteenth century this carried a staggeringly high death rate. The only possible way to avoid the patient dying was amputation of the affected limb, which in itself also carried a high death rate due to wound infection. Lister successfully operated on the young boy with the compound fracture; he reduced the fracture surgically and cleaned the wound with carbolic acid, applying carbolic acid-soaked dressings to the wound.[4] At the time this was considered extremely negatively by his peers. The only possible treatment to their blinkered eyes was limb amputation.

Lister treated more and more cases which other surgeons would not attempt. He was successful, almost entirely because he used carbolic acid to clean and maintain the surgical wounds. After a few years he moved to Edinburgh, where his work continued, and his fame spread. Countless surgeons from across Europe came to see his new technique first hand, most of whom introduced Lister's new approach in their own practice. However, his new approach was not universally accepted. Perhaps predictably, most of his surgical colleagues in London were having none of it. In the end, Lister changed jobs and went to work at King's College Hospital in London. He was met with contempt and hostility by many of his peers. However, this soon changed when they witnessed his work and its outcomes first hand.

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[1] H. C. Cameron, *The Collected Papers of Joseph Baron Lister* (London: Clarendon Press; 1923).

[2] R. Fisher, *Joseph Lister 1827–1912* (London: Macdonald and Jane's Publishers, 1977).

[3] H. Ellis, *The Cambridge Illustrated History of Surgery* (Cambridge: Cambridge University Press, 2009).

[4] J. Lister, "On the Antiseptic Principle in the Practice of Surgery," *The Lancet* 90 (2299) (1867): 353–6.

Lister's work on anti-sepsis and wound cleansing laid the foundations of modern surgery. Today, in operating theatres and surgical departments across the world, "aseptic technique" is practised. This is based on the work that Lister did all those years ago. Perhaps more familiar to non-medics are items in daily use in modern times, including Listerine mouthwash and carbolic soap. A few days before the coronation of King Edward VII of England in 1902, the future king developed appendicitis. In those days, abdominal operations carried a very high mortality. Lister was consulted and advised regarding the antiseptic technique. The king survived, and Lister was showered with honours by a grateful monarch, in addition to those already bestowed by his mother, Queen Victoria, before him.

CHAPTER FORTY-FOUR

ROTTERDAM, 2012

Following our initial collaboration, Bendy Boy and I became great friends with our colleagues in Toulouse. They were bright, enquiring, permissive, and fantastic company. I realised, following our initial visit to their magnificent institution, that we stood absolutely no chance if we competed with them in investigating the HEV story. All we had was a part-time NHS lab that we had to use at night, our eyes and brains, and virtually no money. The guys in Toulouse had a properly funded state-of-the-art lab that covered five floors and more research staff than you can shake a stick at. They also had other significant advantages. Toulouse, as we now knew, is an hyperendemic area for HEV genotype 3, making it the place of choice to study this infection. Equally importantly, and quite uniquely, all their solid-organ transplant recipients (of whatever organ variety) are cared for in a single institution led by a dynamic, highly intelligent man who can speak six languages—seven, if you count the language of HEV. This is my friend Nassim Kamar. I decided there was no point to try to compete with our French friends, and we should, wherever possible, work side by side.

However, we did not go completely naked into the emperor's chamber, as we had the jaundice hotline. This, at the time, was unique (but has since been adopted in some of the NHS), and complemented the strengths of our collaborators in Toulouse. The Toulouse group discovered the issue of chronic infection with HEV in solid-organ transplant recipients; uncovered important aspects of its biology and natural history; and (most importantly from a patient's perspective) how it should be recognised and treated. Our contribution to this process was modest, as we have a tiny and rather disparate (in terms of patient management) transplant population. In contrast, the way we had set up the jaundice hotline gave us very significant advantages in terms of uncovering the epidemiology, recognition, and treatment of acute HEV genotype 3 infection. Thus, although we were very much, and quite literally, the poor partner in the intellectual relationship, our mutual strengths were complimentary. One concrete example of how well we work together is the review paper we

co-authored for *The Lancet* in 2012,[1] one of the most cited papers in the medical literature regarding HEV. It was a great pleasure to work with our friends from Toulouse (and also China) on this paper.

We communicated mostly by email, with occasional telephone calls, and this was functionally pretty successful. However, sometimes communicating in this way is just not sufficient. Following our initial successful visit to Toulouse, we asked them to return the favour. Four colleagues from France came over to see us: three Professors and a senior laboratory virologist. We tried our best to look after them well, and to return their previous generous hospitality in full. We took them to a beach-side bistro, and we wined, dined, and accommodated them (unavoidably and quite willingly from my own pocket). We had an inspiring few hours talking about HEV. They were incredibly polite about the shed.

Following this, I was invited back to Toulouse on a number of occasions. I had no source of funds to cover the costs of these trips, and I did not want to overstretch the generosity of my French friends. It was with this in mind that I applied for the Dame Sheila Sherlock travelling fellowship for a second time. On this occasion, I got my application in before the closing date, and in due course I received a very welcome email saying that the Committee at the Royal College of Physicians in London would be happy if I would accept the full fellowship and two thousand pounds of Dame Sheila's generous legacy. This funded two further trips to Toulouse, which I almost began to regard as my second home. I know where all the decent restaurants and cafes are, as well as all the decent virologists.

I lost the front teeth in my upper jaw many years ago. This has been a personal source of shame, pain (both physical and financial), embarrassment and, just occasionally, enormous hilarity. I was in Toulouse, talking HEV to my friends. We finished early and, for reasons that escape me, we decided to eat dinner at the most ungodly hour, by French standards, of six thirty pm. We went to one of the many fantastic restaurants in the city and, as might be expected at this early hour, the place was deserted. We were the first customers. There were six Toulouseans and I, now (at least in my head) an honorary Toulousean. We sat down, ordered aperitifs and our earlier conversation continued in English, occasional bad French from me, and the language of HEV.

During the course of this conversation, I learned that everyone around the table, including myself, had had themselves tested for previous exposure to HEV. All six of my French colleagues had been exposed to

[1] Kamar et al., "Hepatitis E" (2012).

the virus in the past. I was the only person round the table who had never been exposed, perhaps somewhat predictably given what we knew about the comparative viral pressure of HEV in humans in the Midi-Pyrénées compared to the United Kingdom. After about ten minutes of conversation, I developed an enormous sneezing fit. I had not been unwell, so it was some kind of allergic reaction, or maybe just a bit of French dust up my nose. Whatever the reason, it was extremely violent and persistent, and after five minutes I had to excuse myself or otherwise the table was in danger of being covered in generous globules of fresh English snot.

I retired to the lavatory where the sneezing went on unabated, despite the use of liberal amounts of toilet paper and deep breathing. While in the gents I had a particularly vigorous bout of sneezing while, unfortunately, my mouth was half open. This resulted in my false teeth being ejected from my mouth, landing with a "plop" dead centre in the water in the toilet pan. For a moment, I did not know what to do. Then I realised I had no choice—hand down the toilet, teeth rinsed and cleaned with soap, then rinsed again and again and again in hot water. I returned to the table twenty minutes later looking rather pale and sweaty, but otherwise not much the worse for wear. My French colleagues were unaware of what happened. On my return home, I had myself retested for exposure to HEV, as I knew enormous amounts of HEV genotype 3 had been found in human sewerage. I was negative, indicating that transmission of HEV via potentially infected false teeth recovered from a French toilet is unlikely. An alternative explanation is that maybe French restaurants clean their toilets particularly well prior to opening their doors.

One time I went to Toulouse I was due to take the morning direct flight on a Friday and give a seminar to the whole faculty later that afternoon. Unfortunately, the flight got delayed. First by an hour; then two hours; then four hours. In the end, the flight took off seven hours late, and by the time I arrived it was mid-evening and my seminar had been cancelled. I was rather irritated to say the least. My bad temper was compounded by the fact that the flight was full of Welsh rugby fans who were on their way to watch their team, the Ospreys, play Toulouse, a game that was scheduled for the following day. It does not take too much imagination to guess what the two hundred or so Ospreys fans got up to during the seven-hour delay at the airport—they got pissed as farts and rather over-boisterous. I appeared not to be able to avoid them, despite whichever little corner of the small airport I tried to secrete myself in.

When I eventually arrived in Toulouse my friends came to pick me up. I had a very long face, but the French guys were full of smiles—they had re-arranged my seminar for Saturday morning. Not only that, they had a

special treat for me to cheer me up. They'd bought tickets for the Toulouse versus Ospreys match on the Saturday afternoon. The seminar went well and produced a number of collaborative projects. The rugby match went even better, as to my great amusement the Ospreys were annihilated. To be frank, they did not have much of a chance, as Toulouse are, and were, an excellent team and have won the European rugby competition on numerous occasions. This is not only due to a combination of the quality of their players and coaching, but also the quantity and enthusiasm of their support, which I witnessed first-hand. The place was packed, with nearly thirty thousand vociferous French and two hundred rather quieter Welsh with hangovers. The Toulouse band was at one end of the ground with trumpets, drums, and all manner of instruments singing their hearts out. It was a fantastic way to spend a couple of hours and included a hot dog (Toulouse-style) at halftime. I knew the virological risk, but I took it, and it was absolutely delicious. When I got home on the Sunday, I sent a one-line email: "Je suis un Toulousean."

One of the issues that came up during our meeting and subsequent informal discussions was that of neurological injury (damage to the nervous system) associated with HEV infection. We had seen a few cases of neurological damage in acute HEV infection in patients in Cornwall; our friends had seen some cases in their transplant recipients in Toulouse with chronic infection with HEV. We had both, and quite independently, written up the cases and sent them to numerous neurological and infectious diseases journals. We'd both had the same response— "non": "association does not mean causation"; "implausible"; "not congruent with the interests of the journal's readership"; "too few cases to draw any conclusions."

We agreed to merge our data and write the cases up together as a single paper. This process was achieved within a few days, as it was only a matter of cutting and pasting existing documents and a little tweaking of Nassim's "Franglais." All the leg work had been done by Nassim and myself prior to our mutually futile attempts to get our data published separately.

Together, we had seven cases of patients with HEV infection and associated damage to the nervous system. The range of neurological injury was wide, and in some cases HEV was recovered from the spinal fluid, indicating that HEV might be directly toxic to the nervous system, in much the same way it is to the liver. Most of the patients survived, but some were left with long-term neurological disability, and one patient died. We sent the paper to *Emerging Infectious Diseases*, one of the premier journals in the field. The paper was accepted with minor

amendments only and was rapidly published.[2] Although there had been case reports of neurological injury published previously, mostly from Asia in the context of HEV genotype 1, our paper was the most comprehensive description of HEV and neurological injury by quite a margin. Writing the paper up got me thinking. I started reading neurology journals, particularly those describing Guillain Barré syndrome, a condition we found in one of our seven cases.

I first saw a case of Guillain Barré syndrome thirty years ago when I was working in London. It was a sixty-year-old man who had just returned from a cruise-liner holiday around the Canary Islands. Towards the end of his holiday he thought he had the flu, then he started getting pins and needles in his feet. He turned up at A&E when I was on call, and by this stage the pins and needles were up to his knees and both lower limbs had lost power. He could not walk, could barely stand, and his ankle reflexes were absent. I admitted him to my ward. Two hours later both legs were completely paralysed, his knee reflexes had disappeared, and he could not stand. Over the next few hours the lack of sensation and muscular weakness crept northwards from his groin to his abdomen and then to the bottom of his chest. The patient was petrified and, to be frank, so was I, although I tried not to show it. I knew if the neurological damage continued its ascent, he would not be able to breathe and would end up on a ventilator. I came to see him every hour to test his ventilatory function. It remained reasonably stable, and he just avoided being put on a mechanical respirator. Over the course of the next few weeks his symptoms gradually resolved, but not completely. His feet were both weak, but he was well enough to go home.

Guillain Barré syndrome is a post-infectious polyradiculopathy; i.e. it is an ascending paralysis of the nervous system usually, but not always, starting in the feet that is triggered by an infection. About a third of cases are triggered by *Campylobacter jejuni* infection, the most common origin for which is infected poultry. Some viral infections can also trigger the disease, but in fifty percent of cases no infectious trigger could be identified. What interested me about Guillain Barré syndrome was that, in addition to the cases we wrote up, thirty percent of patients with the condition have slightly abnormal liver blood tests at the start of their

[2] N. Kamar, R. P. Bendall, J. M. Peron, P. Cintas, L. Pruhomme, J. M. Mansuy, L. Rostaing, F. Keane, S. Ijaz, J. Izopet, and H. R. Dalton, "Neurological Disorders: an Emerging Extra-hepatic Manifestation of Hepatitis E Virus Infection," *Emerging Infectious Diseases* 17 (2011): 171 7.

illness.[3] I read quite a lot about Guillain Barré syndrome over the next few months. It's an uncommon condition, in which ten percent end up on a ventilator (sometimes for very many months and occasionally years), many are left with significant long-term disability, and three percent die. I wanted to find a neurologist to collaborate with and reading through the latest papers on the subject left me with a shortlist of five "possibles": one from the United Kingdom, two from Europe, and two from the United States. In addition to their expertise in Guillain Barré syndrome, other criteria were just as important in my intended collaborator. They must be open-minded, have banked samples from a large number of cases from an area I knew to have decent amounts of circulating HEV genotype 3 in the local population, and be willing to work with a slightly unusual and very single-minded impecunious English "virus hunter." After endless calls and emails, I settled on Bart Jacobs from Erasmus Medical Centre in Rotterdam, the Netherlands.

Bart was to prove a good choice. He fulfilled all the criteria in spades, but I also found him to be a lovely fellow member of the human race, and arguably one of the smartest guys I have ever met. Like many doctors and most neurologists, however, Bart is conservative, particularly when it came to prizing out his precious Guillain Barré syndrome blood samples from his freezer, which had been assembled over the course of his twenty-five-year career. To start with, he would only test ten of his two hundred samples from his Dutch Guillain Barré syndrome cohort. As luck would have it, one of them (a case from many years ago) turned out to have had HEV infection when they presented with neurological symptoms. Bart's residual reticence evaporated at this news. All 201 Guillain Barré syndrome blood samples were rooted out of the freezer and tested for HEV, as were 201 samples from controls. Ten cases of Guillain Barré syndrome had HEV infection; none of the controls did. We wrote the paper quickly, which was accepted by the leading neurology journal with minor revisions.[4]

Almost identical data subsequently emerged from Japan and Belgium (genotype 3) and Bangladesh (genotype 1). A causal relationship between

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[3] P. G. Dames, F. G. van der Meché, and R. P. Kleyweg, "Liver Function Disturbances in Guillain-Barré Syndrome: a Prospective Longitudinal Study in 100 Patients. Dutch Guillain-Barré Study Group," *Neurology* 46 (1) (1996): 96–100.

[4] B. van den Berg, A. A. van der Eijk, S. D. Pas, J. G. Hunter, R. G. Madden, A. P. Tio-Gillen, H. R. Dalton, and B. C. Jacobs, "Guillain-Barre Syndrome Associated with Preceding Hepatitis E Virus Infection," *Neurology* 82 (2014): 491–7.

HEV and Guillain Barré syndrome is now beyond dispute.[5] [6] [7] What intrigued me, though, was that in some cases of HEV-associated Guillain Barré syndrome the liver blood tests were normal. This observation was thought provoking because hepatitis E virus, as the name suggests, was considered an infectious disease primarily affecting the liver. However, in some of the cases of HEV-associated Guillain Barré syndrome the liver blood tests were normal and HEV appeared to be causing no damage to the liver whatsoever.

Naturally, the work with colleagues in Rotterdam included mutual visits in person. I had enough money left to cover some of these trips from the Travelling Fellowship because, as needs must, I had been pretty frugal. Dame Sheila, thank you again, this time from the very bottom of my heart.

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[5] J. Fukae, J. Tsugawa, S. Ouma, T. Umezu, S. Kusunoki, and Y. Tsuboi, "Guillain-Barre and Miller Fisher Syndromes in Patients with Anti-hepatitis E Virus Antibody: a Hospital-based Survey in Japan," *Neurological Sciences* 37 (11) (2016): 1849–51.

[6] C. H. Geurtsvankessel, Z. Islam, Q. D. Mohammad, B. C. Jacobs, H. P. Endtz, and A. D. Osterhaus, "Hepatitis E and Guillain-Barre Syndrome," *Clinical Infectious Diseases* 57 (9) (2013): 1369–70.

[7] O. Stevens, K. G. Claeys, K. Poesen, V. Saegeman, and P. Van Damme, "Diagnostic Challenges and Clinical Characteristics of Hepatitis E Virus-associated Guillain-Barré Syndrome," *JAMA Neurology* 74 (1) (2017): 26–33.

CHAPTER FORTY-FIVE

NIJMEGEN AND 'S-HERTOGENBOSCH, 2012

Concurrently with the work on Guillain Barré syndrome, I got interested in a related condition called Parsonage Turner syndrome. Confusingly, this condition also has two other names: "neuralgic amyotrophy" and "brachial neuritis." As a simple non-Neurologist, I prefer the latter, as it describes the condition at hand: brachial (of the arm) and neuritis (inflammation of the nerves). Brachial neuritis presents most commonly in middle-aged males and is caused by damage (of unknown cause) to the nerve plexus under the armpit, resulting in severe pain in the shoulder followed by wasting of the muscles around the shoulder and/or down the arm. The pain can be excruciating and unremitting, and in some cases even large doses of morphine will not relieve it. Some patients recover completely, others are left with a permanently paralysed shoulder.

I was intrigued by this condition for two reasons. Firstly, as in Guillain Barré syndrome, in twenty-five percent of patients with brachial neuritis the liver blood tests are not quite normal at symptom onset. Secondly, five years ago I saw two cases of brachial neuritis in Cornwall, both caused by HEV genotype 3. Both had surfed at the same Cornish beach at around the same time. Although the beach in question is in a fabulous setting of outstanding natural beauty and the waves can be excellent in surfing terms, it is notorious in the Cornish surfing community. The reason for this is that there is a massive sewerage pipe which discharges out to sea, which at times of heavy rainfall releases significant amounts of untreated human effluent into the Atlantic Ocean. We did not know how the two surfers had become infected with HEV. Naturally, we considered HEV-contaminated human sewerage spewing out into the ocean as one possibility, but we were quite unable to prove a definitive link.

It was time to investigate these cases and check all our other cases of brachial neuritis for HEV to see what was going on. We trawled through endless patient records. Bendy Boy trawled through his freezer for residual blood samples. We also teamed up with colleagues from Nijmegen and 's-Hertogenbosch in the Netherlands thanks to an introduction from Bart. These guys are among the world's leading researchers on brachial neuritis.

They got some of their blood samples out of the freezer and tested them as well. Together, of forty-seven cases tested from the United Kingdom and the Netherlands, five had HEV infection and four had minor abnormalities in the liver blood tests, but in one case they were normal.[1] This study is the quickest I have ever done—six weeks from the start of the project to submission of the manuscript—and was subsequently published as a back-to-back paper with the Guillain Barré syndrome data.

I subsequently went on to devise, coordinate, and complete a mammoth study of 118 patients with brachial neuritis with thirty-four collaborators from six different European countries, just under fifty percent of whom had an associated HEV infection. We found that patients in whom the brachial neuritis was associated with HEV had more extensive neurological damage which affected both shoulders and were more likely to have damage to other nerves. This included the phrenic nerve (which innervates the diaphragm) producing intractable breathlessness, and the lumbosacral plexus (located deep inside the pelvis and innervating the lower limbs) producing pain and weakness in the legs.[2] This study took over eighteen months to complete and write up and was a logistical nightmare.

The most recent work in this area was a study dubbed "Operation Blunderbuss." This was a prospective look at all patients presenting to hospital with acute neurological injury, other than that caused by trauma. It was a "shotgun" technique, in which we basically tested all comers presenting with nervous-system damage for HEV to see what turned up. We teamed up with our colleagues in Toulouse and the Netherlands and between us tested 464 consecutive patients for HEV infection. We found eleven patients had HEV infection (genotype 3). Three of the cases had brachial neuritis affecting both arms, which came as no surprise in light of our previous work, and in my mind completely nailed down the causal

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[1] J. J. van Eijk, R. G. Madden, A. A. van der Eijk, J. G. Hunter, J. H. Reimerink, R. P. Bendall, S. D. Pas, V. Ellis, N. van Alfen, L. Beynon, L. Southwell, B. McLean, B. C. Jacobs, B. G. van Engelen, and H. R. Dalton, "Neuralgic Amyotrophy and Hepatitis E Virus Infection," *Neurology* 82 (2014): 498–503.

[2] J. J. van Eijk, H. R. Dalton, P. Ripellino, R. G. Madden, C. Jones, M. Fritz, C. Gobbi, G. Melli, E. Pasi, J. Herrod, R. F. Lissmann, H. H. Ashraf, M. Abdelrahim, O. A. B. A. L. Masri, M. Fraga, D. Benninger, T. Kuntzer, V. Aubert, R. Sahli, D. Moradpour, H. Blasco-Perrin, S. Attarian, R. Gérolami, P. Colson, M. T. Giordani, J. Hartl, S. Pischke, N. X. Lin, B. N. Mclean, R. P. Bendall, M. Panning, J. M. Peron, N. Kamar, J. Izopet, B. C. Jacobs, N. van Alfen, and B. G. M. van Engelen, "Clinical Phenotype and Outcome of Hepatitis E Virus-associated Neuralgic Amyotrophy," *Neurology* 89 (9) (2017): 909–91.

relationship between HEV and brachial neuritis. What was even more interesting was that we found HEV infection in four patients presenting with a stroke, two patients presenting with seizures, one with encephalitis (direct infection of the brain, causing fever and confusion), and one with VII and VIII nerve palsy (nerves supplying the face and ear, causing face drop and deafness). Again, there was little or no evidence of damage to the liver in these cases, and in seven the liver blood tests were normal.[3] A causal relationship between HEV and these latter cases remains to be proven.

During the course of the above work I visited the Netherlands on several occasions. The final time, instead of staying in a hotel I was invited to stay at my colleague's house with Jeroen van Eijk and his lovely family. I felt honoured to be invited into their home. Jeroen, though, worked me hard—data to check; papers to draft and submit; and a seminar to deliver to the faculty at the University Hospital in Nijmegen. I did my normal lecture and then sat down with three senior faculty members, all of whom were neurologists. There followed a conversation which ranks as one of the most stimulating of my academic career. Three top Dutch neurologists and a slightly crazy, single-minded English virus hunter. We talked about all sorts of stuff, including the neurotropism (ability to live and replicate inside nerve cells), the range of possible neurological injury, and how we might go about tracking it down with various studies. The discussions went on for several hours, until it was time for them to leave.

Jeroen, who knows me well, knew I was itching for a beer and to chain smoke two fags, as I normally do straight after a lecture. On this occasion, it had been delayed by the conversation. We jumped in his car, and off we went to a local bar. After we had finished our refreshments Jeroen asked me what I would like to do. I told him that I would like to visit the war cemeteries just outside Nijmegen where the mortal remains of those who had died in the Second World War were buried. I wanted to go there as I knew that many paratroopers from the Allied forces (especially Canadians and British) had been killed in Operation Market Garden, made famous by the film *A Bridge Too Far*. This was an ambitious and rather ill-advised Allied attempt to secure a crossing over the Rhine into Germany towards

[3] H. R. Dalton, J. J. J. van Eijk, P. Cintas, R. G. Madden, C. Jones, G. W. Webb, B. Norton, J. Pique, S. Lutgens, N. Devooght-Johnson, K. Woolson, J. Baker, M. Saunders, L. Househam, J. Griffiths, F. Abravanel, J. Izopet, N. Kamar, N. van Alfen, B. G. M. van Engelen, J. G. Hunter, A. A. van der Eijk, R. P. Bendall, B. N. Mclean, and B. C. Jacobs, "Hepatitis E Virus Infection and Acute Non-traumatic Neurological Injury: a Prospective Multicentre Study," *Journal of Hepatology* 67 (5) (2017): 925–32.

the end of the war. The paratroopers and other forces were cut off, and hundreds died. The cemetery at Nijmegen containing their remains, like all such war cemeteries I have visited, are kept immaculately. The crosses marking the final resting places were pristine white, equally spaced, and exactly symmetrical in whichever direction the eye looked. What a waste of humanity.

After visiting the cemetery, I asked Jeroen to take me to a flower shop as I wanted to buy his wife some flowers to show my appreciation for her hospitality. We arrived at the flower shop in Nijmegen just before it was due to close. I bought a large bunch of yellow roses, scented. I gave the elderly lady in the flower shop a fifty euro note, and as she prepared my change we started talking. I told her I had just been to the cemetery, and the feeling of human waste it had given me. She disagreed.

"No," she said. "If it wasn't for those young boys, my life would be completely different and almost certainly much worse."

She then recounted the following story. After the war, every year the flower shop, at that time run by the old lady's mother, was visited by a retired major from the British paratroopers. Every year he bought five bunches of flowers. These he took to the nearby war graves and laid them by the foot of five of the headstone crosses. This was out of respect for five of his men who had been killed in the battle at Nijmegen. They were five brothers. Every year he came and did the same. Then he stopped coming. He had presumably died himself, so the old lady took five bunches of flowers and laid them by the brothers' graves, and she now does the same every year on the anniversary of the battle of Nijmegen.

"These are now my boys," she told me. She offered me my change, which I refused.

"That's for your boys' flowers," I said.

CHAPTER FORTY-SIX

ROY

At the hospital we have an informal early-warning/monitoring system for patients with new onset of abnormal liver blood tests. The way this works is that colleagues in the biochemistry lab send me an email or call when they find abnormally high liver tests, above a certain threshold. I then get on the case. The first thing to do is find where the patient is and what their story is. Adopting this approach, alongside our rapid-access jaundice hotline, has resulted in many new cases of HEV infection being discovered, often at a very early stage. Such was the case with Roy.

It was late one afternoon when I got the email about Roy's blood tests. They were moderately abnormal, but he was not jaundiced. I saw that the blood tests had been ordered the day before by Roy's general practitioner. I also saw from the records that Roy was fifty-eight—the correct age and sex for a case of HEV, and the pattern of liver blood test abnormality would fit. To my mind, the likeliest diagnosis was HEV infection until proven otherwise. Now I had to track the patient down. I checked the hospital computer system and found that Roy had been admitted to hospital earlier in the afternoon. I was curious about this, as the liver blood test abnormality was not so severe to warrant hospital admission on its own. I needed to go and find him and see what was going on. I was due to be on call that evening, so I started early and popped over to the admission ward to take a look.

When I found him, I understood why he required hospital admission. He had very severe pain in the shoulders, to the extent that he was crying. He'd been given some painkillers, which had not worked. I found the nurse looking after him and prescribed a decent dose of morphine. This was given by injection. Within ten minutes he was more comfortable, but still had significant residual discomfort. He was, however, now able to tell me what had happened to him. Roy said that he worked for the local council as a gardener. Three days previously he had been cutting an overgrown area with a ride-on strimming machine. During this process, his machine, in addition to clearing the overgrown weeds and brambles, had mashed up a dead hedgehog. The hedgehog got severely smashed by

Roy's machine, and he ended up covered in blood and guts from the dead animal. Roy had previously been very fit for his years. He was of Dutch extraction, as his father had moved to England after the Second World War and married a Cornish girl. Roy drank moderate amounts of alcohol and ate copious amounts of salami, a habit shared by his late father.

I tried to examine his shoulders, but they were very sore. I got little useful information from this futile attempt. I thought Roy had hepatitis E infection, but the main area of injury was not the liver, it was the nervous system. My provisional clinical diagnosis was HEV-associated brachial neuritis. To confirm this, I took some blood from him and popped over to the microbiology lab with it. It was just before five pm, when the lab doors are locked and everybody heads for the car park. I found one of the lab technicians and told him the story. I gently twisted his arm to do a HEV IgM strip test. This gives provisional, and usually very accurate, result in five minutes. I waited in the lab, looking over the technician's shoulder. It was positive—my diagnosis was correct. I then picked up the phone to the National Reference Centre lab in London. I arranged for Roy's samples to be sent by courier and formally tested for HEV the next day. This would include a PCR test to see if Roy still had HEV in his blood stream, or whether he had already cleared it with the virus having done a sneaky "hit and run" on his nervous system.

The next day, Roy was much worse. He was a little unsteady on his feet, but more troublesome was that he had become breathless. I arranged various tests to work out why. These showed that, in addition to damage to the nerves around the shoulders, his HEV infection had severely damaged both his phrenic nerves. The phrenic nerve innervates the diaphragm, and there are two of them, left and right. When the phrenic nerve is damaged, especially when both sides are involved, as in this case, the diaphragm cannot fulfil its normal function to help us breathe. The patient becomes breathless at rest, and even gentle exercise such as walking becomes difficult or impossible. Roy could barely even walk to the ward toilet. That afternoon, the results came back from London. Roy had large amounts of HEV in his blood stream. It had not just done a hit and run—the virus was still inside, continuing to damage his neurological structures.

I considered what to do. I thought treatment with an antiviral drug might help, but I was in uncharted territory here. This case was, at the time, unique as antiviral therapy had not previously been used as a treatment for such a case. I picked up the phone and spoke to Bart Jacobs in Rotterdam and Nassim Kamar in Toulouse. I also asked advice from my friends and colleagues in Nijmegen, who are the world's leading experts in brachial neuritis. We then did a conference call together to discuss what

should be done for the patient. Following these deliberations, I decided to treat Roy with ribavirin, an antiviral drug to which HEV is very sensitive. I reasoned that this drug should clear the virus from Roy's body quite quickly, although it's likely effect on Roy's neurological damage was uncertain. I gave Roy ribavirin for one month. It killed off the HEV in Roy's body within a few days, but unfortunately had no effect on the existing damage to his nervous system. Three years after the event, Roy still cannot lift either arm above shoulder lever, has considerable residual pain requiring regular medication, and struggles to walk one hundred yards.

I still see every few months in my clinic. He knows I cannot help him, but I have not given up. I recently went to give a lecture in Nijmegen, and I showed them a video of Roy's residual neurological damage. They told me that they have a unique method of rehabilitation for cases like Roy's which is often successful. This is not available on the NHS, so when I get the time I'll take him over to see if they can help. Roy was happy to have a video of his condition made. He consented for me to show it at the various meetings and conferences I attend. When I have done so, I always give him a quick call to check how he is, and to tell him he is now a film star in Berlin or Barcelona, or wherever it is I have been talking.

We subsequently had the HEV we found in Roy sequenced (genetically fingerprinted). The result was curious. The HEV found in Roy was not the usual strain found in UK pigs or humans. Somewhat ironically, it originated from the Netherlands, but Roy had not visited his mother country for many years. I wondered how Roy had become infected. Maybe it was the salami he was so fond of eating? It certainly wasn't from the bits of dead hedgehog he'd been covered with three days before presentation, as the incubation period for HEV is two weeks minimum, and HEV has never been found in hedgehogs, although I am not sure anybody has looked.

CHAPTER FORTY-SEVEN

STUDENTS

At the start of my investigation into the HEV story I did most of the work myself, with laboratory support from Bendy Boy and a single helpful, but very part-time, lab technician. Doing decent research is time consuming. There are endless forms to complete; endless data to capture and accurately record; statistical analysis; writing and submitting the papers; and responding to peer review, which in extreme cases almost doubles the work required to take the project to completion. I invited and cajoled the junior medical staff on my clinical team to help. It was to prove a relatively fruitless task, as they were already completely overwhelmed by clinical work and frequently leaving for home at eight or nine pm when they should have left at five. I understood this, so I did not push them too hard. I also understood that, these days, unlike previously, publishing clinically relevant papers is not a prerequisite for obtaining the rank of consultant sausage-factory attendant. Inquisitiveness appears now not to be encouraged in the "modern" NHS.

I tried to obtain grants for my work, so I could fund a team of helpers to relieve the pressure on me a bit. I applied twice to the Medical Research Council with HEV projects of good quality. These applications literally took months of preparation and hundreds of hours of my time, which mostly had to be done in between my clinical work. The applications were judged as excellent, but not funded. One of the reasons is that top-end funding bodies such as the Medical Research Council very infrequently award significant grants to institutions outside the "magic-circle" of Oxford, Cambridge, and London. Cornwall is a long way from these august institutions, both intellectually and geographically. Basically, to these guys, an application from sleepy old Cornwall is virtually dead in the water before submission, no matter what the quality. I did manage to get a small grant (the Vera Down Grant) from the British Medical Association to study the neurological complications of HEV, for which I was very grateful.

It was under these circumstances that I turned to the medical students for help with my work on HEV. At first, it started in a small way, and I

offered a three-week special study unit in hands-on research. The three weeks were spread throughout the academic year and was a very short period of time in which do anything useful, but most of the students I involved in this way did many hours of additional work in their own time to complete the project in a timely fashion. I became more and more enthusiastic about involving the students as members of the HEV research team, and it was not long before I had students knocking on my door volunteering to help. It has been an enormously satisfying experience working in this way with these bright young doctors to be. I worked the students hard, but I looked after them well. They have been co-authors on sixty-two occasions on twenty-six of my peer-reviewed papers. After qualification, many of them have retained an interest in research and are pursuing an academic career in various parts of the United Kingdom and abroad.

During the course of engaging the students in this way, I have met some remarkable individuals. The first who comes to mind is the Major, who pitched up in my office one day at the start of his research attachment. Looking at him it was immediately obvious he was a mature student. It was also clear that he was not the normal run-of-the-mill student, mature or otherwise. He introduced himself, and then I asked him to sit down next to me at my desk in the shed.

"What did you do before you started medical school?" I asked, looking at him over the top of my specs.

"I used to kill people, Dr Dalton," was his reply.

It transpired that the Major had previously been a Major in the Royal Marines (part of the British Navy) for some years. I suspected he'd been in the Special Forces, but he declined to answer when I asked him directly. Instead, he looked me in the eye and told me that if he answered this question either way he would have to kill me. The Major is a black belt at more than one martial art, and I would not have liked to have met him on a dark night when he was operative. The Major brought many qualities to the research team: he helped man-manage the other students in a marvellously constructive and light-handed way; his logistics skills and drive were of the highest Royal Marines standards; and his intellect was sharp and enquiring. I pushed him very hard, as I knew he could take it. I also was aware that he'd found much of his previous education at medical school somewhat disappointing.

In addition to his considerable intellect, the Major brought with him a military flavour to our problem solving. When we arranged to meet in the shed, it wasn't nine am in the morning but "zero nine hundred hours." Projects got named in military-style jargon and included such projects as

"●peration Surfers Back" and "●peration Blunderbuss." However, the most memorable was "●peration Pumphandle." We had discussed the work of John Snow at length, and now we had a sufficient number of cases to analyse we decided it was time to take a serious look at the geographical location of the cases of HEV, much as Snow had done in the London cholera outbreak 150 years previously. After a serious discussion in the shed, which started at zero eleven hundred hours, we agreed a plan of action, logistical support, and timing. The plan was to put our HEV cases on a map and look for evidence of geographical clustering and determine the relationship to a number of variables, including the distance from the adjacent pig farms and coast, socioeconomic status, and climatic conditions such as heavy rainfall. We used cases of other causes of hepatitis as controls. The study was named, appropriately enough, ●peration Pumphandle, and involved appointing two "liaison officers" (students) to engage with the local Health Protection Agency and the Met ●ffice. The projected completion date for ●peration Pumphandle was six months hence.

The data that the Major produced, with significant support from other students, were interesting. What he showed was that, compared to controls, cases of HEV were significantly more likely to live within 1.5 kilometres of the Cornish coastline. There was no relationship to distance from pig farms or climatic/socioeconomic variables. We pondered why this might be and wondered about possible beach contamination with HEV.[1] In the end, the Major came up with the "pig toilet hypothesis," which in outline is as follows:

- Pigs excrete huge amount of HEV in their stools
- During periods of rainfall this is flushed from the fields in which they are reared into nearby streams
- HEV-contaminated stream water makes its way towards the coast and contaminates the local beaches
- The reason cases map to the coast might be that these individuals are more likely to use the beaches than controls and become infected due to the environmental contamination

[1] J. G. Hunter, R. G. Madden, A. M. Stone, N. ●sborne, B. Wheeler, L. Vine, A. Dickson, M. Barlow, J. Lewis, R. P. Bendall, N. X. Lin, W. E. Henley, W. H. Gaze, and H. R. Dalton, "Coastal Clustering ●f HEV; Cornwall, UK," *European Journal of Gastroenterology & Hepatology* 28 (3) (2016): 323–7.

This is just a hypothesis—it may be right, it may be wrong. However, what is beyond doubt is that the Major holds the current record for the length of time it took from starting the project to getting it published. Instead of the six months we had agreed at our operational meeting in the Shed, the project took four and a half years. This compares unfavourably with the current record of five months held by two subsequent students. The Major had not factored in the vagaries of the medical research peer-review process. I am not sure what the Major's commanding officer would have said to him if he had performed like this in the Royal Marines. I just smile at the irony, but, of course, will never ever let him forget it, and gently tease him at every available opportunity. The Major went on to co-author eight papers with me prior to qualification, a remarkable achievement, and quite rightly was awarded the medical school's research prize in addition to numerous other awards. He's now long qualified, and still involved. Whenever I get really stuck with something, I almost invariably give the Major a call to get a naval view, a process that is, of course, quite distinct from navel gazing.

Most of the students were enthusiastic about being involved in virus hunting. This was not "normal" teaching for them—we were tracking down a potentially lethal virus and trying to catch glimpses of what it sometimes did to our fellow human beings. I suppose the educationalists of today would call it "learning in action" or some such thing. I think the key to it was a combination of intellectual engagement and, on occasion, sheer and unbridled enthusiasm. A good example of the latter is as follows. We decided to look at the way patients infected with HEV tried to fight off the infection, i.e. their immunological responses to HEV. To do this, we needed samples from as many patients as possible who we knew for certain had been infected and become unwell. About forty patients agreed to help. The problem was, they were scattered all over Cornwall and a couple had moved to neighbouring Devon, and we needed to get the samples on the same day to analyse them in an appropriate way. This was a logistical issue, solved by the Major who split us (a couple of young doctors, three students, and myself) into three teams. The Major and I went east, and the other two teams covered central and west Cornwall.

The latter group of field researchers comprised a young registrar and a third-year medical student. We arranged for the patients to attend the West Cornwall Hospital in Penzance. The medical student was extremely enthusiastic and wanted to get the most and biggest samples. He achieved both, but in the process of trying to force a patient's blood into the blood sample tube, his enthusiasm escaped him a little. He wanted to fill the tube to the brim. Unfortunately, he momentarily forgot the laws of physics and,

on forcing the last drop into the tube from the syringe, the rubber bung came off the top of the test tube and the bloody contents ended up all over the patient, student, and walls of the room he was using. The mess was duly cleaned up, with apologies all round.

During the course of my work on HEV, my students have presented their findings to countless national and international hepatology meetings. Some of these meetings are enormous and the bigger ones are attended by over ten thousand hepatolologists from across the world. These conferences can be unnerving for the students due to their sheer size. The choice of what to attend is also bewildering, as commonly there may be ten or twelve sessions running concurrently. However, what the students find most stressful is presenting their research work to their senior colleagues, many of whom have been qualified for thirty or forty years. The audience for these presentations varies from a couple of hundred to a couple of thousand. Naturally, I prepare the students well before setting off, a process which takes several "dry runs" and a considerable amount of tinkering with their presentation slides. The students, to a man and woman, have excelled themselves in this process—a real pleasure to witness.

On one occasion, I was worried about one of my students. The content of her presentation was outstanding, but her delivery was not. She was rather shy and very nervous, and her voice was very quiet in volume and monotonous in quality. I considered how I might best help her. I decided we better have a dry run in the actual lecture hall she was due to speak in: it was an enormous two thousand-seater at the Conference Centre in Amsterdam. We sneaked in there at lunchtime to do a dry run before the live presentation later that afternoon. There were a few American hepatologists in the front row of the lecture theatre, who were using the empty theatre for an ad hoc meeting. I asked them if they would mind my student practising her lecture, and explained that she was young, nervous, and this was her first time. They asked me if they should leave. I said no, but if they would like to listen and give her some feedback, we would both appreciate it very much. The student did her dry run. The verdict from our US colleagues was: content, brilliant; execution, too quiet and monotonous. Agreed, but how could we improve this with only two hours to go? In the end, I took her around the back of the conference centre to find a completely private spot, with nobody else around. We then spent five minutes talking to each other at increasing volumes. We chose a single word with which to do this voice-coaching exercise and, given the student's Welsh heritage, the word we chose was "tidy." By the end we were both shouting "tidy!" at each other at the tops of our voices.

Thankfully, nobody witnessed this rather bizarre event, and the student went on to do an outstanding presentation to an audience of approximately fifteen hundred hepatologists later that afternoon. Very tidy indeed.

My most recent project is to study deaths from HEV infection, and factors which predict this outcome. The project involves six European countries, plus the United Kingdom. Understandably, the logistics are challenging and require a sizeable team of helpers. Over a couple of months, I put together a team of young doctors from across the United Kingdom, many of whom had previously been my students. Their key task was to help with UK data collection. We decided that we needed to meet to discuss the details of the project and chose the John Snow public house in London as a venue. The intention was to iron out what needed to be done over lunch, and then have some photos taken next to the famous pump handle situated just outside. We had a productive meeting, but the photos were not possible as the local council had recently had the pump handle removed from the street and placed in some museum.[2] I was pretty disappointed about this. The more I thought about it, the crosser I became. It seemed to me an act of wanton historical vandalism. Soho is now a very trendy and expensive place to live with top-end shops, restaurants, and hotels. This was not so in the past, as in the time of Snow it was a place of great poverty and subject to large outbreaks of all manner of infectious diseases, in addition to cholera. In my view, taking the pump handle away from Broadwick Street has impoverished the historical context of the area, as now, to all intents and purposes, it is just another upmarket area of central London. When the pump handle was in place together with its descriptive plaque it reminded residents and visitors that this was not always the case. I reckon John Snow would have also been pretty cross about this, as was a visitor from Cincinnati, a doctor, who we met that afternoon and had travelled to London from the United States specifically to see the pump handle in situ.

[2] After an absence of several years, the pump handle was returned to the street outside the pub in 2018.

CHAPTER FORTY-EIGHT

BLOOD DONORS II

Because HEV infection is very common and very commonly asymptomatic, it is no surprise that it has found its way into the human blood supply. What has astonished colleagues in the blood transfusion community is the very high numbers of viraemic donors (donors who have virus in their bloodstream at the time of donation) found in many countries. HEV is found in one in six hundred blood donors in the Netherlands,[1] one in eight hundred in Germany,[2] one in two thousand in France,[3] one in nine thousand in the United States,[4] and one in 14,250 in Scotland.[5] Transfusion-related HEV infections have been documented in numerous countries, including the United Kingdom, France, Germany, and Japan.

In a study in southeast England, one in 2,848 of 225,000 donors tested were viraemic at the time of donation.[6] Donors had no symptoms and the liver function tests were frequently normal. Of forty-three recipients inadvertently given HEV-contaminated blood products and followed up,

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[1] H. L. Zaaijer, "No Artefact, Hepatitis E is Emerging," *Hepatology* 62 (2015): 654.

[2] D. Westhölter, J. Hiller, U. Denzer, S. Polywka, F. Ayuk, M. Rybczynski, T. Horvatits, S. Gundlach, N. Fischer, M. M. Addo, S. Peine, B. Göke, A. W. Lohse, M. Lütgehetmann, and S. Pischke, "HEV Positive Blood Donations Represent a Relevant Infection Risk for Immunosuppressed Recipients," *Journal of Hepatology* 2018 69(1) (2018): 36-42.

[3] P. Gallian, S. Lhomme, Y. Piquet, K. Saune, F. Abravanel, A. Assal, et al., "Hepatitis E virus infections in blood donors, France," *Emerging Infectious Diseases* 20 (2014): 1914 17.

[4] S. L. Stramer, E. D. Moritz, G. A. Foster, E. Ong, J. M. Linnen, B. M. Hogema, et al., "Hepatitis E virus: Seroprevalence and Frequency of Viral RNA Detection among US Blood Donors," *Transfusion* 56 (2) (2016): 481 8.

[5] A. Cleland, L. Smith, C. Crossan, O. Blatchford, H. R. Dalton, L. Scobie, et al., "Hepatitis E Virus in Scottish Blood Donors," *Vox Sanguinis* 105 (4) (2013): 283 9.

[6] P. E. Hewitt, S. Ijaz, S. R. Brailsford, R. Brett, S. Dicks, B. Haywood, et al., "Hepatitis E Virus in Blood Components: a Prevalence and Transmission Study in Southeast England," *The Lancet* 384 (9956) (2014): 1766 73.

the transmission rate was forty-two percent, but only one patient developed symptomatic hepatitis. Blood products were given to ten patients with varying degrees of immunosuppression, some of whom went on to develop asymptomatic chronic infection requiring treatment. Unsurprisingly, patients who were given blood products with high HEV RNA concentrations were more likely to become infected. In other countries, recipients given infected blood have sometimes had a poor outcome, with a number of deaths.

Given the high numbers of viraemic donors in many developed countries, the issue of whether donors should be screened for HEV has become a hot topic in the blood-transfusion community. Antagonists argue that screening is not cost-effective, as HEV generally produces an asymptomatic or self-limiting infection in recipients. In addition, as transfusion-related infection accounts for only one percent of infections with HEV genotype 3, screening will have a minimal effect in reducing the overall burden of infection in humans, ninety-nine percent of which is caused by the consumption of infected foodstuffs and environmental exposure. In contrast, screening protagonists argue that we have been unwittingly infecting recipients with HEV (probably for very many years) and should we knowingly continue to do so when our understanding of the epidemiology and adverse effects in humans is still incomplete?

The protagonists are winning this debate, entirely appropriately in my view, as universal HEV screening of blood donors was introduced in Ireland in January 2016 and targeted screening (in blood products destined for "high-risk" groups, including the immunosuppressed) in the United Kingdom in March 2016. Initial data from the UK indicated that the incidence of infected donors was an order of magnitude higher than anticipated. As a result of this, and other factors, as of April 2017 in the United Kingdom every blood donor is now screened for HEV before their blood is used. The Netherlands and Switzerland have also recently adopted the same approach. In virtually every other European country the issue of screening blood donors for HEV is under active debate. The exception to this is Denmark. The Danes have decided that screening for HEV is not appropriate,[7] despite having the highest pig/human ratio anywhere on the planet, and data which shows that about one in three thousand of their blood donors have the HEV in their donated blood.

We appear to have come a long way in our understanding of HEV in developed countries. Only ten years ago it was thought to be completely

[7] D. Domanovic, R. Tedder, J. Bhunel, H. Zaaijer, P. Gallian, C. Niederhauser, et al., "Hepatitis E and Blood Donation Safety in Selected European Countries: a Shift to Screening?" *Euro Surveillance* 22 (16) (2017): pii: 30514.

irrelevant in this geographical context. We now know this was quite wrong and are currently spending millions screening our donors to keep our blood supply safe. How come HEV slipped under our radar?

CHAPTER FORTY-NINE

THE INVISIBILITY CLOAK

HEV is an unusual virus for many reasons. Now HEV can be cultured relatively easily, the basic biology of the virus is starting to emerge. One way in which HEV behaves is fascinating and, for me as a simple non-virologist, translates to how the virus behaves clinically in human beings. When HEV enters a human cell, like other viruses it hijacks the cell's reproductive system to make millions of copies of itself. When this process is complete, the HEV progeny need to exit the human cell to find other human cells in which to continue their prodigious propagation. The exact mechanisms of cell exit are not completely understood, but what we do know is that when the HEV progeny leave human cells they steal a bit of the host human cell membrane during the process, which forms a protective "pseudo-membrane" around the virus as it enters the human blood stream.[1] In other words, it covers itself in an invisibility cloak, analogous to the one used so successfully by Harry Potter.

This is a neat trick and may explain quite a bit about how this virus behaves. To my simplistic and non-virological mind it may explain, for example, the difficulties we had with the first and second generation of diagnostics for HEV, which were frankly hopeless. It is tricky to develop diagnostic tests for a virus that hides in this way. Also, HEV genotype 3 hides in many places in human beings, and it has been quite difficult to spot it—maybe the invisibility cloak is the reason. Examples where HEV hides include blood donors, transplant recipients, and patients with various neurological syndromes. HEV has been hiding successfully in these places for a long time and has been playing hide and seek with us humans for decades. Until recently, HEV has been winning the game, but now we know. It is hiding under Harry Potter's invisibility cloak.

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[1] Z. Feng and S. M. Lemon, "Peek-a-boo: Membrane Hijacking and the Pathogenesis of Viral Hepatitis," *Trends in Microbiology* 22 (2) (2014): 59–64.

CHAPTER FIFTY

WASHINGTON DC, 2012

As time went by and the HEV story began to unfold, I got more and more invitations to deliver lectures at international conferences to present my findings and overview. At first, this was mainly in Europe, but then they came from all over the world. I was somewhat bemused by all the fuss, but I willingly accepted the invitations and started jetting off all over the place. I took study leave for some of this work, but as the invitations flooded in I soon used up my ten days NHS allocation and had to take many of these invitations on my own annual leave. I tried, wherever possible, to mitigate the loss of my holidays by staying on a few extra days at selected venues I was invited to in order to have some personal downtime. In the end it got out of hand, and I had to limit myself to ten lectures per year. I was sorry to decline many kind invitations, but I had no choice.

Whenever I give a lecture or seminar, irrespective of whether the audience is five or five thousand, I invariably get nervous. I pace up and down a lot and do last-minute tweaks to my presentation slides. I make friends with the IT technician, and then go through my slides with them to make sure my clinical videos work on the host IT system. The reason for this is that I was once giving a lecture in Paris, and a clinical video (of Roy) was the denouement. I pressed the button to start the video and nothing happened. I pressed the button again and again: nothing, zero, zip, *de nada*, *rien*. I stood there like a lemon and had to verbally explain the video contents. I wanted the ground to open and swallow me whole.

I have additional rituals which I always observe when giving a talk. I have the slides for my talk in three formats: on a memory stick which never leaves my trouser pocket; on my laptop; and I email it to myself as well. I sneak into the lecture theatre before the session begins and play with the slide controls at the lectern. I also get a feel for the place in which I will talk. I look the room over and choose a point on the back wall that I will address when talking. I always go for a pee just before entering the lecture theatre, irrespective of whether I have received the appropriate signals from my bladder or not. I empty my trouser pockets, otherwise I unconsciously jangle my loose change when in full flow. Just prior to

standing up I become quite anxious and tachycardic, and I have the sensation that I want to urinate. My bladder is, of course, empty. My mouth dries. I take a sip of water at the lectern. Then I begin. Once my first slide is gone the nerves disappear and I'm away. I am not sure why I get so anxious, as I have delivered lectures hundreds of times, and I know I am the master of my brief. I guess it's just a physiological response which is a prerequisite for me to deliver a talk of high quality. When it's over, I take the questions, and then have an overwhelming urge to drink a small beer and chain smoke two fags.

I realise that I am only as good as my last lecture. I spend many hours thinking about my audience and adjusting the talk to their level. The talks are always in English, which thankfully is the language of modern medicine. I very frequently give lectures to an audience where English is not their native tongue and whose comprehension of it varies from excellent to virtually non-existent. I therefore make sure I talk slowly and have a minimum of writing on my slides but plenty of pictures. Getting the balance of such a talk correct is not easy. I need to make my presentation accessible to as much of the audience as possible, without patronising the English speakers. I have enormous admiration for my overseas colleagues who have to stand up and deliver a lecture in their non-native tongue. Generally, the Dutch are particularly good at this, the French less so. I once attempted to give a lecture in French to my colleagues in Toulouse. It was a disaster. They said: "Harry, please stop! Do the talk in English!" At least I tried.

When talking, I try to leaven my presentation. What I mean by this is that when an audience is listening to a lecture, after ten minutes or so many of the audience start to "drift." Their attention levels can dip to virtually zero. This is a normal human response in this situation. To minimise this, I utilise a number of techniques. Sometimes I put a "blank" slide in at eight minutes. Sometimes I put a slide of a painting or photograph in that is completely unrelated to the topic under discussion. These I term "mental break" slides. They bring back the audience's attention before they have a chance to drift away into their subconscious selves. I tell the story about three French and two English on a beach in Cornwall betting on HEV with the prize of champagne, and it mostly gets a laugh. I also use videos of my patients (with their consent). These are patients who have had neurological damage caused by HEV and are quite dramatic and attention grabbing. My favourite is Roy's video, which has been shown countless times across the world, much to his amusement. My approach would appear to work as they keep inviting me back.

One of the interesting things about the unfolding HEV story has been the differential rates in which colleagues have switched from the previous received wisdom of HEV being a rather exotic tropical disease, to the new paradigm of porcine HEV being a significant health threat in developed countries. The French and Bendy Boy and I led the way. It was accepted early by the Dutch and Germans. Most other European countries have been a bit slower on the uptake, particularly those of Eastern Europe. The Danes have tried to ignore it. However, most colleagues in the United States still do not get it. I am not sure why this should be. Maybe it's to do with intellectual arrogance, an "if it was not discovered in the United States, it does not exist" type attitude. Maybe it's because there are no licensed diagnostic tests for HEV in the United States: "we cannot test for it, we do not see it, therefore it does not exist." Or maybe it is a combination of the two. Whatever the reason, the thinking about HEV in the United States still lags considerably behind that in Western Europe.

I have been invited to the United States to lecture on HEV on only three occasions. The first time was to the Centers of Disease Control and Prevention in Atlanta. This was in the early days. I told them what I thought, they disagreed, and I got a roasting. This was followed some years later by an invitation to the National Institutes of Health in Bethesda. This was before Bob Purcell had retired, and the reception here was much more positive. The last time I went was to the Food and Drug Administration (FDA) in Washington DC. This latter meeting sticks in my mind. The reason for the meeting was to discuss the possible testing of US blood donors for HEV in light of the emerging data from Europe. I was asked to talk for twenty minutes, and I prepared my lecture slides carefully, using my usual format. What I had not realised was that this was a formal committee meeting. The whole thing was videoed, oaths had to be sworn, and the main audience was twenty or so members of the FDA blood safety committee, all of whom were suited and booted. I had not appreciated the formality until the meeting had started. Shit! I'd included my story about the three French and two English betting on HEV. I did not have the opportunity to take it out before I was scheduled to talk as I was third up, just before the mid-morning break. I had to give my talk as it was. The committee members, previously dead serious and straight-faced, laughed like drains at the story.

I needn't have worried. They voted to explore testing of the US blood supply,[1] and subsequently one in nine thousand US blood donors were

[1] https://www.healio.com/infectious-disease/gastrointestinal-infections/news/print/infectious-disease-news/%7Bfbb549f8-85bb-4fcf-9b0c-d3b2d493006 3%7D/fda-panel-votes-to-specify-risk-for-hepatitis-e-in-blood-transfusions

found to be infected with HEV genotype 3 at the time of donation.[2] This latter observation would suggest that I was correct when talking to the Centres of Disease Control five years previously. But best not rub it in too much. I'm just a simple country doctor from Cornwall.

[2] Stramer et al., "Hepatitis E Virus," 481–8.

CHAPTER FIFTY-ONE

SWITZERLAND AND GERMANY, 2014

The European Association for the Study of the Liver (EASL) was established over fifty years ago, and among the founding fathers and mothers was Dame Sheila Sherlock. EASL's mission[1] is:

> to be the "Home of Hepatology" so that all who are involved with liver disease can realize their full potential to cure and prevent it. In particular, EASL: promotes research in the science of liver disease (Hepatology); provides state-of-the-art education for physicians and scientists; fosters public awareness of liver diseases and their management; acts as an adviser to European Health authorities; facilitates scientific exchanges and catalyses European multi-centre studies; and supports young investigators to ensure that the liver remains at the forefront of research.

EASL's headquarters are in Geneva, Switzerland, and it is from here that the annual meeting is organised. It is also the headquarters of the official journal of EASL which is called the *Journal of Hepatology*, the leading journal in the field, with a high impact. It is pretty difficult to get a paper accepted by it; I had tried on a number of occasions, and (until last year) all my submissions were politely, but swiftly, rejected. It was thus with utter astonishment that I received a letter from the journal asking me to become a member of the editorial board. I thought they had made a mistake, so I called the editor. No, there was no mistake, they wanted me on the board. I was humbled by this invitation and could not quite understand it. The irony of all their previous rejections of my work would not leave me. I accepted the invitation.

As part of their educational remit, EASL produce clinical guidelines for the management of various liver complaints. The guidelines are exhaustive in detail, pan-European in scope, and regularly updated and written by the leading experts in the field. They inform current practice in

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[1] "Why does EASL Exist?" EASL, http://www.easl.eu/discover/what-is-easl/why-does-easl-exist

a fundamental way. The portfolio of liver complaints for which there are EASL guidelines is comprehensive. I received an invitation last year from EASL, asking: "would you be prepared to be chairman of the Clinical Guidelines Group for HEV?" I agreed. Now I was completely humbled. The first HEV Clinical Guidelines were finally published [2] after over eighteen months of hard work with five colleagues from Europe, including two from Germany (see Appendix 1). Hopefully, they will help clinicians across Europe and further afield take the issue of HEV infection more seriously, with advice on clinical features, diagnosis, treatment, and prevention.

I studied German when I was at school. I was not particularly good at this language, despite spending two weeks on German exchange which included me staying with a German host family in what was then West Germany. I had not visited the country again for over forty years, and my grasp of German as a consequence has deteriorated from weak to virtually non-existent. Then, a few years ago, I was invited to give two lectures in Germany and, as luck would have it, they were only a few days apart. This allowed me to combine my revisit to Germany into one trip.

First up was the Paul Ehrlich Institute near Frankfurt. Paul Ehrlich was a medical pioneer in the early twentieth century and was involved in, among many other things, devising the early treatment of syphilis with arsenic-based compounds. The institute which bears Ehrlich's name is Germany's national centre for the quantitation and validation of compounds and tests used in Germany and beyond. This includes work for the World Health Organisation in areas such as the Zika virus, and more latterly HEV. It was a great honour for me to be invited, and I spent many hours preparing my lecture before I set off. As usual, I was given a tour of the institute, which was very impressive. Most remarkable though was the small museum, which contained artefacts and documents from Ehrlich's work over one hundred years ago. In addition, it contained Ehrlich's death mask. This was made very shortly after Ehrlich's death by applying warm wax to his face. The wax was allowed to cool and then carefully removed and applied to a head mannequin. Very ghoulish to say the least. In the summer it has to be kept in a fridge, or otherwise the wax will melt resulting in a terminal case of face drop.

I next travelled to Hannover by train. I had been invited to visit the Faculty of Hepatology and give a lecture by Heiner Wedemeyer, professor of hepatology, and Sven Pischke his younger and very gregarious protégé.

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[2] "EASL Clinical Practice Guidelines on Hepatitis E Virus Infection. European Association for the Study of the Liver," *Journal of Hepatology*, 68(6) (2018): 1256-71.

Heiner is one of Europe's leading hepatologists, ex-secretary general of EASL, and a fantastic speaker. I have heard him lecture many times, and his grasp of complex data and new developments is awe-inspiring. However, it is his ability to communicate this so well in his second language that leaves me speechless. One of the other things I respect most about Heiner is his open-mindedness. One example of this was when the first descriptions of chronic infection with HEV were published from France in 2008. Apparently, he started to write a letter to *The New England Journal of Medicine* which basically said that chronic infection with HEV was impossible. When he had finished the first draft of this letter he started to think, "what if the French guys are right?" He decided to check for himself and asked one of his lab technicians to get some blood samples from the freezer from transplant patients with abnormal liver blood tests following their transplant. He tested them for HEV and, sure enough, some of his German patients also had chronic infection with HEV. The French were correct, and Heiner put his draft letter in the bin. Since this time, along with Sven Pischke (who now works in Hamburg), Heiner has become a real "HEVologist"— real enthusiasts.

I gave the same lecture as I did in Frankfurt, which was well received. I was somewhat startled at the end of my talk as the audience started drumming their desks with their knuckles. I had never witnessed this before, but apparently this is the German custom, used instead of clapping. There then followed twenty minutes of questions from the audience, followed by a tour of the faculty and hospital. I met many bright and enthusiastic men and women, but no sign of patients queuing on trolleys. We then went into town and had a fantastic dinner at the new Rat Haus (new town hall) attended by thirty or forty faculty members. The food was delicious, the conversation stimulating.

After dinner, Heiner and Sven invited me for a "digestive"—Schnapps, as I recall. We went to the old Rat Haus and continued our conversation. Heiner explained to me that Hannover was heavily bombed in the Second World War by the British Royal Airforce, and the old Rat Haus was one of only two buildings left standing in the centre of town after the war. By the time we finished our Schnapps it was nearly midnight, and time to be thinking about going to bed, but Heiner had other ideas.

"Harry. I'd like to show you the only other building in Hannover still left standing after the war," he said. This was just around the corner. It was an old church and had been left in its post-war condition as a memorial to those who died. It had no roof, just the four walls standing illuminated by low-intensity orange footlights. I found this experience very moving and told Heiner so.

"Harry," he said, "I am a European. This cannot be allowed to happen again."

When the United Kingdom voted to decide if we were to leave the European Union in 2016, I had Heiner's words in my mind. When the result was announced for Brexit (i.e. for the UK to leave the EU) I was not completely surprised, but I was deeply saddened. For me, the result was not about the country losing money (it will cost the United Kingdom tens of billions of pounds), but about what it means for the future political stability of Europe. Brexit, in my view, makes the European Union much less stable and increases the chance of European disintegration. Were this to happen this would significantly increase the chance of another war in Europe. Perhaps not in my lifetime, but possibly in my children's.

CHAPTER FIFTY-TWO

NEPAL, 2015

At 11.56 Nepal Standard Time on April 25, 2015 a massive earthquake struck Nepal, just to the north of Kathmandu. This was followed a month later by another huge quake. At least nine thousand people were killed and twenty-two thousand injured. In affected areas, much of the already fragile infrastructure was shattered.

In the aftermath of the earthquakes there was concern that there might be an outbreak of HEV infection in Nepal. The reason for this concern was that the existing sanitary infrastructure, such as it was, had been badly damaged and increased the risk of drinking water being contaminated by human effluent infected with HEV genotype 1. An outbreak of HEV could potentially occur on a massive and unprecedented scale. I started to worry about this. I talked to one of my Nepali collaborators—he was very worried too. After this discussion we decided to form an international group of experts to raise awareness of this potential issue. This included twenty-one colleagues from all over the world, including from South Asia. Following an extensive set of emails and teleconferences, we ultimately sent the following letter to *The Lancet*, who published it very shortly afterwards.[1]

> The recent earthquakes in Nepal killed thousands, displaced tens of thousands, and destroyed much of the country's infrastructure. Thousands of Nepalis are living in makeshift camps, with limited or no access to clean drinking water. There is now considerable risk of infectious diseases in affected areas.
>
> Of particular concern is the risk of an epidemic of hepatitis E. Sporadic cases of hepatitis E are common in Nepal. Most have a self-limiting illness, but pregnant women have a mortality of 25%. There have been a number of large outbreaks of hepatitis E in Nepal, including one in 2014, which

[1] B. Basnyat, H. R. Dalton, N. Kamar, D. B. Rein, A. Labrique, J. Farrar, P. Piot, and twenty-one signatories, "Nepali Earthquakes and the Risk of an Epidemic of Hepatitis E," *The Lancet* 385 (9987) (2015): 2572–3, reproduced with permission from Elsevier.

involved more than 10,000 cases. Earthquake-affected areas are faced with a "perfect storm" of risk factors: large displaced populations with limited access to clean drinking water, lack of sanitary facilities, the approaching monsoon, overburdened health-care infrastructure, large amounts of circulating hepatitis E virus (HEV), and an at-risk population who mostly lack protective antibodies (approximately 70% of the at-risk population lack protective anti-HEV IgG antibodies). As a group of HEV and infectious disease international experts we estimate the risk of an outbreak of hepatitis E as very high, imminent (likely onset: monsoon season, July September), with possibly more than 500 deaths among pregnant women.

A safe and effective vaccine (HEV239) is available but is currently only licensed for use in China. HEV239 has not yet received WHO vaccine prequalification, and WHO's Strategic Advisory Group of Experts on Immunization did not recommend its routine use in highly endemic areas because of the need for additional safety and efficacy data, particularly in pregnant women. However, their recently released hepatitis E position paper states that the current WHO position should not preclude the use of the vaccine in specific situations. "In particular, the use of the vaccine to mitigate or prevent outbreaks of hepatitis E should be considered as well as the use of the vaccine to mitigate consequences in high-risk groups such as pregnant women." Its use in Nepal, if an outbreak occurs, might prevent the deaths of more than 400 pregnant women, according to our estimates.

To minimise risk to human health, we recommend: first, deploy an active surveillance mechanism to identify cases of hepatitis E using point-of-care testing; second, the Ministry of Health of Nepal should initiate a request for HEV239 vaccine, and pre-emptively build a local reserve of vaccine doses; third, development of targeted deployment strategies and guidelines for the use of HEV239 on the basis of identification of high-risk populations and the available organisational capacity for safe implementation and monitoring of outcomes.

I followed this up with a demonstration in Whitehall, London with my students, colleagues, friends, and the Nepali community. It was the first time I had ever been on a demo. We had placards, megaphones, and a letter for the British Prime Minister asking for support. We got the girls to paint their faces yellow and to stick a balloon up their jumpers and had a mass "die in" at the end of Downing Street of "pregnant" females with jaundice. It was fun day out, but unfortunately was ignored by the powers that be, except for a Lord of the Realm who happened to be passing on his way to the House of Lords. He got interested and sent a very nice letter voicing our concerns to Margaret Chan, then director general of WHO. We thought she'd ignored us too, but I was wrong. At the next major HEV meeting in Berlin a senior official from WHO's Global Hepatitis Programme did turn up, and she listened.

As it turned out, despite our very grave concerns, there was no outbreak of HEV in Nepal following the earthquake. I am not sure why that was. However, I do recall one colleague from India (and a very senior HEV-ologist) who joined our group saying: "Harry it is really very difficult to predict an outbreak of hepatitis E." Very sage advice, in retrospect.

CHAPTER FIFTY-THREE

ON CALL

I learned much of my hands-on medicine while on call. When I was a young doctor I was resident, i.e. in the hospital. I had two bleeps, one for every day run-of-the-mill stuff, while the other was known as the "crash bleep." When this went off, the doctor carrying it had to immediately stop what they were doing and depart urgently to wherever the emergency was, usually a patient who'd had a cardiac arrest, or was about to have one. The incident could occur at any location in the hospital site, and in some of the larger hospitals this might be some distance away. I remember on one occasion during the depths of winter when the crash bleep went off. I had to run up a hill covered in six inches of snow to a far distant isolation ward. By the time I got there, the patient had thankfully been revived by the nursing staff. This was just as well, as I was in no fit state to do much as I was covered in sweat and developed a bout of bronchospasm brought on by the exertion and cold. Like the patient, I required resuscitation myself as I was wheezing like an old church organ. I made an excellent response to a Ventolin inhaler, which was promptly presented to me by one of the nurses on the ward.

Bleeps are the bane of every young doctor's life. They frequently go off at the most inconvenient times, day or night, and sometimes incessantly. I recall one time many years ago when the bleeps would just not stop—they went on and on and on. I'd been on call all weekend and had had very little sleep. I was due to finish work at nine am on the Monday, but from four thirty am the bleeps just went crazy. There was one crash bleep after another, an almost endless series of patients in serious danger. I was meant to hand the crash bleep over to one of my colleagues at nine am, but because of the persistent and incessant nature of the calls I was receiving there was no chance to do so. I had no choice but to simply rush from one emergency to the next.

One of the cases was a man of West Indian origin in his mid-forties. He was previously fit, big and strong, and had played cricket as a fast bowler to a very high standard. He wasn't fit for high-quality fast bowling when I saw him in A&E, though—he was desperately ill. His ECG tracing

showed an irregularity called ventricular tachycardia. This is potentially a very serious condition, as at any moment it can change to ventricular fibrillation, where the pumping of the heart stops completely. The patient was hooked up to oxygen and an ECG/blood pressure monitor attended by two nurses, who looked very concerned, but mightily relieved to see me turn up at a run. When I arrived, he was alert and responded to my initial questions; pulse 200, blood pressure 105/65. Within the next minute or two the patient's ECG started to change and began to wander. At the same time his blood pressure nose-dived, his eyeballs drifted north, his eyelids drifted south, and he became uncommunicative. I asked the nurses for the defibrillator paddles and gave him a two hundred Joules synchronised electric shock to his chest wall. Bang! His ECG and blood pressure went straight back to normal. He instantly woke up and took a swing at me, as he thought I'd punched him in the chest, which I suppose I had. He missed, but I had no time to ponder what would have happened had he connected as the crash bleep went off again for another patient in extremis. I legged it to the next call down the corridor and called to the nurses over my shoulder to get him up to the Coronary Care Unit. By two pm the carnage stopped, and I managed to transfer the crash bleep to one of my colleagues. I had just worked fifty-three hours straight, with little rest, but funnily enough this did not bother me as much as not being able to brush my teeth on that final morning; my mouth felt rank. At two thirty pm I gave my teeth a good clean, lay down on my bed in my clothes, and slept for eighteen hours straight.

One day when I was on call, I was asked to see a circus clown from Scotland. He was in his mid-fifties and looked like a circus clown—a wrinkled, lived-in face, large nose and a broad, sad smile. He told me that he had experienced a sudden onset of pain in the right side of his chest that was sharp in nature and made worse when he breathed in or coughed. He had also been a bit breathless and had coughed up a small amount of fresh blood. These symptoms were compatible with a diagnosis of a pulmonary embolus (a blood clot on the lung). This is a potentially very serious condition, as further clots can ensue, which can prove fatal. I duly started an infusion of heparin, an anticoagulant that thins the blood and prevents further clots from forming. As he was in quite a bit of pain, I wrote him up for morphine, to be given as and when the patient required it. He required quite a lot.

The next day he went for a lung scan to confirm the diagnosis—it was negative. I went back and looked through the details of the case again. When I first saw him, I noted that his pulse rate was normal. Patients with a blood clot on the lung nearly always, but not invariably, have a

tachycardia (a high resting pulse rate of over one hundred beats per minute). Also, I noted that the oxygen levels I had checked were also normal. Patients with a pulmonary embolus usually have low levels of arterial oxygen, as the clot prevents the blood in the lungs picking up the normal amount. He also required a large amount of morphine for pain relief. I became suspicious. I rang up his general practitioner in Edinburgh and told him the story. Before I could finish, he cut me short, and said:

"Och, not this bloke again!"

"What do you mean?" I replied.

"First, He's never been my patient. Second, I've had at least twenty phone calls from doctors from all over the UK about him in the last twelve months. Always the same story—suspected pulmonary embolus, requiring lots of morphine, scans are negative."

I put the phone down and went to talk to the patient about it. He promptly "did a runner." This patient had Munchausen's syndrome. This syndrome was first fully described by Richard Asher in 1951,[1] and is named after Karl Friedrich Hieronymus, Baron Munchausen. The Baron was an eighteenth century "noble" who had a penchant for recounting grossly exaggerated accounts of his life and travels. Patients with Munchausen's syndrome make up their symptoms (i.e. they give a fictitious account of their "illness") for personal gain. The reason for this behaviour is uncertain, as the personal gain sought by such patients is to be admitted to hospital and undergo investigation and/or surgery. The "Munch," as such patients are commonly referred to, usually gives a dramatic, but extremely convincing, account of their symptoms. They often have a history of numerous procedures at different hospitals. Although rare, Munchausen's syndrome can be a very difficult condition to diagnose, as the above case illustrates. This relates to the fact that doctors rely heavily on the patient's account of their symptoms to reach a diagnosis, and often there is little to find on clinical examination. The diagnosis is often only considered when the tests all come back negative. Patients with Munchausen's syndrome usually have underlying psychological problems that are almost impossible to treat. They almost invariably continue in their abnormal illness behaviour long term and have a reduced life expectancy due to complications arising from their endless and needless medical treatment.

One of the more unusual tasks I had to perform when on call was during the 1980s when I was working in London as a registrar. I was on

[1] R. Asher, "Munchausen's Syndrome," *The Lancet* (February 10, 1951), 339–41.

call every fourth weekend and, as regular as clockwork on the Sunday evening, I would get a call from the surgical team:

"Harry, could you do us a favour please? We have a couple of patients that we don't not know what is wrong with them. When the boss comes around tomorrow on his ward round, he'll go nuts!"

The boss in question was an (in)famous surgeon. He was technically brilliant and had an international reputation but, unfortunately, he appeared to be stuck in a time warp which seemed to pre-date the Dickensian era. He was a very big man, with an ego to match. He was, quite simply, a bully. His staff were terrified of him, and so were many of his patients. I have heard recounted numerous accounts of some of the more notable incidents, one of which I witnessed first-hand. It is said that he once asked a cleaner to desist from using his cleaning machine on the ward during his rounds. The poor cleaner was rather taken aback and was unsure how to proceed. The surgeon in question saw the hesitance. He knew how to "operate" and grabbed the cleaning machine, which was still plugged into the electrical mains, and threw it out of the ward window. It is also alleged that, on one occasion, an unknown individual had the temerity to park in his space, just outside the hospital front door. ●n return to his car, the poor soul found that somebody had ripped up an adjacent concrete bollard, which now resided in his front seat, having been hurled through the front windscreen. Finally, a colleague, peer, and friend of mine was operating with the surgeon one day. The operation was not going too smoothly, and my friend was "requested" to "keep the fucking retractor in the fucking right place and at the right fucking tension." Unwittingly, as was the surgeon's usual *modus operandi*, he jabbed the air with his hand in my friend's general direction. However, the surgeon forgot he had a very sharp scalpel in his hand and punctured my friend's ante-cubital vein through his surgical garb. My friend started to bleed, the blood creeping rapidly down his surgical gown. Cool as a cucumber, he said to the surgeon: "Sir, I appear to be about to bleed into the wound. Could you kindly excuse me for a moment while I change my theatre scrubs?"

So, it was with some misgiving and trepidation that I went to the surgical ward on those Sunday evenings to help my junior surgical colleagues and the undiagnosed patients in their charge. I always tried very hard to come up with some bright ideas, together with a plan of action. This usually took quite a bit of time, but I mostly came up with something vaguely sensible. Just occasionally, I would be stumped, with no real clue how to advise my surgical colleagues how to proceed. ●n the odd occasion that this happened, it was met by total horror by the surgical

registrar. At first I did not understand this reaction, then I was told by my junior colleagues the reason why.

The surgeon in question liked his ward round short, crisp, and without question. This was the only way he could possibly proceed, as he thought in a totally reductionist manner and could only see in black and white. He liked to see post-surgical patients that he had operated on doing well. He liked to see patients with a clear diagnosis who were awaiting surgery the following day. His mind simply could not compute, or deal with, a case that was not clear cut with no diagnosis—these were "grey cases." I never witnessed first-hand this surgeon's response to such a grey case, but allegedly it was a completely uncontrolled explosion, and extraordinarily unpleasant for all attending medical and nursing staff. The ward staff, long used to his foibles, resorted to extreme lengths to avoid the inevitable eruption of Vesuvian proportions. It was simple—such patients were removed from their beds, and placed on the ward balcony, their beds stripped and freshly made up just prior to the Monday ward round. Seeing an empty bed pristinely tucked in with freshly starched linen was acceptable to the surgeon in question—it was brilliant white. God only knows what the poor patients must have thought, who were left shivering on the balcony outside.

In the 1970s and 80s, when I was training, this kind of senior colleague was not unusual, but perhaps not quite so extreme in outlook or response. Nowadays, this kind of behaviour is, quite rightly, not seen in the NHS where there is an attitude of zero tolerance to bullying. However, the "rebadging" of beds is increasingly commonplace, but the reasons for this are quite different.

CHAPTER FIFTY-FOUR

STOCKHOLM, 2016

The European Centre for Disease Prevention and Control (ECDC) is based in Stockholm, Sweden. It was established a few years ago, with the remit of strengthening the European Union's defences against infectious diseases. It's very much a diminutive first cousin of the United States version—the Centers for Disease Control and Prevention in Atlanta.

ECDC started responding to the threat of HEV to human health a couple of years ago, and called a series of meetings, to which they invited experts from across Europe to attend. They invited me to kick off the meeting with an overview, and then data was presented from all EU countries that had sent attendees. What became apparent from the presentations was that the number of cases of HEV diagnosed across the EU was rising. In western EU countries such as France, Germany, the Netherlands and the United Kingdom, the rise was almost exponential.[1] There could only be two explanations for this rise in the number of cases. It was either due to improved case ascertainment, i.e. as doctors became more aware of HEV they tested more patients and so increased the number diagnosed, or there was a true increase in incidence due to increased amounts of circulating HEV in the human population. On the data presented, it was impossible to be sure which one of these factors was driving the increased number of confirmed cases. It could be that both were.

As further data became available from more and more countries, it became apparent that there were several "hotspots" of HEV infection from a number of different places across Europe. We already knew that the

[1] C. Adlhoch, A. Avellon, S. A. Baylis, A. R. Ciccaglione, E. Couturier, R. de Sousa, J. Epštein, S. Ethelberg, M. Faber, Á. Fehér, S. Ijaz, H. Lange, Z. Mandáková, K. Mellou, A. Mezalevskis, R. Rimhanen-Finne, V. Rizzi, B. Said, L. Sundqvist, L. Thornton, M. E. Tosti, W. van Pelt, E. Aspinall, D. Domanovic, E. Severi, J. Takkinen, and H. R. Dalton, "Hepatitis E Virus: Assessment of the Epidemiological Situation in Humans in Europe, 2014/15," *Journal of Clinical Virology* 82 (2016): 9–16.

Midi-Pyrénées area around Toulouse in southwest France was hyperendemic for HEV genotype 3 from the work that our French friends and colleagues had done. Further fascinating data from the Toulouse group showed that the amount of circulating HEV was not uniformly geographically distributed in France in general, and the Midi-Pyrénées in particular.

Ariège is a rural department in southwest France of outstanding natural beauty, about an hour's drive south of Toulouse. It is situated in the Pyrenees adjacent to Andorra and is famous for its prehistoric cave paintings and wild-boar hunting. It is now also famous for being the place with the most circulating HEV in humans on the planet, as the seroprevalence is eighty-two percent, and 4.6 percent of the population are infected or re-infected every year. In contrast, a department of France named Haute-Loire only 250 kilometres to the northeast of Ariège has a seroprevalence of eight percent, and only 0.4 percent of the population is infected with HEV each year. The reason for this tenfold difference in human exposure to HEV is unknown. Other hotspots for HEV in France include Corsica, the area around Marseilles, and a region in northeast France adjacent to the German border three hundred kilometres east of Paris. The main pig-rearing area in France is Brittany, which has only moderate amounts of circulating HEV compared to the hotspots just mentioned.[2]

In addition to the French HEV hotspots there are others which have recently become apparent. These include the Netherlands, where up to one in six hundred blood donors are asymptomatically carrying HEV at the time they donate blood.[3] In addition, the seroprevalence in young Dutch donors has doubled in the last few years. In northern Germany, one in eight hundred blood donors are viraemic when donating blood.[4] In the Czech Republic they have had an enormous number of laboratory-confirmed cases per head of population.[5] In western central Poland, the seroprevalence is around fifty percent.[6] In the Abruzzo region of central Italy, the seroprevalence is forty-nine percent, in contrast to neighbouring

[2] Mansuy et al., "A Nationwide Survey of Hepatitis E Viral Infection in French Blood Donors."
[3] Zaaijer, "No Artefact, Hepatitis E is Emerging,"
[4] Westhölter et al., "HEV Positive Blood Donations Represent a Relevant Infection Risk for Immunosuppressed Recipients."
[5] Adlhoch et al., "Hepatitis E Virus."
[6] M. Bura, M. Lagiedo, M. Michalak, J. Sikora, and I. Mozer-Lisewska, "Hepatitis E Virus IgG Seroprevalence in HIV Patients and Blood Donors, West-central Poland," *International Journal of Infectious Diseases* 61 (2017): 20 2.

Lazio where the seroprevalence is eight percent.[7] In Ticino, the Italian-speaking region of southern Switzerland, there have recently been an enormous number of cases of HEV infection, particularly cases with neurological involvement.[8]

The reason why these areas have large amounts of circulating HEV is not known. As each of these hotspots were discovered, I paid them a visit for a couple of days of "virus hunting." I wanted to see each area for myself. I considered the topography; I checked out where all the pigs and wild boar were; I sampled the local cuisine, and spent hours discussing local culinary culture with restaurant waiters and chefs. This was a great deal of fun, but I could not work out a common thread which might link these areas, which appear to me to be disparate both geographically, culturally, and in terms of risk factors for HEV exposure.

[7] C. Lucarelli, E. Spada, G. Taliani, P. Chionne, E. Madonna, C. Marcantonio, P. Pezzotti, R. Bruni, G. La Rosa, G. Pisani, L. Dell'Orso, K. Ragone, C. Tomei, and A. R. Ciccaglione, "High Prevalence of Anti-hepatitis E Virus Antibodies among Blood Donors in Central Italy, February to March 2014," *Euro Surveillance* 21(30) (2016).

[8] Van Eijk et al., "Clinical Phenotype and Outcome of Hepatitis E Virus-associated Neuralgic Amyotrophy."

CHAPTER FIFTY-FIVE

WHITE COATS

The way someone dresses says something about the wearer. It's an overt expression of personality, style, and sometimes substance. Unfortunately, I have developed a liking for Italian suits. I am not sure why, but when I put an expensive one on it feels good. Somehow, it's my shape, it seems to have been made for me, myself; it feels part of my body. Most times when I go to Italy, which is quite a lot, I am tempted to buy one. Unfortunately, I seem to have travelled to Italy many times in recent years, so I have to restrain myself, which does not sit easily on my rather impulsive but well-tailored shoulders.

The last time I went to Italy was to give a lecture in Florence. As is the norm on such occasions, I was hosted extremely graciously and generously by my Italian colleagues, stayed in a nice hotel, and was taken out for dinner after the event. When I arrived at the University Hospital, following a coffee and a chat in the professor's office, I was given a tour of the faculty. What did I see? I saw a world-class facility with staff who were happy, smiling, and looked extraordinarily professional. The nurses wore pristine white uniforms. The doctors wore freshly pressed and starched white coats with short sleeves, slightly cut in at the waist and buttoned up to the side of the neck, the top two buttons left stylishly unfastened. I have spent most of my life working in hospitals, and I knew on first going through the door that, if I were sick, I would be happy for these guys to look after me. This feeling was instant, overwhelming, and irrespective of their well-groomed looks and equally well-earned international research reputation. I just knew.

The same goes for nearly every other place in the world I have been invited to, including some low-income countries. I have been to Colombo in Sri Lanka a couple of times. It's a very poor country, reflected in the rather shabby but nevertheless spotless hospital premises. Although the paint was peeling on the walls in places, I saw a sea of brown faces, white smiling teeth, and brilliant white coats and nursing uniforms. These guys were happy, they had sunshine in their hearts. What I never witnessed in any of these visits to various hospitals in Continental Europe and beyond

are endless queues of elderly sick patients waiting on trolleys and wheelchairs for hours on end just to be seen and assessed by a doctor.

When I get invited to lecture in the United Kingdom the same kind of thing happens. I am looked after well by my hosts, and often as not I get a tour of the local faculty. What do I see? I see long-faced medical and nursing staff who are rushed off their feet, trying to avoid eye contact with all and sundry. I hear moans, groans, and complaints from the overworked and harassed staff when I talk to them. I cannot tell the doctors apart; they look just like people you might observe walking down the street. The reason for this is that doctors in the United Kingdom were banned from wearing white coats in the wards about ten years ago, and now most just wear their ordinary civilian clothes. The reason for this change in dress code was purportedly the risk of cross infection. The evidence for this comes from a single study that shows if white coats are not washed for eight weeks, the bacteria *Staphylococcus aureus* can be cultured from them. This is no surprise, but our friends on the Continent are sceptical to say the least. They argue that wearing civilian clothes on the wards does not reduce the risk of cross infection, least of all to their families when they return home from work. They all wear clean white coats to work, which are changed every day.

I have visited the hospital in Toulouse where my friend Nassim works several times. Following these visits, I am very jealous of two things. First, he had his own car parking spot with his name on it, for which he did not have to pay—unheard of in the NHS. Second, he has his own office which contains a wardrobe containing seven freshly starched and pressed short-sleeved white coats embroidered with his name. I told him the story about the situation in the United Kingdom, recounted above. One month later, a parcel arrived from France. Nassim had sent me one of his white coats and had gone to the trouble of having my name placed on the breast pocket. This was a lovely gesture from a true gentleman. Nassim's white coat is my pride and joy. I took a picture of myself wearing it in the shed and sent it to him with my gratitude. However, I am too scared to wear it on the wards at home—there is no doubt whatsoever that I would get into serious trouble from the "infection police."

My gripe about the white coats may sound petty, and, taken on its own, it probably is. However, it is just one of an increasingly large tranche of politically-motivated measures that have been introduced in the NHS over the last few years with the specific aim of de-professionalising and disempowering doctors. The others include: removal of doctors' dining rooms; removal of on-call rooms where one can sleep when not busy on call; lack of any edible food for the staff out of office hours (or even in

office hours, in many places); targets for this, targets for that; overwork; underfunding; and destruction of the "firm" system of working. This has been dressed up with the spin of creating a modern NHS. As one walks around any NHS hospital you will see trite and meaningless notices saying such things as: "NHS Trust; we listen; we treat with compassion; we care." To me, this is stunningly vacuous. Given my interest in pigs, I am somewhat surprised that nobody has inserted the Orwellian porcine footnote: "Four legs good, two legs better."

However, the biggest piece of political "spin" in recent times came at the time of the junior doctors' (hospital doctors who have not yet reached consultant status) strike a couple of years ago. The young doctors had a new contract forced on them by the NHS. The doctors were not happy about this as they felt—quite rightly in my view—that it would put patients at risk, particularly on overstretched weekends where there is only a skeleton staff on the rota, with increasing numbers of rota gaps, i.e. when somebody fails to show up for work. They were taken on by Jeremy Hunt the health secretary at the time, who, through a series of interviews and interventions, span the young doctors as money-grabbing, idle toads. This included many an interview in the media. Unfortunately, one of the UK's most distinguished radio broadcasters made a mistake with the health secretary's name when interviewing him on national primetime breakfast radio. The interviewer in question inadvertently replaced the "H" in Mr Hunt's name with a "C." This was a terrible and completely indefensible mistake. I'm not sure what Sigmund Freud would say, but nevertheless the moniker stuck, at least among some young doctors in private. When they were on strike, my consultant colleagues and I covered their duties, and did so happily. It was the depth of winter, and when they were outside the hospital door with their placards I would take them out a tray of steaming hot coffees. They had my complete support. I also guessed that the consultant staff would be the next in the firing line.

The health secretary won the battle but lost the war. The young doctors caved in after several days of all-out strike action, and the new working contract was imposed. One of the results of this is that the NHS is now probably a more dangerous place in which to be a patient. This is bravely set out by Rachel Clarke, an ex-journalist and junior doctor involved in the strike, in her recent book *Your Life in my Hands*.[1] This is a must-read for any consumer or potential consumer of the NHS, and it details the spin and misinformation supplied and how desperately underfunded the NHS really is. It is currently woefully understaffed by disgruntled and

[1] R. Clarke, *Your Life in My Hands* (London: Metro Books, 2017).

disenfranchised bright young doctors. The response from many of these young colleagues has simply been to leave the United Kingdom for jobs in other countries. As a result, many of the junior doctor training posts in UK hospitals and general practices remain unfilled. A recent initiative has been announced to recruit five thousand new doctors from Europe to fill the gap—on the new NHS contractual terms, naturally.

The one incident that speaks most about how fundamentally unhappy the young doctors are occurred last year, just as the strike was ending. I hadn't seen John for some time. I taught him when he was a student, and he had been my house physician. He was a good man, very bright, and he cared about the human side of medicine as well as its technical side. He'd been off to New Zealand to work for a year, and had enjoyed the experience, having worked in the same hospital that I did in Auckland ten years previously. I stopped to talk to him in the corridor.

"Hey John, how was New Zealand?" I asked

"Fantastic," was the reply. We swopped various New Zealand stories and anecdotes from our shared Antipodean adventures.

"What's it like to be back?"

"Harry, it's terrible. I'm thinking of either going back to New Zealand for good, or maybe giving up medicine together."

This man is one of the best young doctors I have ever had the privilege to work with. His training cost the UK taxpayer a minimum of 250 thousand pounds. He has spent five years working his socks off for the NHS since he qualified. He now has had enough. He's been ground to dust. The most priceless asset of the NHS, as in any organisation, is the staff that work there. My dispirited and disillusioned young colleagues, like John, do not feel valued. Many of them would like to leave if possible. Never mind, maybe we will be able to attract more colleagues from the EU to come and work in the United Kingdom? This may prove difficult, as many EU colleagues currently working in the UK tell me they do not feel quite so welcome after the Brexit vote. A significant number are thinking of moving elsewhere.

CHAPTER FIFTY-SIX

DIFFA, 2017

A couple of years ago I was invited to give a talk in Switzerland. It was an exclusive, by invite only meeting which was held on an annual basis. Each year they invite one international speaker, and this year they had chosen me. When I looked down the list of glitterati they had previously invited from abroad I was deeply impressed, and once again humbled. The venue was in a small town in the middle of the Alps; it was mid-winter and knee-deep in snow. There was the opportunity to do some skiing following the meeting. However, I did not appreciate the scenic beauty, nor was I tempted to take to the slopes. Mum had died the week before; my mind was elsewhere, and her funeral was the day following my talk. I'd be going straight home as soon as I had completed my task. The organisers knew of my bereavement and told me they would understand if I cancelled. I decided to go ahead and do the talk, as I knew Mum would have wanted me to do so.

I got up and did my usual style of talk. Afterwards, I got some tricky questions from a very informed group of infectious disease experts and hepatologists. The final question was from the back:

"What do you think about the situation in the African refugee camps? Should we be using the HEV vaccine from China?"

"The situation in the African refugee camps is a major ongoing issue," I replied. "There have been thousands of cases of HEV infection with genotype 1, due to the appalling sanitary conditions in the camps. Scores of pregnant women have died. These are potentially preventable, as there is a safe and effective vaccine sitting on a shelf somewhere in China. The problem is that it is not licensed for use elsewhere. This situation needs to be unpicked as a matter of priority. We need to find a way of getting it from China to the African refugee camps."

After my talk, I headed to my room to pack and leave, but was collared by my final questioner on the way out. He turned out to be the deputy director of Médecins sans Frontières (MSF). We discussed the situation in Africa at length and talked about the vaccine. Getting the vaccine to Africa was a priority for MSF, but it was proving impossible. I agreed to help

MSF in any way I could. MSF subsequently asked me to review their updated operational guidelines for the management of HEV in the field. This took several hours of my well-spent time. I made various suggestions but was struck with the difficulties of treating a pregnant woman with advanced HEV-related liver failure with limited equipment in a tent that was knee-deep in contaminated floodwater.

A few months later, MSF called a meeting at their headquarters in Geneva. The main objectives were to push HEV up the agenda at WHO, and to facilitate the use of the vaccine in Africa. All the key stakeholders were in attendance, including the vaccine manufacturers and representatives from WHO and CDC, in addition to key staff from MSF. I was asked to kick off the meeting with an overview of HEV across the world. I accepted this invitation with great pleasure.

I was deeply impressed by the commitment of my colleagues at MSF. They work in the most appalling and dangerous conditions. They are paid a pittance by international standards and are away from home on a mission, often in primitive conditions, for up to a year and are not infrequently targeted by local armed insurgent groups. I was most impressed by a talk from an MSF engineer whose job was to sort out clean drinking water in the camps. I learned a lot about boring wells and water filtration under the most trying conditions. I also witnessed great humanity, both from the slides projected on to the wall during the meeting and in person, when talking to the guys from MSF during the breaks. I was less impressed by WHO. They understood the urgency of the situation but identified a number of issues which were problematic. The most important, I guess, was that there are only limited data on the safety and efficacy of the vaccine in pregnant women. Good point well made, but if we do nothing up to twenty-five percent of the pregnant women and their unborn offspring would perish. Giving the vaccine a go seemed a "no-brainer" to me. But then there were other issues, including the WHO "prequalification" process. This is a nearly endless series of criteria that have to be met in order to get WHO's blessing, without which the politics in affected countries made the potential use of the vaccine impossible. I left the meeting in a gloomy mood. It seemed to me that it was going to take years to get the vaccine to the camps.

Northeast Nigeria is not on many people's holiday itinerary. Even the most intrepid of travellers would not dream of going there for a bit of rest and recreation. It is a very, very dangerous place, largely to due to the activities of the Boko Haram insurgents. The conflict has been going on since 2009 and has resulted in wanton destruction of the region's infrastructure and thousands of civilian deaths, some of them due to

suicide bombings. As a result, there has been famine and the mass displacement of refugees to camps, including in neighbouring Cameroon and Niger.

In the spring of 2017 there was an outbreak of hepatitis E (genotype 1) in refugee camps in Diffa, Niger. Hundreds of displaced Nigerians were affected and there were scores of deaths in pregnant women.[1] MSF were straight in, helping as much as they could and, of course, using their updated treatment guidelines. I volunteered to go in to the field, if they thought I could be of use. I was told it was extraordinarily dangerous, particularly for Caucasians. However, I was aware that the situation with regards to the HEV epidemic was likely to significantly worsen in the rainy season, which was due to start in July and last two to three months. WHO also went straight in to help, but there was no sign of the vaccine.

In May 2017 there was an additional outbreak of HEV in the refugee camps of northeast Nigeria, just across the border from Diffa. I got a call from the head of the WHO's Global Hepatitis Programme. She'd been recently appointed to this role and turned out to be an old classmate of mine from medical school. She was off to the field in northeast Nigeria with WHO to coordinate the response to the HEV outbreak. She asked me if I would urgently review the updated WHO guidelines for the management of HEV infection in the field. The issue of possible use of the vaccine was on the agenda but would be addressed separately. I reviewed the guidelines with a couple of colleagues; this was a straightforward task, as little had changed since I reviewed MSF's guidelines on the same subject only a few months previously. Then she set off to Nigeria to "work in an environment which is extremely challenging, including almost daily attacks with improvised explosive devices." I considered how she would deal with all this and wondered how on earth she would cope. But cope she did. She came back in one piece and made a significant contribution, but with no sign of the vaccine yet. I'm holding my breath—the rainy season is about to start.

[1] "Preventing the Spread of Hepatitis E," Medecins Sans Frontiers (November 1, 2017), http://www.msf.org/en/article/niger-preventing-spread-hepatitis-e.

CHAPTER FIFTY-SEVEN

ALCOHOL

When I was a student I had to write an essay on the physiology of blood pressure. I found this a surprisingly complex subject, as I discovered that many factors are involved in causing hypertension, including alcohol consumption. I recall consulting one of the fist papers written about this subject—naturally enough from France in the 1930s and 1940s—which compared blood pressure to the amount of alcohol consumed. What struck me, though, was how the study authors categorised the amounts of alcohol consumed per day: "buveurs," less than one litre of wine per day; "grand buveurs," one to two litres of wine per day; and "trés grand buveurs," more than two litres per day. If memory serves, the study found that only trés grand buveurs had high blood pressure.

Of course, as this story illustrates, in those days the amounts of alcohol consumed in France (mostly wine) were enormous, and an order of magnitude higher than seen in most other developed countries at that time. The consequences of this were very high French death rates from liver cirrhosis and associated liver cancer. However, over the last couple of decades things have changed considerably. The amount of alcohol consumed by the average French person has reduced by seventy-five percent, and with it the associated deaths from liver disease. In contrast, in the United Kingdom the amount of alcohol has gone up, particularly in the younger age groups. I have seen the consequences of this change in behaviour at first hand. At the start of my career, end-stage alcoholic liver disease was not so commonly seen on my ward and was largely restricted to individuals in their fifties and sixties. Now, we commonly have a good number of patients on the ward at any one time with alcohol-related cirrhosis, but these days they are typically in their thirties and forties. We recently lost a young man of twenty-five who literally drank himself to death. Two bottles of Drambuie every day before lunchtime is not a good idea.

Looking after patients with alcoholic liver disease can be challenging for a number of reasons. First, we need to manage alcohol withdrawal—the "DTs," delirium tremens. In people who drink a lot, such as the trés

grand buveurs, alcohol withdrawal is not just a case of a large hangover the following morning and can be very serious and potentially life threatening. Patients become agitated, sweaty, drop their blood pressure, get visual hallucinations, become confused and often violent in language or action; sometimes, they have withdrawal-induced epileptic fits. This means that alcohol withdrawal needs to be done as an inpatient for up to a week or more in an area experienced in preventing and dealing with such problems. In other words, my ward. Second, patients with a failing liver are very prone to developing infections. These need to be spotted and treated instantly, otherwise the patient is pretty likely to die. This also needs to be done on my ward. Thirdly, although alcoholism affects individuals from all walks of life, alcoholics not infrequently have a very colourful non-conformist history with associated challenging points of view and behaviours. The latter are often exacerbated and magnified by their physical illness and need an expert approach to successfully manage. Again, on my ward. Finally, the biggest challenge of all is to get these patients off the booze and keep them off. This is the hardest task of all.

My ward has thirty beds and, at any one time in recent years, we generally have six or seven patients with very serious alcohol issues, including liver failure. They can be spotted from a distance—bright yellow, pot-bellied males aged thirty to forty wandering down the hospital corridor in a dishevelled hospital gown, cigarette in hand, rushing (as best they can, as they are usually unsteady on their feet) to get outside the hospital front door for a smoke, which will wait for more-or-less nothing. We do see women with alcoholic liver disease, and increasingly so, but they are still outnumbered by men by quite a margin.

As these kinds of patients require a careful and unified approach that involves considerable monitoring, and they are often put together in a bay on the ward which holds four patients. This is quite helpful from a logistical point of view, but if handled correctly has other, perhaps less measurable, outcomes. When I look after the alcoholics in the male four-bedded bay on the ward, the first thing I do is go and introduce myself to them all together, after closing the door and leaving the rest of the ward team in the corridor. I then say something along the following lines:

"Guys, this is known by some as the 'bad boys' room.' You all know you've been bad in the past. I'll leave it up to you to decide, between you, which of you has been the worst. Oh, and by the way, if you misbehave while you're here I'll introduce you to Matron. Best not mess with Matron, boys!"

The ward round continues, with some hilarity and laughter when we come to each case in turn, wherever I can. This is not always possible, as

the mortality rate of patients admitted to the bad boys' room is about twenty percent. I have had the pleasure and privilege to look after some very bad boys indeed, not all of whom made it out of the door, but with most I had a laugh and a joke. There is no privacy in the bad boys' room, just four beds, around which flimsy curtains can be drawn at times of necessity. In terms of soundproofing: nil. One patient I saw was a man in his fifties; a "Jack-the-lad," with a velvet tongue. Within a day of coming into the ward he'd completely charmed the nurses and become the self-appointed leader of the bad boys' room. He had a serious liver condition and was luminous yellow. As is common in such circumstances, his legs became swollen, which we tried, with minimal success, to treat with diuretics. I did the consult behind his curtains with my house physician. Just I was leaving, he said:

"Hey, Harry! There's something else—I have a problem in the trouser department. It's my bollocks. They appear to be growing, and now they're enormous!"

"Okay, let's have a look," I replied.

He dropped his pyjama bottoms to reveal the worst case of scrotal oedema, caused by fluid retention, I have ever witnessed.

"Blimey, they are big." I turned around to the nursing staff and said "Matron, this man needs a large scrotal support. On second thoughts, make that extra-large."

Of course, this was all overheard by the rest of the bad boys. I could hear them trying to suppress their laughter, sniggering like naughty schoolboys. As soon as I left the bad boys started talking, having a laugh and a joke. It came as no surprise that the patient in question was given the nick name "Big Bollocks." I think he was rather proud of this moniker.

As they are often on the ward for a couple of weeks, the bad boys, once they have gelled, look out for each other. A good example of this was when one patient in the bad boys' room told me on the ward round:

"Hey Doc, you know Rodney who was in last week? He's not so well again and arrived in A&E twenty minutes ago. He's just sent me a text. He'd like you to pop down and see him, if you have time."

At the end of the ward round I did so and arranged for him to be readmitted to the ward, so cutting out the middlemen in A&E, much to their surprise and delight.

Although I had many a laugh and joke with Big Bollocks, he had a very serious problem, and very nearly made it into the bottom twenty percent. He had liver failure, coupled with severe fluid retention and a small liver cancer caused by his cirrhosis. The only solution for him was a liver transplantation. We worked him up to this, and he required numerous

tests to check his heart, lungs, and kidneys. He also needed an endoscopy, as patients with liver disease can have associated stomach problems. The night before his endoscopy was scheduled, events intervened. At four thirty am I got a phone call at home. Big Bollocks was in serious trouble as he had just vomited huge quantities of fresh red blood, and despite a transfusion of three units of blood his systolic blood pressure was in his boots. I rolled out of bed straight into the car and was in the endoscopy room within an hour with the endoscope down, looking at a tidal wave of blood moving northwards.

Big Bollocks had ruptured his oesophageal varices. This occurs in cirrhosis when the liver becomes scarred and non-compliant, making it difficult for blood to pass through and back to the heart. The blood finds an alternate way back to the heart via veins that are normally tiny and inconsequential. The veins in question were not tiny or inconsequential in Big Bollocks—they were the size of a bunch of grapes, situated in the lower oesophagus and bleeding like buggery. There is a large suction port in the endoscope through which I sucked up the blood that was coming from his ruptured varices. The problem was that there was so much blood spurting from the ruptured varix I could barely keep up by sucking it away up the endoscope. He lost a lot of blood, and by this stage he had received five units of blood via emergency transfusion, which was barely keeping up with the amount he was losing. As a result, his blood pressure was becoming dangerously low—he was quite literally bleeding to death. I needed to stop the bleeding pronto as I was aware that the mortality from bleeding varices is approximately thirty percent. In this case it was probably higher, as the bleeding was very severe, as was his underlying liver disease. The only two things that Big Bollocks had on his side were his relative youth and my skill, or otherwise, with the endoscope.

After twenty minutes sucking away at the blood pouring out of his ruptured vein, I was making no progress. Big Bollocks' life was now in the balance. I had to adopt a different approach, as I was no nearer sorting this than I was before I started. I decided to change the endoscope and use "Big Bertha" instead. Big Bertha is an endoscope that has a greater diameter than a standard scope, and the suction channel is also considerably wider. This allows greater suction power, and I was hoping this would allow me to visualise the bleeding point through the red sea. Also, it has a washing device, somewhat akin to a car jet wash. I put Big Bertha down the oesophagus and simultaneously hit the jet wash and suction button. Suddenly the red waves parted, and there it was—a menacing-looking purple grape-like structure spurting a red plume of blood in a graceful arc. Now I could see the field, at last. There was no time to lose. I managed to

stop the bleeding by deploying a rubber band across the bleeding vein, down the endoscope. Bang: band applied, scope out, job done. By this time it was seven am. No point going home, just the start of another day.

Big Bollocks got his liver transplant quite promptly. Predictably, he had all the staff at the transplant centre in London eating out of his hand in no time at all. He sailed straight through the operation and was discharged at day seven. The transplant cured him. It also helped him to stay off the booze, as he knows someone had to die and generously donate their liver to him in order for him to survive. He's had no problem staying off the booze, and I knew he wouldn't. On occasion, when I am stuck with a very difficult alcoholic, I ask Big Bollocks to come and talk to the patient. This can help quite a lot. He tells them about the size of his bollocks, and the fact that he had cancer too. This gives patients hope, as if you passed Big Bollocks in the street all you would see is a good-looking man in his mid-fifties who looks as fit as a flea. His bollocks, perhaps somewhat to his disappointment, have resumed their pre-morbid status.

This kind of case is becoming more common and, as a result, so is being called out of bed to deal with it. This is not a problem at the time of such a call, as adrenaline kicks in, producing a response from me that is usually measured, appropriate, and without background weariness. When I was younger, I could work the next day with no problem. When I turned fifty, not only did I grasp the sense of my own mortality (curiously previously absent, despite all the human catastrophes I had witnessed), but my ability to cope with sleep disturbance took a nosedive. When called in the night I found I could still respond well, but the consequences of sleep deprivation took increasing lengths of time for my body and mind to recover. More recently, after being called out in the night, it takes me at least a week, sometimes two, to get over it. I suppose I am, somewhat begrudgingly, getting old. Maybe it's time for me to call it a day with frontline medicine.

CHAPTER FIFTY-EIGHT

THE BREXIT VIRUS, UNITED KINGDOM, 2017

I noticed something happening three or four years ago. The number of cases of HEV infection I was seeing at the jaundice hotline increased considerably. Looking at our data, the number of cases had more than doubled. We had not changed the way we tested patients, there just seemed to be a lot more. I wondered why this might be. My impression at the coal-face was backed up by national data from Health Protection England. The number of laboratory-confirmed cases in England and Wales increased by a factor of greater than three from 358 in 2010 to 1,243 in 2016.[1] Analysis of the number of patients tested compared to the number of cases diagnosed suggests that the increase in the incidence of HEV infection in England and Wales is due to a significant increase in the virus circulating in humans. In other words, this is a true increase in incidence rather than ascertainment bias due to increased clinician awareness and increased testing.

In 2012–13, the number of blood donors in England who were viraemic when donating blood was one in 2,848.[2] Initial results following the introduction of the screening of donors for HEV in the United Kingdom in 2016 show that the number of viraemic donors has increased. Most spectacularly, in Scotland the number of viraemic donors has rocketed from one in 14,250 to one in 2,481: a five-fold increase.[3] This has been accompanied by a twofold increase in HEV seroprevalence in donors from Edinburgh. This increase is mainly due to increase in exposure to HEV in blood donors under the age of thirty-five. Considering all these

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[1] Adlhoch et al., "Hepatitis E Virus."

[2] Hewitt et al., "Hepatitis E Virus in Blood Components."

[3] K. Thom, P. Gilhooly, K. McGowan, K. Malloy, L. M. Jarvis, C. Crossan, L. Scobie, O. Blatchford, A. Smith-Palmer, M. C. Donnelly, J. S. Davidson, I. Johannessen, K. J. Simpson, H. R. Dalton, and J. Petrik, "Hepatitis E Virus (HEV) in Scotland: Evidence of Recent Increase in Viral Circulation in Humans," *Euro Surveillance* 23 (12) (2018). doi: 10.2807/1560-7917.ES.2018.23.12.17-00174.

data together, there is no doubt in my mind that we are in the middle of an epidemic of HEV infection, and my estimate of the number of cases per year in the United Kingdom (most of whom will have no symptoms) is at least 250,000. What on earth is going on?

The key observations were again made by Health Protection England. Before the incidence of HEV infection increased so spectacularly, starting from around 2010, the strain of HEV found in humans in the United Kingdom was similar to that in UK pigs. The virus was skipping from UK pigs to UK humans; the route of infection was uncertain. From 2010, the strain of HEV found in humans started to change. A new strain of HEV started to appear in humans in the United Kingdom. Although it was still genotype 3, it was significantly different to the strains of HEV found in UK pigs. It was identical to that found in pigs from Continental Europe, especially from the Netherlands, Denmark, and Germany.[4] [5] [6] [7] The year-on-year increase in human cases of HEV infection between 2010 and 2016 was almost entirely due to the strain of HEV from Continental European pigs.[8] This observation strongly suggested that, over the last few years, there has been a significant perturbation in the UK food chain with respect to HEV-infected foodstuffs emanating from Continental Europe. It seemed to some observers that this was almost akin to an "early Brexit leaving present" from our friends on the Continent. The strain of HEV concerned was dubbed by the UK and international media as the mutant "Brexit virus." The story subsequently went "viral" in the UK and international media.[9]

In addition to the epidemic of the Brexit virus we are seeing in the United Kingdom, there appears to be an identical epidemic in Continental Europe caused by the same strain of HEV genotype 3. The best example of this is in the Netherlands, where the seroprevalence in young adults has

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[4] S. Ijaz, B. Said, E. Boxall, E. Smit, D. Morgan, and R. S. Tedder, "Indigenous Hepatitis E in England and Wales from 2003 to 2012: Evidence of an Emerging Novel Phylotype of Viruses," *Journal of Infectious Diseases* 209 (8) (2014): 1212–8.

[5] S. Grierson, J. Heaney, T. Cheney, D. Morgan, S. Wyllie, L. Powell, D. Smith, S. Ijaz, F. Steinbach, B. Choudhury, and R. S. Tedder, "Prevalence of Hepatitis E Virus Infection in Pigs at the Time of Slaughter, United Kingdom, 2013," *Emerging Infectious Diseases* 21 (8) (2015): 396–401.

[6] M. J. Ankcorn and R. S. Tedder, "Hepatitis E: the Current State of Play," *Transfusion Medicine* 27 (2) (2017): 84–95.

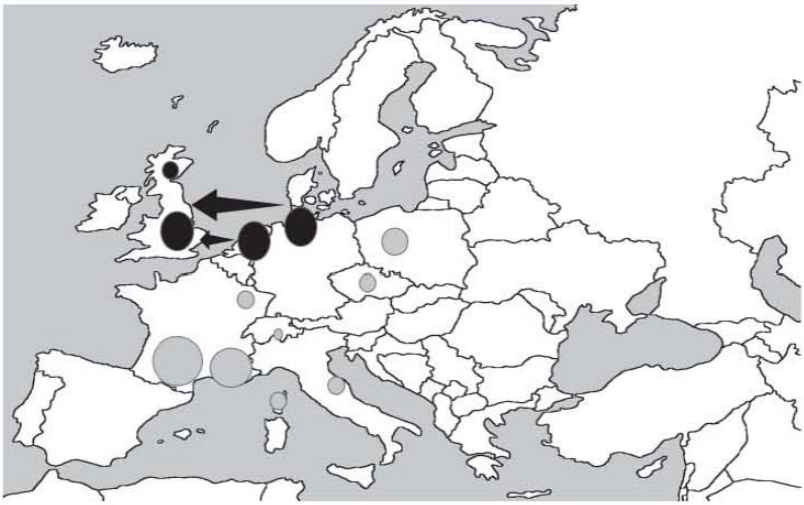
[7] B. Said, S. Ijaz, M. A. Chand, G. Kafatos, R. Tedder, and D. Morgan, "Hepatitis E Virus in England and Wales: Indigenous Infection is Associated with the Consumption of Processed Pork Products," *Epidemiology and Infection* 145 (12) (2017): 2417–23.

[8] Ibid.

[9] J. Leake, "'Brexit Virus' Feared in 10% of Sausages," *The Times* (May 21 2017).

dramatically increased over the last few years, and the number of viraemic donors has jumped from one in 2,600 to one in six hundred.[10] [11] In northern Germany, where blood donor screening has very recently started, the number of viraemic donors is now one in eight hundred.[12] These observations raise a number of questions, the most pressing of which are: (a) How is the Brexit virus getting across the North Sea from Continental Europe to the United Kingdom? (see Fig. 1 below); and (b) what has caused this epidemic?

Fig. 1: Hotspots of HEV infection in Europe



There are several hotspots of HEV infection that have been identified in humans in Europe caused by HEV genotype 3. These include southwest, southeast, and northeast France; Corsica; Abruzzo in central Italy; Ticino, southern Switzerland; the Czech Republic; west/central Poland (all shown in grey in Fig. 1 above); northern Germany; the Netherlands; the United Kingdom (all shown in black). The areas shown in black show are where strains of the Brexit virus (HEV genotype 3c; clade 1 group 2) infect humans. In the Netherlands and Germany, the same HEV strains are found in local pigs. This seems not to be the case in the United Kingdom. Quite how the Brexit virus is crossing the North Sea is uncertain.

[10] Slot et al., "Silent Hepatitis E Virus Infection in Dutch Blood Donors, 2011 to 2012."

[11] Zaaijer, "No Artefact, Hepatitis E is Emerging,"

[12] Westhölter D et al, "HEV Positive Blood Donations Represent a Relevant Infection Risk for Immunosuppressed Recipients.".

The most credible source of the Brexit virus in the United Kingdom is in the human food chain. The likelihood of this being due to HEV-contaminated meat was strengthened by a study from the Netherlands which showed that meat eaters are almost twice as likely to have been exposed to HEV, compared to vegetarians.[13] Further studies by Health Protection England showed that UK patients with HEV infection were more likely to have consumed pork sausage, pork pies, and processed ham, compared to control subjects.[14] A further study of UK patients with HEV infection, none of whom had travelled abroad in the preceding two months (the maximum incubation period of HEV), showed that patients infected with the Brexit virus were more likely to have purchased pork products (particularly sausage and processed ham) from a single UK retailer.[15] The retailer was named in this study, somewhat mysteriously, as "Supermarket X." These data suggest that the Brexit virus is skipping across to the United Kingdom from Europe inside pork products produced in Continental Europe, mostly within the supply chain of a single UK supermarket—supermarket X. There was public outrage when this was reported in the UK press,[16] and calls for the supermarket to be named, which it duly was. However, the issues involved are not the fault of a single supermarket but relate to more general issues of farm husbandry and the process of manufacturing pork products for human use.

One way of avoiding being infected with HEV is to cook pork thoroughly. Laboratory experiments show that cooking temperatures of 70°C for twenty minutes are required to ensure that HEV is killed; this is considerably longer than most UK punters cook their sausages.[17] So, one effective way of avoiding getting infected is to cremate your sausages; I've started to bake mine for twenty minutes. They don't taste so good as sausages cooked by more commonly used methods, but any lurking virus is dead. What is more concerning is that precooked processed ham is also implicated in Brexit virus transmission. How can processed ham transmit HEV? To my mind, there are only two possibilities. The first is that the

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[13] Slot et al., "Meat Consumption is a Major Risk Factor for Hepatitis E Virus Infection."

[14] B. Said, M. Usdin, F. Warburton, S. Ijaz, R. S. Tedder, and D. Morgan, "Pork Products Associated with Human Infection Caused by an Emerging Phylotype of Hepatitis E Virus in England and Wales," *Epidemiology and Infection* 142 (7) (2014): 1467–75.

[15] Said et al., "Hepatitis E Virus in England and Wales."

[16] Leake, "'Brexit Virus' Feared in 10% of Sausages."

[17] Emerson, Arankalle, and Purcell, "Thermal Stability of Hepatitis E Virus."

cooking process when preparing the ham is insufficient to kill the Brexit virus; the second is that HEV-infected material is added to the ham *after* the cooking process.

When ham is prepared for processing, the first thing done is to cook it in boiling water. Providing the cooking process is long enough, this should kill all the HEV that may be lurking inside. Following this, the second step in processing is to slice the ham in preparation for packing and subsequent sale. When ham is sliced, small holes appear in the ham slices where the bits of fat and gristle were. For reasons that escape me, European food manufacturers appear to think that having such holes in processed ham is unacceptable to European consumers. To get around this issue, the food manufacturers fill the holes up to produce a nice even, glossy slice of ham, which is now ready to pop inside a sandwich to put in one's lunchbox. Unfortunately, the material used as this processed ham "meat-filler" is air-dried pig serum taken at the time of slaughter. This meat filler is stuffed full of Brexit virus.[18] Smakelijk eten; velbekomme; Guter apetitie—Idioter; idioten; idioten.[19]

[18] I. L. A. Boxman, C. C. C. Jansen, G. Hägele, A. Zwartkruis-Nahuis, J. Cremer, H. Vennema, and A. S. L. Tijsma, "Porcine Blood Used as Ingredient in Meat Productions May Serve as a Vehicle for Hepatitis E Virus Transmission," *International Journal of Food Microbiology* 257 (2017): 225–31.

[19] "Bon appétit—idiots" in Danish, Dutch, and German.

CHAPTER FIFTY-NINE

MUM

Mum was born into a working-class family in my home town in Yorkshire just after the First World War. Her father worked in the local woollen mills. She was a bright child and won a place at the local grammar school aged eleven. She was marked out as a potential future teacher, which was her dream. Events intervened as she became sick and was carted off to spend a year in a hospital, some two hundred miles to the south. I asked her many times what was wrong with her at that time. She always replied: "I had a dicky chest, and it has not been quite right since."

On a number of occasions, I asked her if it was TB. She always vehemently denied this, but that is most certainly what it was. I can think of no other reason why she would have been sent to a remote hospital situated in the green countryside just outside London. It had to have been a TB sanatorium. Of course, in those pre-antibiotic days, TB carried both significant social stigma and often a death sentence. Maybe she was never told she had TB. Maybe she was, and she just blanked it out. Whatever the case, her chest x-ray showed the typical appearance of previous pulmonary TB, with a scarred and shrunken left lung, which was the site of her recurrent chest infections that was to plague her intermittently for the rest of her life.

After a year in hospital she returned home but was not allowed to continue her studies to be a teacher by my grandparents. The reason for this was that the family was poor, Mum had missed a year of her schooling, and her younger brother, who went on to be a professor of mathematics, had also got a scholarship to the grammar school. The family simply could not afford to have two children in "extended" (in 1930s terms) education. So, Mum went to work in the local woollen mill at the age of fourteen, along with her father and most of her peers. Mum worked hard all her life. Bringing up five kids was a challenge, and, in addition, she had all sort of jobs including cleaning, shop work, factory work, and a post as a healthcare assistant. The latter was a job caring for the elderly in their homes, attending to their basic needs—a job she liked, and did on her bike. She painted, she cleaned, she cooked, and was up and down ladders

well into her eighties. Another thing about Mum was there was no malice in her body at all, unless you count the long-dormant TB organisms still residing in the remnants of her scarred and shrunken left lung. I rarely, if ever, recall her speaking badly about anyone. This sense of altruism was deep seated. In later years, when we talked for any length of time, she would always remind me:

"Harry, When I am dead and gone, I want to leave my body to medical science, just like your dad did. You won't forget now."

"No, Mum."

Mum did not slow down until she turned eighty. At about this time she lost her sense of visual depth. This resulted in an unfortunate incident where she drove her car down the street and knocked off every parked car's wing mirror that had parked on her side of the street for a distance of one hundred yards or more from her house. The funny thing is, she did not miss a single parked car—they all lost their off-side wing mirrors. She had no choice but to reluctantly give up her car keys. Then, gradually, her body started to complain, her chest infections were more frequent, and she had a fall in the street and broke her arm. This sapped her confidence and she never completely recovered her pre-morbid sprightliness. She then started becoming a little forgetful; first a little, then quite a lot. It wasn't until she started wandering that we realised she was some way down the road to full-blown dementia.

Mum then developed a major issue with rubbish disposal. For whatever reason, she decided to decline the services of the local council's weekly refuse collection. Instead, she burned it. This caused quite a stir down the street because she could not burn the rubbish in the house as it had no fireplace. Instead, she burned it in a small alleyway down the side of her small two-up two-down, nineteenth-century, back-to-back house. At this stage of her illness, Mum's definition of "rubbish" was somewhat broader than most other people's might have been and included most of the family photos. It was as if she was clearing up after her brief stay on this mortal coil. She liked things tidy; she was preparing to die. Mum lived just fifty yards from my brother and his family, who looked after Mum brilliantly on a day-to-day basis, still allowing her to live independently long after she would have otherwise been able to. Then she became very distressed. She was confused, disorientated, and extraordinarily anxious. Nothing seemed to calm her. Following family discussions, we agreed that Mum needed residential care. We eventually found a place ten minutes' drive from my home town. Inexplicably, as soon as she was settled in her new home, all her anxiety dissipated, almost overnight.

The nursing home that Mum went to was "par for the course" in terms of the quality one might expect from such a state-funded institution in the United Kingdom. In reality, it was awful. It was full of mainly old women, like Mum, with advanced dementia and varying degrees of dis-mobility. It smelt of urine, bleach, and decaying human flesh. The inhabitants all sat around three of the four sides of the dayroom waiting to die. The fourth side of the day room was given over to a huge TV screen, to "entertain" the residents, the volume usually up quite high. Of course, none of the residents could follow the television for more than a few seconds, given their mutual and profound neurological degeneration. The television was there, continually blaring total drivel, as a meaningless prop. What about a bit of Chopin instead, guys? Occasionally, the nursing home would put on specific entertainment for the residents. This included a musician who toured the local nursing homes singing songs with his ukulele, of the George Formby ilk. Mum got to sit right next to him. Poor love—she hated George Formby and went off to bed at five pm with a headache and in a huff.

One time I went to see my mum at the nursing home, I could not find her. I knew she was there somewhere, as she was in a lockdown area—no escape for the inmates. I asked the carers where she was. "She's in the day room," I was told. I could not work this out, as that's the first place I checked. Television blaring, inmates backed up against the walls in oblivion to the man with the silky voice and spray-on orange tan trying to flog cheap jewellery at exorbitant prices. I went to Mum's room. It was empty. I went back to the dayroom and looked again. Now I saw her but had to look twice. She had on garish pink lipstick and her nails had been painted red. Never, ever did Mum wear any make-up, lipstick (kosher, halal, or otherwise), or cosmetics of any description, at any time in her long and humble life. I simply did not recognise her. She was oblivious to both the state of her face, nails, and my very profound inner distress. I tried, probably unsuccessfully, to put it to one side and we got down to the business at hand—a few serious games of dominoes. Mum loved to win. I let her win six times straight. I left her smiling, with the cheap lipstick smeared on my cheek.

During Mum's two-year stay at the nursing home, I lost count how many times she was admitted to the local hospital as an emergency. These admissions were usually, but not invariably, precipitated by her dicky chest. Other occasions were following falls, temperatures, infections in her swollen legs, and farting the wrong way. Each time she was sent to hospital by ambulance. Each time she was admitted, underwent countless tests and treatments, and each time she came back to the nursing home a

little more confused and disorientated than previously. When faced with a patient like this, my younger doctoring colleagues sometimes get a bit carried away. This is, to some extent, understandable. They want to be thorough; they want to do the right thing à la textbook/guideline; they do not want to be perceived as ageist. I understand this, but my mum did not need two CT scans, three echocardiographs, countless chest x-rays (all showing the same TB-scarred lung), and more than one hundred blood tests during the last two years of her life. Did I really need to know she had critical aortic stenosis? So what? It was not going to make any difference to her, me, my family, or the doctors looking after her. Her case needed what I term "soft-hands"—minimal or no tests, a decent dose of antibiotics for a few days, plenty of oral fluids, and good nursing care. She did not need to be in an emergency hospital bed, as this care could potentially and easily have been done without moving her

In the end we had a family discussion. We decided to not allow Mum to be admitted again to hospital under any circumstances. This caused a bit of consternation in the nursing home. The requisite forms were filled and that's what happened. We should have come to this decision much earlier. It wasn't long after that I saw her for the last time, just after the George Formby incident. The veins in her neck were up, and her ears were waggling—ominous signs in aortic stenosis. I knew this was going to be the last time I saw her. She died peacefully in her sleep a few days later. I cried at her funeral. She'd had a good, long, and fulfilling life, but she was my mum. I got more overtly upset than my brothers and sister. Perhaps I'm more emotional than them. I know for certain it advanced my own sense of mortality. Also, against her express and repeated wishes, she ended up getting cremated. I'd assumed she'd filled in the forms to leave her body to medical science at the same time my dad did—she hadn't, or at least they could not be found. Maybe she inadvertently burned them by the side of the house while "clearing up." I do not know, but it upset me. A final indignity.

When I walk into the A&E department of my hospital, the same sight always greets me; a sight that is now, more or less, universal in any such institution in the United Kingdom. There is an almost endless line of patients and their relatives waiting. They are waiting in the corridor, mostly on trolleys and wheelchairs. They wear expressions of weary acceptance, except the increasing numbers of patients like Mum who are oblivious but often confused by the surroundings which are noisy, brightly lit, and full of important-looking people going to and fro. These patients are in the corridor, waiting be "seen." Some wait many hours.

Earlier this year I was driving to work. It was early in the morning, I wanted to be there by seven thirty as I was "on the wards," and I like to check all the in-patients' results before the ward round starts at eight thirty. As usual, I listened to the news on the car radio; mostly depressing stuff as normal. Following the news, the presenter did an in-depth interview with the president of the Royal College of Physicians in London. I pulled over as I wanted to listen to what she was going to say without any distractions from other motorists. She explained that the NHS was not working, and the reason for this was that there were insufficient beds, doctors, and nurses to care for the numbers of patients, increasingly very elderly and frail, requiring hospital admission. As a result, the flow of patients through the hospital was compromised, and they were backing up in hospital corridors all over the country where they were awaiting assessment. She went on to explain that many hospitals in the United Kingdom had appointed doctors and nurses whose *sole* responsibility is to attempt to administer care for patients waiting in the corridors. None of what the president said was news to me, except the latter point. It would now appear that making elderly patients wait in corridors is somehow normal. It is not. We are treating our fellow human beings like animals.

At any one time on my ward we have nine or ten patients like my mum. I try my best to treat them gently, but appropriately. This generally means taking the soft-hands approach, but occasionally I will send a patient in their nineties for a major operation. We all wear our bodies out at different rates, and such cases are mostly biologically ten years younger than their chronological age would suggest. Returning very elderly patients from whence they came, once their medical treatment is complete, however, is problematic. They have to undergo endless assessments (physio and occupational therapy, social work) which seem to take forever. Then they are "listed." The lucky ones return home. The unlucky ones, who are now incapable of looking after themselves, are listed for a "residential" or "nursing" home. The problem with this is threefold. Firstly, there are not enough residential and nursing home places to keep up with spiralling demand. Second, the funding and transfer of patients to such homes is not fit for purpose. Finally, and as Mum experienced, the quality is somewhat variable, in terms of patient-centred care. Patients awaiting such placements—and I have witnessed them waiting several months on my ward in extreme examples—are referred to by some colleagues as "bed-blockers." I think this is an offensive way to refer to some of our seniors. But they do wait. They wait for ages, again. The way they are handled is the root of the malaise in the NHS in terms of

functional patient flow, and, more generally, reflects poorly on the British as a nation. Shame on us all for making this acceptable—it is not.

Hospital beds are not just at a premium in the "modern" NHS, they are like gold dust. Staff are regularly exhorted to discharge all patients at the first opportunity, all the time, always. League tables are kept in many NHS institutions to encourage us doctors to discharge early. I do not do particularly well at this exercise as, in my apparently increasingly dinosaur-like view, I was taught to discharge patients when they were ready to be discharged. Period. Other colleagues, brutalised by "discharge early" edicts from on high, do much better than me at clearing the ward. Bully for them!

The bed issue really is problematic though. Most NHS hospitals run on 100–105 percent bed occupancy. It was established many years ago that the optimal bed occupancy in hospitals is eighty-five percent, so it is no surprise the NHS is dysfunctional. I am not sure how some places run at 105 percent bed occupancy, but it probably relates to the problem-solving skills of management. The technical term in management-speak is bed "rebadging." Whole sections of A&E departments have been rebadged as wards. Day-care areas have been filled with beds and rebadged as wards. Balconies have not been used yet, as far as I am aware. That was in a different era, and for a different reason.

CHAPTER SIXTY

THE WANDERING DANE

Last year, during a moment of reflection, I tried to work out how many consultations I had done in my career. Maths is not my top subject, but by my reckoning I have completed just under half a million consults since I first started in medical school over forty years ago. That is a lot of hot air from me. Mostly average hot air I suppose; a few terrible ones; and an occasional exceptional one. To do medicine properly, in my view, the doctor should give the patient something. I'm not talking about pills or operations. I mean a smile, a gesture, a touch, a gentle few words, hope. I guess when I do this I give a little of myself, and doing so half a million times takes a toll. An old colleague and friend told me many years ago, as he was retiring: "Harry, there is a finite number of patients one can see in a professional career in medicine."

I think this is correct, and I began to realise I was quite near that finite number. I had extra duties due to sickness of two colleagues. Being on call became more onerous. Being called in to perform an emergency endoscopy in the middle of the night also increased in frequency. This was not always because of an un-delayable, pressing clinical imperative, but due to some guideline or other manufactured by the modern NHS. I realised I was slipping down towards the black hole again. In fact, I was looking over the edge into its murky depths. I began to sleep badly. I also looked in the mirror. As we age, our skin and other tissues lose their elasticity, and I am no exception to this inevitability. What struck me when I looked in the mirror, though, were the bags under my eyes, which were triple, puffy in nature, and dark in colour. This, I realised, was a new tool to measure my health, which I named the "bag-ometer." Three big bags, not sleeping, equals take some time off work, Doc.

I saw my doctors, who recommended I stop doing clinical work for an extended period, but continue with my HEV stuff. They also suggested a complete break from Cornwall, so I went to live with my brother and extended family in Pewsey in Wiltshire for a while. Pewsey is a lovely village of around four thousand souls situated a few miles north of

Stonehenge. The place has a real sense of history and community, together with a couple of excellent public houses.

The British pub is a unique institution. It is a place to drink, to eat, but also to have conversations. The nearest equivalent, I suppose, is the Greek bar or French cafe. But these are not quite the same as they lack the quintessential Britishness of the pub. The pub is under pressure from high rents, low margins, and fierce competition from supermarkets who sell cut-price booze. This is a great shame, and at one point over twenty pubs per week in the United Kingdom were closing their doors for good. This rate of decline has slowed, as many pubs are increasingly turning themselves into restaurants that also serve drinks. However, the old-fashioned pub, essentially a meeting place for locals, tourists, and travellers, is nearing the endangered species list.

When I first walked through the door of the Crown public house in Pewsey, I knew immediately that this was a proper old-fashioned pub.[1] This was a place of conversation, dating from the mid-nineteenth century, with low ceilings, a roaring fire, good beer, a nice landlord and staff, and with people talking to each other. The ancient walls and floor had been worn unevenly by the feet of drinkers over the passage of time, silent witnesses to discussion, argument, laughter, and tears dating back to the pre-Dickensian era. Drinkers and conversationalists are enticed through the door by delicious food, but also events such as chess night, sea-shanty night, and folk night. In addition, once a month or so the landlord (who is also an archaeologist), or invited guest, gives a talk. The subjects of these talks are wide ranging, from "aerial archaeology" to "the Vikings from a Danish perspective." While staying in Pewsey I got my arm twisted and ended up giving a talk on "the threat of HEV to human health."[2]

It was in the Crown that I had the pleasure of meeting Bo Pedersen. Bo is a wandering Dane, a temporary resident of Pewsey. He has been meandering across the globe for many years following the death of his wife from ovarian cancer at the age of fifty-one. He wanders geographically, he wanders intellectually, he wanders emotionally. When I first met him I thought he was in his eighties. He was grey, shrivelled, slightly unkempt, and hunched over, playing the locals at chess, which he always won. In fact, he was only sixty-four, and when he was a young man was in the Danish Lifeguards, assigned to protect the Queen of Denmark as a bodyguard. You would not have guessed that looking at him

[1] Crown Inn, Pewsey, Facebook page, https://www.facebook.com/crownpewsey.

[2] "Brexit Virus / Hepatitis E Virus Lecture by Dr. H. Dalton," Crown Inn, Pewsey, Facebook page, https://www.facebook.com/crownpewsey/videos/1613244165373217.

now. Bo had never, and will never, get over the loss of his wife. This has aged him well beyond his years, and emotionally I do not think he cared whether he lived or died. He had, almost, given up the will to continue.

I played him at chess and got very soundly thrashed. I started to talk to him. He told me the history of Denmark. We talked politics and religion. However, the most interesting discussions for me related to the meat industry, as Bo, before the death of his wife, was chief executive officer of a leading international meat production company and was for many years the president of the European Blood Protein Association. This conversation lasted over six months. He told me all about his experience with the international meat industry in general, and the pig-blood industry in particular. Intellectually, the shed had temporarily decamped to the public bar at the Crown, and Bo now had a reason to live.

Human beings, with some notable exceptions, have used farmed and wild pigs for millennia as a food stuff. If we humans are going to kill pigs to eat then I think we should look after them well, slaughter them humanely, and justify and honour their short life by using as much of the dead animal as possible. We should use all of the pig, from tail to nose—as the saying goes, "the only bit of the pig that cannot be used is the oink." However, in my view, there are two important provisos to this carnivorous point of view. First, we should fully respect the wishes of groups who do not want to use or eat pig products. Second, we should ensure that the consumption of pig products is safe, in terms of the health of human consumers.

I had previously not realised, until Bo told me, that the range of products containing porcine materials is bewilderingly broad and long. It includes such things as: paint, paint brushes, fabric softener, washing powder, cosmetics (including moisturisers and lipstick), soap, paper (including toilet paper), bottle corks, photographic film, crayons, shoes, glue, and farm and domestic garden fertilisers. Some cigarettes have porcine haemoglobin in their filters, which supposedly "lessens the risks to human health" from smoking. Porcine gelatine/glycerine is used in a number of products consumed by humans, including ice cream, low-fat butter, as a clarifying agent for fruit juice, wine, and beer, toothpaste, whipped cream, cream cheese, sweets, and prescribed and over-the-counter medications in capsule form.

The above list of pork-containing products is incomplete and is just an illustration. In my view, most of the above carry no risk, or only a miniscule risk, to human health due to potential contamination with HEV. The problem is that there is little or no clarity in terms of content labelling on these products. The contents label on the product may just say

"protein," or perhaps "animal protein." What do we say to the Orthodox Jew who unknowingly paints his front door with pig-containing paint? What do we say to a Muslim chain smoker? What do we say to a vegan couple whose child wants to draw pictures with porcine pencils on porcine paper?

A couple of years ago the European Food Standards Agency (EFSA) held a meeting in London to discuss emerging zoonotic threats to human health.[3] It was held at the Royal Society in Pall Mall in Central London; a most salubrious and historical setting. Three infectious threats in the human food chain were up for discussion, one of which was HEV. I was asked to kick off the HEV part with an overview. As always, before I got up to speak I had my usual nerves, compounded by the fact that the lecture theatre walls had portraits of previous fellows of the Royal Society. As I spoke, I had Isaac Newton staring down at me with a critical eye. No pressure, then!

The meeting lasted two days. The attendees (food industry, regulatory authorities, infectious disease experts in human and animal health) came up with a list of research priorities to tackle the issues. The problem was, we learned at the end, there was no funding. Many of my colleagues regarded this exercise as a more-or-less redundant talking shop. I am not sure what Sir Isaac would have thought. Nevertheless, I was interested to talk to colleagues from the meat industry and EFSA. I asked them how we could identify the pork, and potentially its infectious threat from HEV in the food chain. The answer was simple—this is not possible. The reason for this is that when a product contains less than twenty percent pork, under existing legislation, it is not compulsory to identify the source of a food product's protein as being of porcine origin. This bolstered my unease about members of our society who had no wish to eat pork. It provoked outright disbelief in terms of my understanding of infection control. In summary—yes guys, this may or may not have pork in it, we have no way of knowing for sure. Ergo, we have no way of knowing if it might or might not contain HEV.

Pork-derived therapies have been used in medicine for decades. A good example of this is that patients with diabetes were for many years treated with porcine insulin, extracted from mashed-up pig pancreas. Porcine insulin has now been replaced in medicine by genetically-engineered human insulin. Another example is the blood-thinning injection called heparin, which originates from pig intestine, and is still

[3] "Summary Report of Joint Scientific Workshop on Foodborne Diseases," Centre for Environment Fisheries & Agriculture Science, (October 20, 2016), https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2016.EN-1103.

commonly used in the treatment of deep vein thrombosis in the leg and blood clots on the lung. My guess is that a vast majority of patients will accept treatment with heparin were they to be told it was a pig product, irrespective of their religious or ethical standpoints, as treatment with heparin in these situations is potentially life-saving. I am not quite sure the same applies to the use of heparin as a prophylactic therapy. Patients who are bedbound in hospital, for whatever reason, are prone to developing deep vein thrombosis (known as DVT, a blood clot in the veins of the leg). To reduce the risk of this happening, patients who are bedbound are treated with either special stockings or low dose heparin injections, and both are quite effective in preventing clots. I have prescribed prophylactic heparin on countless occasions over the course of my career, irrespective of the patients' views. The reason for this was that, until recently, I did not know that heparin was derived from pork.[4] I do now. I tested a good number of batches of heparin destined for use in humans to see if any were contaminated. None of them contained HEV.[5] Whether porcine insulin contains HEV is unknown.

Bo also informed me that there are a range of porcine-containing materials derived from pig blood. The pig blood comes in various preparations on sale to the food industry. These products include porcine whole blood that has been spray dried, porcine plasma prepared as a liquid, powder, or frozen, porcine haemoglobin prepared as a powder or frozen, and various serum proteins. Batches of these preparations have recently been tested by colleagues from the Dutch National Institute for Public Health and the Environment in the Netherlands. They found HEV in many of the tested porcine blood products, of the Brexit virus strain.[6] These infected pig-blood products therefore pose a significant threat to human health. They are used in a range of meat products (not just pork) including as a substitute for egg white as a binder, as a natural food colourant, as a substitute for casein and egg protein as an emulsifier, as a means of replacing fat and calories in low-fat preparations, as a meat glue, as a colourant in salami, and as a meat filler in processed ham. In addition, there are a number of non-meat products that porcine blood preparations

[4] I checked this with my Muslim and Jewish medical colleagues, some of whom were also unaware about the porcine origin of the heparin that they too had been obliviously prescribing.

[5] C. Crossan, L. Scobie, J. Godwin, J. G. Hunter, T. Hawkes, and H. R. Dalton, "Is Porcine Derived Heparin a Source of HEV Infection in Human Recipients?" *Infectious Diseases* 19 (2013): 686–8.

[6] Boxman et al., "Porcine Blood Used as Ingredient in Meat Productions May Serve as a Vehicle for Hepatitis E Virus Transmission."

are used in. These include as replacement for eggs in bread and cakes, and as a possible source of dietary iron in products fortified with pig haemoglobin. Finally, pig-blood products are used in animal feed including dog food, cat food, fish food (both domestic and farmed fish), and last, but by no means least, farmed animal food, including that given to pigs.[7] Idioter; idioten; idioten!

[7] "Supplying and Using Animal By-products as Farm Animal Feed," UK Government, https://www.gov.uk/guidance/supplying-and-using-animal-by-products-as-farm-animal-feed#abps-you-can-use.

CHAPTER SIXTY-ONE

HYPOTHESIS

The face of modern medicine was changed forever by Alexander Fleming's discovery of penicillin while working at St Mary's Hospital in London almost one hundred years ago. He did not realise the full potential of his discovery, but subsequently Howard Florey, an Australian working at the Dunne School of Pathology at Oxford University, did. After doing various animal experiments, in 1941 Florey and colleagues used penicillin to treat a policeman with a severe facial infection at the Radcliffe Infirmary, Oxford. The policeman improved considerably, but the supply of penicillin started to run out. Florey's team collected the policeman's urine in a vain attempt to recover more of the new "wonder drug" that had not been metabolised by the patient. In the end, the policeman died, as the very limited supply of penicillin was exhausted. Penicillin was subsequently mass produced in the United States by Merck and Co. and was used extensively for battlefield injuries towards the end of the Second World War. In 1945, Fleming and Florey shared the Nobel Prize for Medicine. Penicillin, and other subsequently discovered antibiotics, has saved countless lives ever since this time.

Antibiotics are useful only for treating bacterial infections and have no antiviral activity. It makes no sense to give antibiotics for conditions such as coughs and colds and flu as these are caused by a number of differing viruses, and not only is antibiotic therapy for these conditions illogical (as it doesn't work), it can lead to antibiotic resistance. Antibiotic resistance is an increasing problem across the world. All types of bacteria are becoming resistant to a range of antibiotics, fuelled by over and inappropriate use of these drugs. Such resistant bacteria include the "superbug" MRSA and, even more concerning, multiple drug-resistant tuberculosis.

When streptomycin was introduced for the treatment of TB in the late 1940s it made a fundamental impact. Countless patients were cured following a few months of injections, and the days seemed numbered for the TB sanatoria and specialised TB hospitals that had been previously required, as I was to discover when I worked at Tehidy Hospital in Cornwall in the early 1980s. Unfortunately, the notion that TB could be

eradicated from the planet by antibiotics proved overoptimistic. As the TB bacteria multiplies it mutates, and some of the mutants are resistant to some of the antibiotics used and undergo Darwinian self-selection favouring the survival of the mutants. In addition, micro-organisms have a number of rather ingenious ways of sharing their genetic material that confers antibiotic resistance, including plasmid exchange. The situation worldwide with multiple drug-resistant TB is now critical, as some patients are effectively untreatable with all known antibiotics. This has led to a sight I thought I would never witness in my professional lifetime, as some of these antibiotic-untreatable patients are now being subjected to antiquated surgical approaches, such as surgically collapsing the affected lung, in an attempt to gain control of the patient's TB. Such surgery has not been used for decades, following the initial success of antibiotics. What is even more worrying is that there are vanishingly few antibiotics in the development pipeline—the cupboard is bare.

To reduce the amount of bacterial antibiotic resistance around the world, the concept of "antibiotic stewardship" has been introduced. What this means is that antibiotics should only be used when there is a clear indication; they should be used for the correct duration; and the correct antibiotic should be used, bearing in mind local antibiotic resistance patterns. Some antibiotics are kept on a "reserve list"—these are the only antibiotics that certain resistant bacteria are susceptible to. Many hospitals all over the world are appointing a chief antibiotic steward. This is usually a microbiologist whose role is to ensure that antibiotics are used in the above way, and whose agreement you need prior to using a reserve-list antibiotic. However, this approach has had only a modest impact on global antibiotic resistance. There are two main reasons for this. First, in many countries in the world antibiotics can be purchased "over the counter," i.e. without a doctor's prescription. No amount of stewardship is going to impact on this state of affairs, in terms of over and inappropriate use of antibiotics. Second is the widespread use of antibiotics in animal feed.

Antibiotics have been used as growth promoters in animal feeds for over fifty years. Over the last couple of decades, the amount of antibiotics used in this way has reached industrial proportions, and in some countries far more antibiotics are used on animals than on humans. Antibiotics used in animal feed is being done routinely, but not because the animals have ongoing bacterial disease, but merely to improve the growth rate of the animals fed with antibiotic-containing feed in order to bring them earlier and more cheaply to their ideal slaughter weight. The levels of antibiotics in the feed are frequently sub-therapeutic and this, together with their very widespread use, has significantly increased antibiotic resistance to a range

of important antibiotics. This includes resistance to the reserve-list antibiotic colistin. The latter point is of particular concern as there are some bacteria which affect human beings that are resistant to every other antibiotic. Were widespread colistin resistance to develop this would be a disaster in medical terms, and potentially life threatening for humans infected with the offending resistant bacteria. As a result of the above, the use of antibiotics as growth promoters in animal feed was banned in the European Union in December 2006[1] and in the United States in January 2017.[2]

Passing a law to ban a practice is easy, but implementing it may not be. This proved to be the case with banning antibiotics as growth promotors in animal feeds in Europe. In most countries, the EU ban made not a jot of difference, as farmers simply "rebadged" their use of antibiotics from that as "growth promoters" to "therapeutic" use. In other words, they claimed their animals were sick and gave them all antibiotics, much as they had previously done. A good example of this is the Netherlands, which traditionally used comparatively large amounts of antibiotic-laced animal feed by European standards. Following the EU ban there was no decrease in antibiotic usage in animal feed at all. This was noted by the Dutch government, who in 2009 introduced a strict target of a fifty percent reduction of antibiotics in animal feed for whatever reason, accompanied by a strict monitoring system.[3] The Dutch initiative was successful, and now the amount of antibiotics used in the rearing of animals is one of the lowest in Europe. The use of antibiotics in many other EU countries, by contrast, remains high and similar to that used prior to the EU-wide ban in 2006.

Since 2009, pig farmers in the Netherlands have been faced with a dilemma. They could no longer use antibiotics in the animal feed to ensure quick growth of their pigs—what should they do to address this? They needed a quick and cheap fix. In stepped the pig-blood industry, with data suggesting that air-dried pig blood as animal feed was an excellent, cheap,

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[1] "Ban on Antibiotics as Growth Promoters in Animal Feed enters into Effect," European Commission press release (December 22, 2005), http://europa.eu/rapid/press-release_IP-05-1687_en.htm.

[2] A. Moodie, "Will New FDA Rules Curb the Rise of Antibiotic-resistant Superbugs" *The Guardian* (January 8, 2017), https://www.theguardian.com/sustainable-business/2017/jan/08/fda-antibiotic-use-in-livestock.

[3] "Farm Antibiotic Use in the Netherlands," http://www.saveourantibiotics.org/media/1751/farm-antibiotic-use-in-the-netherlands.pdf.

and safe growth promotor alternative. This was a double-win for the meat industry. The use of pig blood as a by-product was previously commercially problematic. As is commonly known, pig blood is used to make pig-blood sausage, but the market for this is relatively small compared to the amount of pig blood produced at slaughter—there is only so much black sausage and boudin noir that we humans can consume. Disposing of unwanted pig blood correctly and safely is time consuming and expensive. By marketing pig blood as an animal feed and growth promoter, the industry turns a profit through the sale of the feed, but in addition reduces the costs of the disposal of unused blood. This "win-win" scenario appeared to be a no-brainer to the guys involved.

While there is little doubt that pig-blood based feed is a good growth promotor and is cheap, there is very considerable doubt about its safety, now we know it is almost certainly contaminated with HEV genotype 3.[4] During processing, blood from literally hundreds of pigs is put in a huge vat and air dried. While, perhaps, most of the pigs' blood will contain no HEV, some will contain huge amounts of HEV, thus contaminating the whole batch.[5] Turning pigs into cannibals by feeding them potentially HEV-infected pigs blood could well act as a viral "magnifier" in pig herds fed in this way—a lesson we appear not to have learned following the BSE disaster. HEV-contaminated feed may well result in increased numbers of pigs being viraemic at the time of slaughter. It may also increase the viral loads in pig products on sale to the public. It may be that this practice is at the heart of the epidemic of HEV infection we have seen both in the Netherlands and the United Kingdom, and possibly in other hotspots across Europe. This scenario is a hypothesis. It may be wrong, it may be correct, but whatever the case it certainly bears further detailed scrutiny.

The hypothesis I have outlined is a theory. There are a number of unanswered questions, but it seems to fit the timelines involved. The increases in cases of HEV infection started around 2010 in the Netherlands, and a little later in the United Kingdom. This fits with the change in practice in the Netherlands in 2009 with respect to reduced antibiotic usage and increased use of pig-blood products as a growth promoter. The hypothesis would also explain why HEV genotype 4 keeps popping up in pigs and humans in Europe. HEV genotype 4 is normally only found in East Asia and behaves in a very similar way to HEV genotype 3 found in Europe. Over the last few years, Chinese pig-blood manufacturers have entered the European feeding frenzy, trying to capture

[4] Boxman et al., "Porcine Blood Used as Ingredient in Meat Productions May Serve as a Vehicle for Hepatitis E Virus Transmission."
[5] Ibid.

some of the market which is estimated at £250,000,000 per year in Europe alone. The Chinese are now importing pig-blood products, potentially laced with Chinese HEV genotype 4, to Europe. However, the hypothesis does not really explain why the burden of HEV infection in humans in the United Kingdom appears to be emanating from a single national retailer—supermarket X. Maybe there are unique, additional, and currently unknown factors at play in this particular part of the food chain.

Pigs don't fly—it makes no commercial sense to put them in an aeroplane.

CHAPTER SIXTY-TWO

POSTSCRIPT

The Hepatitis E Virus

Although many questions remain unanswered, we appear to have a major problem with HEV in Europe, both in humans and pigs. At the oblivious heart of the problem are the poor old pigs, which may inadvertently have been turned into viral magnifiers by us humans feeding them with feed dosed with pig-blood contaminated with HEV. This was the root of the problem in the benign spongiform encephalitis (BSE) crisis in the 1980s when we humans also turned herbivorous cows into cannibals by giving them feed laced with cow protein, with a good dash of the prion that causes mad cow disease in the animals concerned, and variant Creutzfeld Jacob disease (vCJD) in humans. The emerging issue with HEV has some parallels with this previous catastrophe.

Like the threat from HEV, the issue with BSE took some time to uncover, following all sorts of misplaced reassurances from the powers that be. This is perhaps best exemplified by a minister of Her Majesty's Government appearing on primetime UK television, trying to encourage his young daughter to eat a beef burger.[1] John, this was never a good idea. Not only were your reassurances empty, you should have eaten the burger yourself! I hear that now the girl in question has grown up she is a vegetarian. The BSE scandal was eventually exposed and tackled by banning the use of cow protein in their animal feed. Symptomatic mad cow disease stopped quite quickly in the UK cow population following this and other measures. However, prion disease is a "slow-burner" in humans, and deaths from vCJD continued for many years in an increasingly small number of humans in the United Kingdom. In fact, the last case was in a classmate of mine from medical school. He died a

[1] "1990: Gummer Enlists Daughter in BSE Fight," BBC News, On This Day (May 16, 1990), http://news.bbc.co.uk/onthisday/hi/dates/stories/may/16/newsid_2913000/2913807.stm.

horrible death three or four years ago. I did not know the cause of his death until I read his obituary in *The British Medical Journal* at the time.

In my view, pig-blood derived animal feed should be banned from use until its safety, or otherwise, is established. In addition, there should also be an immediate moratorium on the use of meat filler derived from porcine blood, especially in food products that are not normally cooked prior to consumption. These actions should be taken immediately and backed by appropriate legislation. The onus should be on the meat industry to cough up for this, not the poor old consumer. I would also advise against the temptation for a member of Her Majesty's Government to appear on television eating a ham sandwich while trying to smile reassuringly.

The Art and Science of Medicine

In days gone by, doctors had a paternalistic, "doctor knows best" attitude to their patients. With the advances in science, the emergence of the cult of the individual/humanism in the late twentieth century, this paternalism became no longer tenable in most westernised cultures. Being a patient is usually not much fun. When somebody is ill in most countries in the world, they generally go and see a doctor. Why do they do so? The majority of patients visit a doctor to: (a) find out what might be wrong, and (b) be given advice about how to fix it. This is no problem for the vast majority of people with more minor ailments—there are countless thousands of such consultations throughout the world every day. What about the more serious stuff?

When patients with potentially serious problems are referred to a specialist, they have the same two basic mechanistic questions: what's wrong, and how do we fix it? In addition, they have other agendas. These vary in magnitude from patient to patient and are, to some extent, common to any relationship between patient and doctor, whether the doctor is a specialist or not. What principles can we glean from the patients encountered in this book?

Patients, even (perhaps especially) the most garrulous such as Eileen (see chapter seventeen), need to feel they have been listened to properly. This is fundamental for most patients. To listen properly the doctor needs the time, an increasingly scarce commodity in today's "modern" NHS, and the inclination to do so. When this key area is ignored by the attending physician, it not only potentially undermines the principal route to the diagnosis (Abe's dictum), it also prejudices the bond of trust implicit in the patient's attendance at the consultation in the first place. When trust is lost, the patient might as well pack up and go and see someone else.

Nearly every patient needs to feel they are being helped though the journey of their illness as an individual, not as another "number"; not just as "another case of x, y or z"; nor as piece of meat, such as a sausage. To achieve this, the attending physician needs to have an appreciation of humanity in the broadest possible sense. The doctor needs to avoid looking at individuals as, for example, "a case of inoperable pancreatic cancer requiring chemotherapy." Instead, they should consider such individuals as individuals, as co-travellers through life, as fellow members of the human race: "this is Terry, a husband, father, friend; mortal, compassionate, fallible; a giant in stature, artistic intellect, and ability; a man with a partially unfulfilled artistic agenda. He's living alongside his inoperable pancreatic cancer. After an honest exchange of views, we have agreed that his treatment should include chemotherapy and, more importantly, an intensive course of freelance, free-range, fine art. In terms of treatment priorities, the painting comes first, the chemo comes second. The two treatments are not mutually exclusive."

Patients with chronic and/or terminal illnesses are often referred to as "sufferers," e.g. cancer sufferers. The term sufferer, when used in this context, may be, and often is, pejorative—it is far too passive to describe the relationship between some patients and their illness. Is Roy a sufferer (see chapter forty-six)? I don't think so. He is full of verve, energy, love, and laughter, despite irreversible damage to the nerves in his arms and diaphragm, alongside which he lives. Other patients with a terminal illness have an almost serene lack of physical imperative (such as Elsie, see chapter thirty-five). Such patients are often, but not exclusively, the very elderly, individuals with a firm religious or spiritual faith, or those with very advanced diseases. They have had a full and fulfilling life and are ready to meet their maker—or not as the case may be, depending on their metaphysical point of view.

In some cases (despite applying Abe's dictum), the diagnosis is uncertain, and so, therefore, is the treatment. Handling this uncertainty can be among the most challenging issues for both patient and doctor. To address problems of uncertainty requires complete honesty and openness from both parties. Also, in cases like this, despite the uncertainty, it is the doctor's job to put the patient in a place from where they might recover. This might sound like psychological mumbo jumbo, but it's not. Let's take the example of Mickey (see chapter twenty-five). The diagnosis was uncertain. He was going down the tubes both physically and mentally. He'd given up and wanted no more of anything. By using a veterinary analogy, he was treated as "a dog" and eventually got better. It's not clear if the drugs he was given were of any use, but the feeding via the

gastrostomy tube most certainly was. He'd never have allowed himself to have this treatment had he not heard of Pavlov, the dogs, and the psychological approach to his case which was "veterinary," almost in its entirety.

Finally, in my view there is no such thing as a difficult patient, with the possible exception of Typhoid Mary. When the label of "difficult patient" is applied, it's not the patient who is in any way at fault—it's the doctor who applied the label.

The National Health Service

I was trained by the National Health Service. It taught me the art and science of medicine. It afforded me the opportunity to develop my skills of scientific enquiry. Above all, it taught me how to look after patients to the highest standards. For that I am very grateful. On the whole, I have enjoyed my time working in the NHS. It has been a great privilege to meet and treat patients from all walks of life. It has been humbling to witness the dignity and fortitude that many patients show in the face of catastrophic and sometimes terminal illness.

I look at the NHS now and what do I see? It is basically a political football, a total mess. This state of affairs, although currently acute, is not new. It derives from UK political dogma (from both corners of the political spectrum) over the last generation, informed by the misguided notion that the NHS is the envy of the world. This is simply not true, and probably never has been. Currently, the whole of the service is driven by "targets" predicated not by clinical need, but by political imperative. The "modern" NHS is in crisis, its consultant and junior medical staff are completely demoralised, and the quality of patient care is demonstrably little better.

Waiting-time targets are taken to ludicrous (and laughable, were it not so serious) lengths. I recently had a patient with pancreatic cancer, which had spread to his liver. It was quite inoperable. He was in his eighties and was the sole carer for his wife with Alzheimer's disease. He came to see me in the clinic. We discussed the pros and cons of him being treated with chemotherapy. The "pro" was that there was a forty percent chance of him showing a response, which might extend his life by a few months. This had to be set against a number of issues including the length of time and frequency of hospital visits, and the potential side effects of the chemo. He requested time to think about it. He wanted to talk to his family about it, as well as his general practitioner. I thought that was a very good idea.

A few days later I was called by an NHS manager and told that the patient in question was about to "breach" if not treated within the next couple of days. In other words, he was about to breach the government target that dictates that he should be treated within "x" weeks. What was I going to do about it? What? This man needed time to think about his treatment. He needed time to weigh up the best course of action. He needed to discuss with his friends, family, and general practitioner, a doctor he had known for over thirty years and whose advice he trusted. In the brave, neo-Orwellian, "modern" NHS this was not acceptable, as he was going to "breach." I always, perhaps naively, thought that a breach was when the baby was coming down the wrong way, but come to think of it that's "breech." The lunatics are running the asylum.

The postmodernist revolution of modern NHS healthcare utilises a "sausage factory" model—treat the patient as a sausage; whatever you do, do not think about what you are doing. Oh, and do more and more and more of it to hit the "target"; describe a complete mess as no problem at all; discharge early; treat your seniors with scant respect as a burdensome "bed-blocker." I despair for my patients. I despair for three of my sons who have decided to make medicine their careers. Where's the quality agenda? Where are the next generation of medical free thinkers coming from?

In many societies in the world, the elderly are revered and treated with respect as, during their long lives, they have experienced many things which results in a wisdom lacking in the young. This philosophical approach is apparent in many low-income societies, including China, India, and many African countries. It is also to be found in more affluent cultures, and the one that springs straight to mind is Japan. I also found a very strong age-related respect in the Maori when I worked in New Zealand. When an elderly family member in such places gets ill, they are cared for by the extended family and local community. They are not put in endless queues in hospital corridors.

In the United Kingdom, the extended family network has fractured, in many instances completely beyond repair. Age is not revered; quite the reverse. It would appear that when an individual becomes financially unproductive as they retire, they become a burden, not a joy. We put them in shitty nursing homes. We make them wait hours on end in corridors. We refer to them as "bed-blockers." I am not sure how we have come to this state of affairs. It may be, in part, related to the rise of post-Thatcherite individualism, bearing in mind the "Iron Lady" was minded that society did not exist. We are one of the wealthiest countries in the world, but we choose not to structure and finance the care of our elderly to an appropriate level.

We are told there is no problem in the modern NHS by the UK government.[2] However, this is simply not true. There are (mostly elderly) patients waiting to be seen and assessed on trolleys in corridors in virtually every hospital emergency department in the country.[3] These patients wait for hours on end. Routine surgery has been cancelled to make extra bed space available, with our surgical colleagues twiddling their thumbs with nothing to do. The extra beds created ease the logjam for a few days, then it is back to square one with the endless corridor waits. We are informed that the optimum ratio of nurses to patients waiting in the corridor is 1:4. It beggars belief that anyone thought to work this out. Patients waiting in corridors is not normal, not safe and not acceptable. Trying to give it a sense of "normality" by working out optimum corridor-staffing ratios is obscene. We really would not treat animals like this, we would simply not be allowed to get away with it.

The cause of the patients waiting in corridors is multifactorial, but not quite so complex, as some try to claim. Like most developed countries in the United Kingdom we have an ageing population with an associated age-related increase in health demand. However, the key change which has produced the endless waiting in UK hospital corridors relates to funding. A few years ago, in the wake of the 2008 financial crisis, "austerity measures" were introduced to try to balance the financial situation. One of the ways this was achieved was by cutting existing funding. This included a significant cut the social care budget. It is this budget that pays for care in the community of the elderly/infirm. As a result of this, the quality of care and number of places in residential and nursing homes have declined. This has produced a block to the effective flow of patients through the hospital, leading to logjams at the entrance of patients waiting in corridors to be admitted.

The failure of patient flow through hospitals in the NHS is somewhat analogous to the condition called aortic stenosis, to which somewat ironically my mum eventually succumbed. In aortic stenosis, the exit valve of the heart (aortic valve) becomes calcified and narrowed, often as an age-related phenomenon (see Figs. 2a and 2b below).

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[2] H. Bodkin, "Hospital Run Out of Beds? 'There are Seats Available,' says Minister in NHS Winter Crisis Debate," *The Telegraph* (January 8, 2018), https://www.telegraph.co.uk/politics/2018/01/08/hospital-run-beds-seats-available-says-minister-nhs-winter-crisis.

[3] L. Donnelly and H. Bodkin, "NHS Hospitals Ordered to Cancel all Routine Operations in January as Flu Spike and Bed Shortages Lead to A&E Crisis," *The Telegraph* (January 3, 2018), https://www.telegraph.co.uk/news/2018/01/02/nhs-hospitals-ordered-cancel-routine-operations-january.

Fig. 2a. The normal flow of blood through the heart is interrupted by narrowing (X) of the exit valve (aortic valve). As a result, the heart expands, but eventually fails due to the additional load

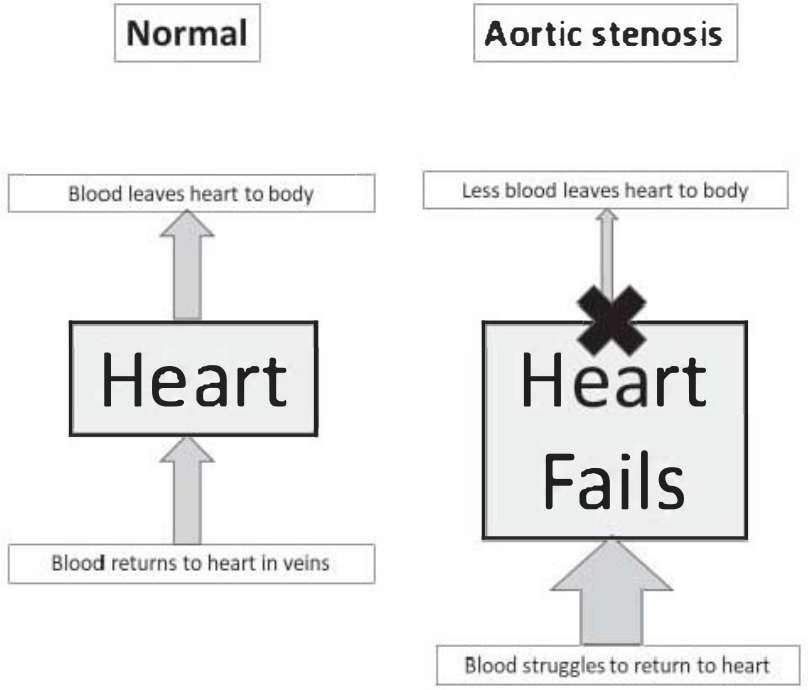
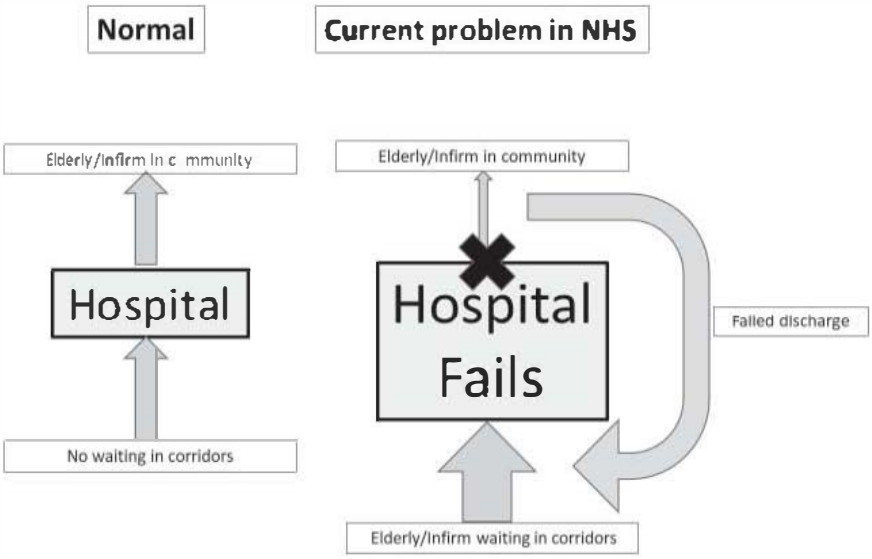


Fig. 2b. The normal flow of patients through a hospital is interrupted by the lack of nursing and residential home beds for the elderly and infirm (X). As a result, the hospital expands its bed capacity (rebadging of beds, cancelling routine work) but eventually fails due to the additional load of elderly/infirm patients with nowhere else to go



Why don't we turn the whole NHS thing on its head? Start with the elderly. Build them state-of-the-art, patient-centred facilities in nursing and residential centres with meaningful activities and experiences that are fully and appropriately financed. Care for them at home wherever possible, again with meaningful support. Let's try not to admit to hospital patients like my mum. Let's get rid of the "bed-blockers," and this hateful term, and then the NHS will function again. Why don't we employ appropriately trained doctors to treat them in their homes, nursing, residential, or otherwise? Regular domiciliary visits by sage and experienced teams of doctors and other healthcare professionals would be the order of the day, with individual care plans devised that take account of their biological age, comorbid conditions, and the patients' own wishes. It sounds a "no-brainer" to me. Ha! But I forgot! All the young doctors are leaving to work abroad, and colleagues of my age are retiring early, and

we are five thousand doctors short, by NHS estimates.[4] So, this plan will not work. Also, I'm not convinced these calculations are correct.

Throughout my life, first as a child, followed by my undergraduate training and experience of treating literally hundreds of thousands of patients, I have developed an increasing sense of what is right and what is wrong, tempered by an obstinacy that I appear to have inherited from my great-grandfather. I have always tried to do the right thing, despite what the "rules" say. Increasingly, I have Martin Luther King's words ringing in my ears from his famous speech in the 1960s[5]: "an unjust law is no law at all." If a rule needs breaking for the sake of the patient, I will put the patient's care first and foremost. This sense of duty and altruism has increased as I have got older and has got me into trouble on more than one occasion. There is no one word that defines the above in the English language, but there is in Greek. The term is *philotimo*.[6] A good example of this was a patient I was asked to see a couple of years ago. She was eighteen years old but looked about fifty. She had seen countless doctors over many years, to no avail. Her mother was beside herself with worry and extremely wound up. She came to see me in my NHS clinic, but she only had a twenty-minute slot; nowhere near long enough. I arranged to see them both a couple of days later in my private clinic. They could not afford it, but I did not charge them; in effect, I paid for the privilege of seeing them, as I had to pay room charges to the private hospital. The consultation took one-and-a-half hours, which was mostly spent with me listening to what had happened. If I had not done this, I would never have got to the bottom of her case, which I eventually did. She is now completely better and looks almost her actual age.

The sense of right and wrong and hence *philotimo* is operator dependent. It depends on one's point of view, politics, culture, and upbringing. It seems that my sense of *philotimo* differs from that found in the modern NHS and its political masters. I simply cannot bear the sight of the old folk queuing in corridors any more. The situation in many UK hospitals, in terms of patients queuing and waiting in corridors to be seen and assessed, is now critical. It has been likened to "battlefield conditions"

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[4] D. Campbell, "Make it Easier for Foreign Doctors to Work in Britain, Minister Told," *The Guardian* (October 10, 2017), https://www.theguardian.com/society/2017/oct/10/gps-should-be-on-list-of-shortage-occupations-royal-college-says.

[5] M. L. King, "Letter from a Birmingham Jail" (1963), African Studies Center, https://www.africa.upenn.edu/Articles_Gen/Letter_Birmingham.html.

[6] Aristotelis Panou, personal communication, Ithaca, Greece, September 2017. *Filos*=brotherly love; *timi*=honour.

by some clinicians working at the "sharp end" in A&E departments.[7] I have never been on a battlefield, and hope I never have to. However, I have been asked on more than one occasion to do a quick assessment of thirty or forty mainly old folk waiting in the corridor. Of course, this is quite impossible to do in a rigorous way. I just used my eyes and forty years' experience of seeing patients. Once, when I was doing this, towards the end of the queue near the hospital front doors I found a little old lady on a trolley on her own. She had been there for several hours. She did not look right and was holding her stomach with both hands. I did a very brief examination of her abdomen in the corridor. No curtains; no privacy; no dignity. As soon as I laid my hand on the lady's stomach the diagnosis was obvious. My palpating hand bounced up and down like a yo-yo. This patient had an enormous abdominal aortic aneurysm, which was about to rupture. This could happen at any moment, and if it did there was a ninety percent chance that she would die. I wheeled her round to CT with the porter. The scan was done immediately, which confirmed the diagnosis. The surgeons took her straight to theatre for emergency surgery. She survived, but there but for the grace of God go I. Come to think of it, there but for the grace of God go all these patients in the queue. The term "battlefield conditions" was strongly refuted by the UK government. I am not entirely convinced about this denial. When I got home very late the evening after doing the corridor run, I wept.

I'm afraid my prognosis for the NHS is terminal. I recently had a conversation with a friend and colleague of twenty-five years standing over lunch. Like me, he has worked all his life in the NHS. Unlike me, he is a "died in the wool socialist" and a great admirer of Aneurin Bevan, who founded the NHS in 1947. We had an interesting and quite intellectual conversation about various issues including those confronting us at work and our mutually impending retirement. He said to me: "Harry, when I retire, I am going to take out private health insurance. I do not trust the NHS anymore." Enough said.

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[7] S. Wooller and N. McDermott, "At Least 16 Hospital Trusts Declare 'Black Alert' Amid 'Battlefield' Conditions," *The Sun* (January 4, 2018), https://www.thesun.co.uk/news/5264507/at-least-16-hospital-trusts-declare-black-alert-amid-battlefield-conditions.

The Nature of Scientific Debate

The medical profession is, by nature, conservative. It is conservative politically, it is conservative emotionally, and it is conservative in its acceptance of new ways of looking at things. In one sense, this is as it should be. A doctor's prime duty is to look after their patients. This needs to be done to the best of the existing evidence, and not on any whim or fancy. But when does a theoretical whim or fancy stop being of no substance and actually the truth? That's an intriguing question. History is littered with examples of medics been "boxed in" by outdated received wisdom, to the detriment of their charges. The story of the rubbishing of Semmelweis's ideas in the mid-nineteenth century is a very good example of this. Joseph Lister was regarded as a reactionary during his early career, with an editorial from *The Lancet* in 1873 warning the medical profession against his "progressive" ideas. Another example from the same era and on a similar theme is that the Germans refuted Snow's waterborne hypothesis for the transmission of infectious diseases as late as 1901 during the Gelsenkirche typhoid epidemic of that year. This was forty-seven years after Snow's historic demonstration of the effect of removing the pump handle in Broad Street,[8] and fifteen years after Louis Pasteur had demonstrated beyond any doubt the microbial theory of transmission of infectious diseases.[9]

I experienced at first hand a similar, but rather less dramatic, example of boxed-in thinking when I took up my consultant post in Cornwall. I was keen to give antibiotic therapy to all patients who had chronic peptic ulcers due to *Helicobacter pylori*, as this would cure them once and for all. We did a small study on this and enlisted the help of local general practitioners. While most were enthusiastic and supportive, just one or two said: "Mm. Let's wait and see how this pans out shall we?"

This was thirteen years after Barry Marshall had discovered *H pylori*, and eleven years after he had unequivocally shown it to be the cause of most peptic ulcers.[10]

I am the first to acknowledge that my potential contribution to the advancement of medical science pales into complete insignificance compared to the Snows, Listers, Pasteurs, Barnards, Sherlocks, and Marshalls of this

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[8] J. Snow, *On the Mode of Communication of Cholera* (London: John Churchill, New Burlington St, England, 1855).

[9] L. Pasteur, "Germ Theory and its Applications to Medicine and Surgery," *Comptes rendus de l'Academie des Sciences* mlxxxvi: 1037–43.

[10] Marshall and Warren, "Unidentified Curved Bacilli in the Stomach Patients with Gastritis and Peptic Ulceration."

world. I also realise that my "what if" hepatitis E scenario might well be considered a potentially damaging "theoretical whim and fancy." I accept that completely. However, I would argue that, while we spend the considerable time and effort necessary to gather the evidence to confirm or refute the hypothesis, we need to stop turning our pigs into cannibals. It is, put simply, virological insanity.

When Galileo Galilei had the temerity to champion the Copernican theory that placed the sun, and not the earth, at the centre of the solar system in 1632 he got into big trouble with the Inquisition. He was charged with heresy, placed under house arrest, and forced into exile in Tuscany. His theory[11] was regarded as preposterous at the time—about as preposterous as the "what if" scenario I have proposed. Many of my colleagues will have difficulties with it as a notion and consider it one step too far. They could be right, but they might be wrong. Maybe I should start building a Churchill-style wall around my house, to shelter from incoming virions and vitriol.

I've often wondered if Albert Einstein, when considering the nature of the universe, ever considered if pigs might fly. I reckon he did.

[11] Galileo Galilei, *Dialogo dei due massimi sistemi del mondo* (1632).

Open Letter

Secretary of State for Health
c/o Cabinet Office
Downing Street, London WC1

Dear Mr Health Secretary

It with deep regret that I request your permission to resign my position as Consultant Gastroenterologist in the National Health Service. I feel obliged to do this, as I have found our senses of *philotimo* are increasingly divergent, to such an extent that I find working in the National Health Service no longer tenable. I would like to thank you and your many predecessors for your support during my medical studies and subsequent employment in the National Health Service that stretches back over forty years. My work has been an enormous privilege that, until relatively recently, I have thoroughly enjoyed.

I understand your task to deliver a first-rate health service for our country is a great challenge. I sincerely hope that this is achieved. I would be grateful if you could kindly see your way forward to accepting my resignation. If you feel able to so, I would also be grateful if you could revise upwards the estimate of the extra doctors required from overseas to fill the current shortage to 5,001.

Your sincerely

Harry Dalton BSc, MB BS, DPhil (Oxon), FRCP, DipMedEd
Consultant Physician and Gastroenterologist

APPENDIX

EASL Clinical Practice Guidelines on hepatitis E virus infection European Association for the Study of the Liver*

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Clinical Practice Guidelines Panel: Chair: Harry R. Dalton; Panel members: Nassim Kamar, Sally A. Baylis, Darius Moradpour, Heiner Wedemeyer; EASL Governing Board representative, Francesco Negro

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Introduction

As a cause of significant morbidity and mortality, infection with hepatitis E virus (HEV) represents an important global public health problem. The European Association for the Study of Liver (EASL) invited a panel of experts in the field to develop Clinical Practice Guidelines (CPGs) with a particular focus on HEV genotype (gt) 3. The objective of these CPGs was not to draft a review article on hepatitis E but rather to define specific suggestions for the management of distinct features of HEV infection, even though the supporting evidence may be weak in many cases. In order to keep the manuscript and the reference list to a reasonable length, these CPGs frequently refer to previous review articles which summarise the evidence on distinct topics in more detail. In addition, despite the increasing knowledge, areas of uncertainty exist and unanswered questions should be defined. Therefore, clinicians, patients, and public health authorities must continue to make choices on the basis of the evolving evidence.

Definitions used in the Guidelines

Term	Definition
HEV	Hepatitis E virus
HEV infection	Infection caused by HEV which is either symptomatic or asymptomatic, including extrahepatic manifestations (e.g. neurological)
Hepatitis E	Clinical or biochemical evidence of hepatitis caused by HEV
Extrahepatic	Damage to tissues/organs outside the liver associated with/caused by HEV (see Table 1)
SVR	Sustained viral response
R_0	The basic reproductive rate This term equates to the number of individuals infected by an index case with an infectious disease. If R_0 is >1 then the infection will spread through a naïve population. The R_0 of HEV in the pig population is up to 8. This means that HEV is highly infectious in the pig population, to a similar extent to measles in a measles naïve human population

Methodology

These EASL CPGs have been prepared by a panel of experts invited by the EASL Governing Board. The recommendations were approved by the EASL Governing Board. They are based as far as possible on evidence from existing publications and presentations at international meetings as well as, if evidence was unavailable, the experts' personal experiences and opinions. Wherever possible, the level of evidence and recommendation is cited. The evidence and recommendations have been graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[1] Thus, the strength of recommendations reflects the quality of underlying evidence. The quality of the evidence in the recommendations has been classified into one of three levels: high (A), moderate (B), or low (C). The GRADE system offers two grades of recommendation: strong (1) or weak (2). Thus, the recommendations consider the quality of evidence: the higher the quality of evidence, the more likely a strong recommendation is warranted; the greater the variability in values and preferences, or the greater the uncertainty, the more likely a weaker recommendation is warranted. It must be noted that only the review of literature was used to inform recommendations. Other criteria or support of recommendations such as cost, feasibility, acceptability, or cost-effectiveness were not considered.

[1] G. H. Guyatt, A. D. Oxman, G. E. Vist, R. Kunz, Y. Falck-Ytter, P. Alonso-Coello, et al., "GRADE: an Emerging Consensus on Rating Quality of Evidence and Strength of Recommendations," *The British Medical Journal* 336 (7650) (2008): 924–6.

Table 1. Level of evidence and grade of recommendations used

Level of Evidence		**Confidence in the evidence**
Level A	Data derived from meta-analyses or systematic reviews or from (multiple) randomised controlled trials (RCTs) with high quality	Further research is unlikely to change our confidence in the estimate of benefit and risk
Level B	Data derived from a single RCT or multiple non-randomised studies	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate
Level C	Small studies, retrospective observational studies, registries	Any estimate of effect is uncertain

Level was graded down if there is a poor quality, strong bias or inconsistency between studies and graded up if there is a large effect size.

Recommendations	
Grade	Wording associated with the grade of recommendation
1 (strong)	"must," "should," or "EASL recommends"
2 (weak)	"can," "may," or "EASL suggests"

Background

HEV was discovered in the early 1980s. At that time, Soviet troops in Afghanistan were affected by large outbreaks of unexplained hepatitis (testing negative for hepatitis A virus [HAV] and hepatitis B virus [HBV]). A pooled sample of affected soldiers' stool was ingested by a Russian scientist. He developed a brisk hepatitis, and a new virus was found in his stool by electron microscopy.[2] Subsequently, the viral genome was cloned and named HEV.[3]

Our understanding of HEV has changed completely over the past decade. Previously, HEV was thought to be limited to certain developing countries and was only ever seen in high-income countries in travellers returning from hyperendemic areas in Asia or Africa. We now know that HEV is endemic in most high-income countries and is largely a zoonotic infection, with pigs as the primary host.[4] [5] [6] Given the paradigm shift in our understanding of zoonotic HEV and that locally acquired HEV is now the commonest cause of acute viral hepatitis in many European countries,[7] the focus of these CPGs will be on HEV gt 3 (and 4).

Virology

HEV belongs to the *Hepeviridae*, a diverse family of viruses infecting mammals, birds and fish. Strains of HEV infecting humans belong to the *Orthohepevirus* genus which is divided into four species (A–D).[8] Human cases of hepatitis E are caused by strains within species A, which

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[2] Balayan et al., "Evidence for a Virus in Non-A, non-B Hepatitis Transmitted Via the Fecal-oral Route."

[3] G. R. Reyes, M. A. Purdy, J. P. Kim, K. C. Luk, L. M. Young, K. E. Fry, et al., "Isolation of a cDNA from the Virus Responsible for Enterically Transmitted Non-A, Non-B Hepatitis," *Science* 247 (4948) (1990): 1335 9.

[4] Dalton et al., "Hepatitis E: an Emerging Infection in Developed Countries"; Kamar et al., "Hepatitis E" (2012); Kamar et al., "Hepatitis E" (2014).

[5] Kamar N, Bendall R, Legrand-Abravanel F, Xia NS, Ijaz S, Izopet J, et al. "Hepatitis E". Lancet 2012;(379):2477 2488.

[6] Kamar N, Dalton HR, Abravanel F, Izopet J. "Hepatitis E virus infection". *Clin Microbiol Rev* 2014; (27):116 138.

[7] Adlhoch et al., "Hepatitis E Virus."

[8] D. B. Smith and P. Simmonds, International Committee on Taxonomy of Viruses Hepeviridae Study G; S. Jameel, S. U. Emerson, and T. J. Harrison, "Consensus Proposals for Classification of the Family Hepeviridae," *Journal of General Virology* 95(Pt 10) (2014): 2223 32.

comprises eight genotypes.[9] Two of these (gt 1 and 2) only infect humans. Gt 3 and 4 are endemic in animal species such as pigs and wild boar; these strains cause zoonotic infections in humans via consumption of contaminated meat or direct contact and other probable routes. At the molecular level, gt 3 is highly diverse and includes related viruses found in rabbits, with evidence of occasional infection with similar viruses in humans.[10] Thus far, gt 5 and 6 have only been reported in wild boar. Recently, HEV gt 7 was identified in a patient who regularly consumed camel meat and milk,[11] and although no further human cases have been reported yet, many strains have since been identified in camels (gt 7 and 8). While HEV is primarily a hepatotropic virus, infection of other tissues, including neuronal, kidney, and placental tissue, has been reported, possibly explaining some of the extrahepatic manifestations.[12 13]

HEV has a 7.2-kb positive-strand RNA genome which encodes three open reading frames (ORFs).[12] ORF1 encodes the functional domains involved in replication of the viral genome (the so-called "replicase"), including a methyl transferase, a putative protease, an RNA helicase, and an RNA-dependent RNA polymerase (RdRp). ORF2 encodes the capsid and ORF3 encodes a protein involved in the release of viral particles from infected cells.

The analysis of stool samples from HEV-infected individuals demonstrated that viral particles are approximately 27–34 nm in diameter.[2] Virus excreted in bile and stool is non-enveloped; however, quasi-enveloped forms of HEV exist in the blood, with virions wrapped in membranes derived from infected cells.[14 15]

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[9] M. A. Purdy, T. J. Harrison, S. Jameel, X. J. Meng, H. Okamoto, W. H. M. Van der Poel, et al., "ICTV Virus Taxonomy Profile: Hepeviridae," *The Journal of General Virology* 98 (11) (2017): 2645–56.

[10] F. Abravanel, S. Lhomme, H. El Costa, B. Schvartz, J. M. Peron, N. Kamar, et al., "Rabbit Hepatitis E Virus Infections in Humans, France," *Emerging Infectious Diseases* 23 (7)(2017): 1191–3.

[11] Lee et al., "Chronic Infection With Camelid Hepatitis E Virus in a Liver Transplant Recipient,".

[12] Y. Debing, D. Moradpour, J. Neyts, and J. Gouttenoire, "Update on Hepatitis E Virology: Implications for Clinical Practice," *Journal of Hepatology* 65 (1) (2016): 200–12.

[13] S. Pischke, J. Hartl, S. D. Pas, A. W. Lohse, B. C. Jacobs, A. A. Van der Eijk, "Hepatitis E Virus: Infection Beyond the Liver?" *Journal of Hepatology* 66 (5) (2017): 1082–95

[14] M. Takahashi, T. Tanaka, H. Takahashi, Y. Hoshino, S. Nagashima, Jirintai, et al., "Hepatitis E Virus (HEV) Strains in Serum Samples can Replicate Efficiently in Cultured Cells Despite the Coexistence of HEV Antibodies: Characterization of

Unanswered questions and perspectives

- Are other animal homologues of HEV capable of infecting humans?
- Our understanding of the molecular virology and pathogenesis of hepatitis E is incomplete

HEV genotypes 1 and 2

The key clinical observations from developing countries were made in the 1950s and 1970s in India. In the mid-1950s there was a major outbreak of unexplained hepatitis in Delhi[16] and in 1978–9 in Kashmir, with high mortality observed in pregnant women.[17] These outbreaks were retrospectively confirmed as being caused by HEV and were the first well-documented observations of excess maternal mortality associated with HEV.

HEV gt 1 and 2 are obligate human pathogens spread by the faecal-oral route via contaminated water. They cause human disease in areas with fragile sanitary infrastructure in Asia (gt 1), Africa (gt 1 and 2), and Mexico (gt 2). Sporadic cases are common, but are sometimes interspersed by large outbreaks involving thousands or tens of thousands of cases. [5] More recently, there have been ongoing, stuttering outbreaks in African refugee camps, including recent and ongoing outbreaks in South Sudan, Niger, Nigeria, and Namibia.

HEV gt 1 and 2 usually cause a brief, self-limiting hepatitis in young adults that is clinically indistinguishable from other causes of acute viral hepatitis. The clinical attack rate on exposure is approximately one in five.[18] Chronic infection with HEV gt 1 and 2 has not been reported so far. The mortality rate in pregnant women is approximately twenty-five percent. Deaths are caused by fulminant hepatic failure and obstetric complications such as eclampsia and haemorrhage, which are associated with a high perinatal infant mortality. The cause of the excess maternal

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HEV Virions in Blood Circulation," *Journal of Clinical Microbiology* 48 (4) (2010): 1112–25.

[15] Feng and Lemon, "Peek-a-boo."

[16] S. S. Naidu and R. Viswanathan, "Infectious Hepatitis in Pregnancy during Delhi Epidemic," *Indian Journal of Medical Research* 45 (1957): 71–6.

[17] Khuroo, "Study of an Epidemic of Non-A, Non-B Hepatitis."

[18] D. B. Rein, G. A. Stevens, J. Theaker, J. S. Wittenborn, and S. T. Wiersma, "The Global Burden of Hepatitis E Virus Genotypes 1 and 2 in 2005," *Hepatology* 55 (4) (2012): 988–97.

mortality is not known. Such patients need to be cared for in a high-dependency setting. Despite its possible teratogenicity there has been interest in the use of ribavirin in pregnant women with HEV infection. However, there are currently no data to support the use of ribavirin in such patients.

Some studies also show a high mortality in patients with underlying chronic liver disease who develop HEV infection. This includes a study from India which shows that the twelve-month mortality rate in such patients approaches seventy percent.[19] However, the mortality of HEV-related acute-on-chronic liver failure varies widely in different studies. Studies from Asia, which mainly involved HEV gt 1 infections, reported mortality rates of between zero to sixty-seven percent in patients with chronic liver disease when experiencing an HEV super-infection.[20] In a cohort in India, HEV most commonly complicated patients with Wilson's disease.[21] In a recent analysis of 368 patients with acute-on-chronic liver failure, HEV-associated cases were described as having a more benign course than alcohol-associated cases.[22]

In 2005, the global burden of disease of HEV was estimated to be twenty million infections, with three million symptomatic cases and seventy thousand deaths per year. [18] This estimate is problematic for two reasons: firstly, it is not a complete estimate of the worldwide burden of HEV, as it only considers infections in a limited number of developing countries where HEV gt 1 and 2 predominate. It took no account of zoonotic HEV, which is endemic in high-income countries. Secondly, the global burden estimate was based, at least in part, on seroprevalence data. These studies used first and second-generation serological assays with very poor sensitivity. For instance, a study in a rural Bangladeshi population was found to have underestimated the true seroprevalence by one hundred percent when a validated highly sensitive assay was used.[23]

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[19] S. Kumar Acharya, P. Kumar Sharma, R. Singh, S. Kumar Mohanty, K. Madan, J. Kumar Jha, et al., "Hepatitis E virus (HEV) infection in patients with cirrhosis is associated with rapid decompensation and death," *Journal of Hepatology* 46 (3) (2007): 387–94.

[20] A. Kumar and V. A. Saraswat, "Hepatitis E and Acute-on-Chronic Liver Failure," *Journal of Clinical and Experimental Hepatology* 3 (3) (2013): 225–30.

[21] Ramachandran et al., "Hepatitis E Superinfection."

[22] Shalimar, S. Kedia, S. J. Mahapatra, B. Nayak, D. Gunjan, B. Thakur, et al., "Severity and Outcome of Acute-on-Chronic Liver Failure is Dependent on the Etiology of Acute Hepatic Insults: Analysis of 368 Patients," *Journal of Clinical Gastroenterology* 51 (8) (2017): 1058-66.

[23] B. L. Kmush, A. B. Labrique, H. R. Dalton, Z. B. Ahmed, J. R. Ticehurst, and C. D. Heaney, "Two Generations of 'Gold Standards': the Impact of a Decade in

Thus, our current estimate of global burden of HEV is of limited value and requires updating urgently.

In some countries, the epidemiology of HEV has changed as zoonotic HEV infection has emerged. The best example of this is China where previously HEV gt 1 was the dominant circulating genotype.[24] In recent years, particularly in eastern China, gt 1 has become much less common and gt 4 is now the most common genotype found in human cases. [5] In addition, the demographic has changed to that seen in high-income countries with zoonotic HEV gt 3 and 4, as hepatitis E is now most commonly observed in middle-aged Chinese men. The reasons for this shift from gt 1 to gt 4 are uncertain. It could reflect improvements in sanitary infrastructure, which have asserted a negative ecological pressure on HEV gt 1. An alternative possibility is that the R_e of HEV gt 4 may be much higher than previously thought. Very recent data show that the consumption of pork is associated with HEV IgG seropositivity in areas previously considered endemic for gt 1, including Nepal[25] and South Africa.[26] The issue of co-circulating zoonotic and non-zoonotic strains in such geographical settings merits further study. In other low-income settings, zoonotic HEV seems to be the dominant genotype. A good example of this is in South America, where HEV infection is almost universally caused by HEV gt 3.[27] The epidemiology of HEV in South America is thus very similar to high-income countries with zoonotic HEV, including Europe.

Hepatitis E Virus Testing Innovation on Population Seroprevalence," *The American Journal of Tropical Medicine and Hygiene* 93 (4) (2015): 714–17.

[24] X. Ren, P. Wu, L. Wang, M. Geng, L. Zeng, J. Zhang, et al., "Changing Epidemiology of Hepatitis A and Hepatitis E Viruses in China, 1990–2014," *Emerging Infectious Diseases* 23 (2) (2017): 276–9.

[25] A. C. Shrestha, R. L. Flower, C. R. Seed, M. Rajkarnikar, S. K. Shrestha, U. Thapa, et al., "Hepatitis E Virus Seroepidemiology: a Post-earthquake Study among Blood Donors in Nepal," *BMC Infectious Diseases* 16 (1) (2016): 707.

[26] R. G. Madden, S. Wallace, M. Sonderup, S. Korsman, T. Chivese, B. Gavine, et al., "Hepatitis E virus: Western Cape, South Africa," *World Journal of Gastroenterol* 22 (44) (2016): 9853–9.

[27] J. Rendon, M. C. Hoyos, D. di Filippo, F. Cortes-Mancera, C. Mantilla, M. M. Velasquez, et al., "Hepatitis E Virus Genotype 3 in Colombia: Survey in Patients with Clinical Diagnosis of Viral Hepatitis," *PLoS One* 11 (2) (2016): e0148417.

Recommendations

- Travellers with hepatitis returning from areas endemic for HEV gt 1 or 2 should be tested for HEV **(A1)**
- Pregnant women with HEV gt 1 or 2 should be cared for in a high-dependency setting and transferred to a liver transplant unit if liver failure occurs **(A1)**

Unanswered questions and perspectives

- There are insufficient data to support the use of ribavirin in pregnant women with HEV infection

The rest of these guidelines are restricted to HEV gt 3 and 4 in developed countries. For more detailed guidance regarding the clinical management of outbreaks of acute HEV in resource-limited settings, please see the World Health Organization (WHO) Guidelines 2018[28].

Epidemiology

Based on recent seroprevalence and very recent blood-donor data, it is likely that there are at least two million locally acquired HEV infections in Europe every year. [7] [29] [30] In high-income countries, including Europe, hepatitis E is mostly a locally acquired zoonotic infection. In France there were approximately two thousand laboratory-confirmed infections with HEV in 2014, and ninety-nine percent were in non-travellers caused almost universally by HEV gt 3, with occasional cases caused by HEV gt 4. An increasing number of animals have been found to carry HEV, most of which have little relevance to human infection. Animals carrying HEV that have implications for human health are more limited and include pigs, wild boar and deer (all gt 3, or 4). In addition, there are more limited data suggesting that other animals may have a role, including rabbits, camels (gt 7) and shellfish. However, the true primary host for HEV is the pig. HEV is found in pigs worldwide but causes no symptoms. HEV is highly infectious to pigs (R_0 = 3.3), and once one animal in a pig herd becomes infected it is almost certain that all the animals in that herd will become

[28] WHO HEV Guidelines in press.
[29] Hewitt et al., "Hepatitis E Virus in Blood Components".
[30] Bura et al., "Hepatitis E Virus IgG Seroprevalence."

infected as well.[31] The evidence suggesting a primarily porcine origin of zoonotic HEV comes from molecular epidemiological studies. These show that HEV recovered from humans has close sequence homology to HEV found in local pig and wild boar populations. In addition, seroprevalence studies have shown high HEV exposure rates in veterinarians caring for pigs and other individuals with close contact with these animals.[4 5 6]

Infectious HEV has been found in every step of the food chain (from slaughter house to grocery shelves) in a number of different countries including in Europe,[32] Japan, and the United States. An important route of infection is by consumption of infected pig meat products which have been undercooked or consumed without cooking, e.g. air-dried sausage such as figatellu, which is a culinary delicacy in southern France. Small outbreaks of hepatitis E have been directly linked to the consumption of products such as figatellu by analysis of HEV sequences in the patients, as well as the sausages.[33] However, there are other possible routes of human infection. When infected, pigs excrete a huge amount of HEV in the stool. This has led to environmental contamination including slurry lagoons, streams, and rivers. HEV has consequently been found in shellfish as well as soft fruits and salads irrigated with infected water.[5 6 34 35] Recent data shows that HEV gt 3 has found its way to the top of the aquatic food chain, as it has been found in dolphins in Cuba.[36] A study from France showed that drinking bottled water protected against exposure to HEV, but whether domestic water supplies are a significant source of human infection remains an open question.[37] HEV gt 4 has been found in cattle in China; it was also documented in their milk and was able to survive

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[31] M. Bouwknegt, K. Frankena, S. A. Rutjes, G. J. Wellenberg, A. M. de Roda Husman, W. H. van der Poel, et al., "Estimation of Hepatitis E Virus Transmission among Pigs Due to Contact-exposure," *Veterinary Research* 39 (5) (2008): 40.

[32] Berto et al., "Hepatitis E Virus in Pork Food Chain."

[33] Colson et al., "Pig Liver Sausage."

[34] V. Terio, M. Bottaro, E. Pavoni, M. N. Losio, A. Serraino, F. Giacometti, et al., "Occurrence of Hepatitis A and E and Norovirus GI and GII in Ready-to-eat Vegetables in Italy," *International Journal of Food Microbiology* 249 (2017): 61 5.

[35] Maunula L, Kaupke A, Vasickova P, Soderberg K, Kozyra I, Lazic S, et al. Tracing enteric viruses in the European berry fruit supply chain. Int J Food Microbiol 167 (2013):177 185.

[36] Montalvo Villalba et al., "Hepatitis E virus in bottlenose dolphins *Tursiops truncatus*."

[37] Mansuy et al., "A Nationwide Survey of Hepatitis E Viral Infection in French Blood Donors."

pasteurisation.[38] This has not yet been confirmed in other regions such as Europe.[39] Finally, although HEV gt 3 is the dominant circulating genotype in Europe, gt 4 has been found in a small number of European pigs, and there are occasional human cases/clusters with gt 4 which have been noted in a number of countries, including Italy and France.[40] How HEV gt 4 has found its way into Europe is unknown.

The incidence of HEV infection varies between and within countries and over time (see supplementary table) for reasons that are unknown. For example, the incidence of HEV infection is particularly high in France, compared to many other countries. However, a recent study has shown that human infection with HEV is not uniformly distributed in France (incidence assessed by anti-HEV IgM ranging from 0.4 percent to 4.6 percent), and is highest in the southwest and southeast of the country. These areas have such a high incidence of HEV infection that they can be considered hyperendemic. [37] The reasons for these observations are uncertain.

Studies have shown that, at least in England, Germany, and Denmark, the seroprevalence of HEV declined in the last few decades of the twentieth century. These data suggest that there was a "cohort effect," with many individuals being infected during the period following the Second World War.[41] More recently, in a European Centre for Disease Control (ECDC) sponsored study, countries in Europe have universally seen very significant increases in laboratory-confirmed cases of HEV infection. [7] This is partly explained by improved case ascertainment, because clinicians have become aware of the importance of locally acquired infection. In addition, there has been a significant increase in incidence in some countries, including the Netherlands, France, England, and Scotland. For example, in Scotland the number of viraemic blood donors has recently increased from 1:14,500 to 1:2,481, which has been accompanied by a one hundred percent increase in seroprevalence in Edinburgh, mainly

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[38] F. Huang, Y. Li, W. Yu, S. Jing, J. Wang, F. Long, et al., "Excretion of Infectious Hepatitis E Virus into Milk in Cows Imposes High Risks of Zoonosis," *Hepatology* 64 (2) (2016): 350 9.

[39] C. Baechlein and P. Becher, "No Evidence for Zoonotic Hepatitis E Virus Infection through Dairy Milk in Germany," *Hepatology* 65 (1) (2017): 394 5.

[40] Bouamra et al., "Emergence of Autochthonous Infections with Hepatitis E Virus of Genotype 4 in Europe."

[41] D. K. Holm, B. K. Moessner, R. E. Engle, H. L. Zaaijer, J. Georgsen, R. H. Purcell, et al., "Declining Prevalence of Hepatitis E Antibodies among Danish Blood Donors," *Transfusion* 55 (7) (2015): 1662 7.

among individuals under thirty-five years of age.[42] Temporally associated with this increase in incidence, the origin of Scottish human HEV infection appears to have changed. Previously, HEV documented in humans had close sequence homology to HEV found in Scottish pigs, but it now bears very close sequence homology to HEV found in pigs from Continental Europe. This implies there has been a recent significant change in the amount of HEV contamination of the human food chain originating from Continental Europe.[43]

In recent years, it has become apparent that there are "hotspots" of HEV infection in Europe. This includes southwest France (incidence 3–4%)[37]; the Netherlands (1:600 blood donors viraemic, 2014)[44]; Scotland (1:2,481 donors viraemic, 2016) [42]; western Germany (1:616 blood donors viraemic, 2015)[45]; the Czech Republic (four hundred laboratory-confirmed cases 2015) [7]; Abruzzo, central Italy (seroprevalence forty-nine percent)[46] and western/central Poland (seroprevalence fifty percent) [30]. There may well be other areas, as yet unidentified, with high levels of circulating virus. Recently, the ECDC has taken an active role in addressing the threat of zoonotic HEV to the human population in Europe, using a "One Health" approach. This has culminated in the establishment of "HEVnet," which is based at the Dutch National Institute for Public Health and the Environment (RIVM) in the Netherlands.[47] The objective of this exercise is to develop a central repository for human and animal HEV sequences, together with key anonymised clinical data from human cases. "HEVnet" is, therefore, likely to be a very important tool for improving the future understanding of HEV epidemiology.

Unanswered questions and perspectives

- How do routes of HEV infections vary by geographical location?
- Why are there "hotspots" of HEV infection in certain locations?

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[42] Thom et al., "Hepatitis E Virus (HEV) in Scotland."
[43] Ijaz et al., "Indigenous Hepatitis E in England and Wales from 2003 to 2012."
[44] Zaaijer, "No Artefact, Hepatitis E is Emerging," 654.
[45] B. Müller, H. Koch, and L. Pichl, "PCR-Screening of Blood Donations for Hepatitis E with the Cobas HEV Test Performed on the New Roche Cobas 8800 Platform in Minipools of 6," *Transfusion Medicine and Hemotherapy* 42 (1) (2015): 1–66.
[46] Lucarelli et al., "High Prevalence of Anti-hepatitis E Virus Antibodies among Blood Donors in Central Italy."
[47] https://ecdc.europa.eu/en/news-events/1st-hepatitis-e-virus-networkhevnet-meeting, accessed March 2018.

- Why has HEV infection increased in some countries in recent years?
- The HEV dose-dependence of clinical and immunological presentation, as well as the variable duration of serological markers of the infection, need to be carefully studied to develop and match serological assays to certain epidemiological settings
- Does person-to-person spread occur with HEV gt 3 and 4?

Clinical aspects: acute infection

Acute HEV gt 3 infection is clinically silent in the vast majority of patients. Only a minority (probably less than five percent) develop symptoms of acute hepatitis with elevated liver enzymes, jaundice, and non-specific symptoms such as fatigue, itching, and nausea. However, HEV infection is the major cause of acute viral hepatitis in many European countries and in Germany, the United Kingdom, and France there were more reported cases of acute hepatitis E than of HAV or acute HBV infections in 2015–16.[7]

Immunocompetent patients with acute hepatitis E can clear the infection spontaneously, but there have been a few reports of cases with more prolonged viraemia. Monitoring liver enzymes and liver function parameters is sufficient during acute hepatitis E infection, in patients who do not suffer from other chronic diseases. Progression to acute liver failure (ALF) is rare in patients with HEV gt 3 infection. However, single cases of ALF due to HEV infection have been reported in several European countries. In a German single centre study of eighty patients with ALF, HEV RNA was found in ten percent of patients and HEV was considered as the probable cause.[48] Patients with confirmed acute hepatitis E should be monitored for aminotransferases (alanine aminotransferase [ALT], aspartate aminotransferase [AST]), bilirubin, and INR. Once HEV infection is cleared, patients develop immunity against HEV, which is not sterilising. Thus, re-infection with HEV is possible even though the likelihood of developing symptomatic hepatitis is reduced compared to non-immune individuals.

In contrast to HEV in developing countries, HEV gt 3 and 4 tend to affect older males. In one study from England the M:F ratio was 3:1, and

[48] P. Manka, L. P. Bechmann, J. D. Coombes, V. Thodou, M. Schlattjan, A. Kahraman, et al., "Hepatitis E Virus Infection as a Possible Cause of Acute Liver Failure in Europe," *Clinical Gastroenterol and Hepatology* 13 (10) (2015): 1836 42, e1832; quiz e1157-1838.

the median age sixty-three.[49] The finding that older males are most likely to develop clinically apparent acute hepatitis on exposure to HEV gt 3 and 4 is a consistent observation, but unexplained. It seems likely that this relates to host factors rather than differential exposure, as individuals of all ages appear to be exposed to HEV. One possible explanation is that clinically apparent hepatitis is more likely to be evident in patients with subclinical hepatic steatosis/fibrosis. In a study from England, some patients with hepatitis E were heavy alcohol consumers and an excess number were diabetic, both of which are risk factors for hepatic steatosis and fibrosis.[50]

Acute hepatitis E is a concern in patients with underlying chronic liver disease. Some cases of acute-on-chronic liver failure are caused by HEV infection. This is a particular problem in elderly patients where acute hepatitis may take a more severe course. HEV infection may be less relevant in European patients with decompensated cirrhosis. Only eleven in 343 patients with decompensated chronic liver disease followed in France or the United Kingdom had acute hepatitis E, and three of those died.[51] Of note is that HEV did not alter the mortality in this study, compared to other causes of hepatic decompensation. These findings are in line with data from France showing a low prevalence of HEV infection in patients with severe acute alcoholic hepatitis.[52] There are only a few case reports of HEV gt 3 and 4 in pregnancy. Excess maternal mortality has not been observed.

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[49] H. R. Dalton, W. Stableforth, P. Thurairajah, S. Hazeldine, R. Remnarace, W. Usama, et al., "Autochthonous Hepatitis E in Southwest England: Natural History, Complications and Seasonal Variation, and Hepatitis E virus IgG Seroprevalence in Blood Donors, the Elderly and Patients with Chronic Liver Disease," *European Journal of Gastroenterology & Hepatology* 20 (8) (2008): 784–90.

[50] H. R. Dalton, R. P. Bendall, M. Rashid, V. Ellis, R. Ali, R. Ramnarace, et al., "Host Risk Factors and Autochthonous Hepatitis E Infection," *European Journal of Gastroenterology & Hepatology* 23 (12) (2011): 1200–5.

[51] H. Blasco-Perrin, R. G. Madden, A. Stanley, C. Crossan, J. G. Hunter, L. Vine, et al., "Hepatitis E Virus in Patients with Decompensated Chronic Liver Disease: a Prospective UK/French Study," *Alimentary Pharmacology & Therapeutics* 42 (5) (2015): 574–81.

[52] S. Haim-Boukobza, A. Coilly, M. Sebagh, M. Bouamoud, T. Antonini, B. Roche, et al., "Hepatitis E Infection in Patients with Severe Acute Alcoholic Hepatitis," *Liver International* 35 (3) (2015): 870–5.

Recommendations

- All patients with symptoms consistent with acute hepatitis should be tested for hepatitis E **(A1)**
- EASL suggests testing for hepatitis E in patients with unexplained flares of chronic liver disease **(C2)**

Unanswered questions and perspectives

- Why are most cases of symptomatic acute hepatitis E seen in older men?
- What is the duration of viraemia in asymptomatic HEV infections?
- What is the role of HEV in decompensated chronic liver disease?
- What is the clinical relevance of re-infection with HEV, and how commonly does this occur?

Clinical aspects: chronic infection

Immunosuppressed patients can fail to clear HEV infection.[53] [54] [55] Such patients develop chronic hepatitis, but this has only been seen in patients infected with HEV gt 3 or 4 to date. Chronic HEV infection has been defined as a persistence of HEV replication for six months. [53] However, in an observational study performed in solid-organ transplant recipients, it was observed that no spontaneous HEV clearance occurred between three and six months after infection, and spontaneous HEV clearance occurred only within the first three months after infection.[56] These data suggest that in solid-organ transplant recipients, patients who are viraemic for more than three months after HEV infection can be regarded as chronically infected and considered for treatment. However, in a small number of

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[53] Kamar et al., "Hepatitis E Virus and chronic hepatitis in organ transplant recipients";

[54] N. Kamar, J. M. Mansuy, B. Cointault, J. Selves, F. Abravanel, M. Danjoux, et al., "Hepatitis E Virus-related Cirrhosis in Kidney and Kidney-pancreas-transplant Recipients," *American Journal of Transplantation* 8 (8) (2008): 1744–8;

[55] Gerolami, Moal, and Colson, "Chronic hepatitis E with cirrhosis in a kidney-transplant recipient."

[56] N. Kamar, L. Rostaing, F. Legrand-Abravanel, and J. Izopet, "How Should Hepatitis E Virus Infection be defined in organ-transplant Recipients?" *American Journal of Transplantation* 13 (7) (2013): 1935–6.

cases, spontaneous clearance has been observed between three and six months.[57]

The clinical presentation of chronic HEV infection has mainly been described in the setting of organ transplantation but is similar in other immunosuppressed groups, including patients with haematological disorders, individuals living with HIV, and patients with rheumatic disorders receiving heavy immunosuppression. In a series of eighty-five solid-organ transplant recipients, only one-third of patients were symptomatic, with fatigue as the main symptom.[58] The majority of patients are asymptomatic and present with mild and persistent liver function test (LFT) abnormalities. In one study of chronically infected transplant recipients, the ALT, AST, and gamma-glutamyl transferase levels at diagnosis were 260 ± 38 IU/L, 155 ± 25 IU/L, and 308 ± 56 IU/L, respectively. It is important to note that some patients had normal or only very slightly increased liver enzyme levels. In addition, in some patients with persistent HEV replication. both anti-HEV IgG and IgM remain negative. [58] It is therefore mandatory that such patients are assessed with nucleic acid amplification techniques (NATs) using serum or plasma and, if possible, stool samples.

One-third of solid-organ transplant recipients infected by HEV have resolving hepatitis, and the remaining patients develop chronic hepatitis. [58] [59] Other smaller studies show that progression to chronic infection occurs in less than fifty percent of patients.[60] In solid-organ transplant recipients infected with HEV gt 3 rapid progression of liver fibrosis has been observed, leading to cirrhosis and, in some cases, decompensation and death. [53] [54] [55] [59] There appears to be no difference in HEV RNA

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[57] S. Meisner, S. Polywka, M. Memmler, B. Nashan, A. W. Lohse, M. Sterneck, et al., "Definition of Chronic Hepatitis E After Liver Transplant Conforms to Convention," *American Journal of Transplantation* 15 (11) (2015): 3011 12.

[58] N. Kamar, C. Garrouste, E. B. Haagsma, V. Garrigue, S. Pischke, C. Chauvet, et al., "Factors Associated with Chronic Hepatitis in Patients with Hepatitis E Virus Infection who have Received Solid Organ Transplants," *Gastroenterology.* 140 (5) (2011): 1481 9.

[59] N. Kamar, F. Abravanel, J. Selves, C. Garrouste, L. Esposito, L. Lavayssiere, et al., "Influence of Immunosuppressive Therapy on the Natural History of Genotype 3 Hepatitis-E Virus Infection after Organ Transplantation," *Transplantation* 89 (3) (2010): 353 60.

[60] S. Pischke, P. Stiefel, B. Franz, B. Bremer, P. V. Suneetha, A. Heim, et al., "Chronic Hepatitis E in Heart Transplant Recipients," *American Journal of Transplantation* 12 (11) (2012): 3128 33.

concentration between patients with or without progressive liver fibrosis.[61] Interestingly, liver fibrosis can regress after HEV clearance. [59] Extrahepatic HEV-associated manifestations, i.e. neurological and renal injury, have been observed both during acute and chronic HEV infection (see below).[62] [63] [64] In solid-organ transplant recipients, a low lymphocyte count at diagnosis and the use of tacrolimus (rather than cyclosporine A) are associated with the development of chronic infection after exposure to HEV. [58] Among patients with HIV infection, chronic HEV infection has mostly been described in those with a CD4+ T-cell count <200/mm^3.[65] No predictive factor(s) for the development of chronic HEV infection have been identified in other immunosuppressed groups.

Recommendations

EASL recommends HEV testing in all immunosuppressed patients with unexplained abnormal LFTs. **(A1)**

Unanswered questions and perspectives

- What is the definition of chronic HEV infection?
- When should therapy be initiated? How long should we wait?

Extrahepatic manifestations

Extrahepatic manifestations of HEV infection are increasingly recognised (see Table 2 below), the most important being neurological. [63]

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[61] F. Legrand-Abravanel, N. Kamar, K. Sandres-Saune, C. Garrouste, M. Dubois, J. M. Mansuy, et al., "Characteristics of Autochthonous Hepatitis E Virus Infection in Solid-organ Transplant Recipients in France," *Journal of Infectious Diseases* 202 (6) (2010): 835–44.

[62] N. Kamar, R. P. Bendall, J. M. Peron, P. Cintas, L. Prudhomme, J. M. Mansuy, et al.,"Hepatitis E Virus and Neurologic Disorders," *Emerging Infectious Diseases* 17 (2) (2011): 173–9

[63] H. R. Dalton, N. Kamar, J. J. van Eijk, B. N. McLean, P. Cintas, R. P. Bendall, et al., "Hepatitis E Virus and Neurological Injury," *Nature Reviews Neurology* 12 (2) (2016): 77–85;

[64] N. Kamar, H. Weclawiack, C. Guilbeaud-Frugier, F. Legrand-Abravanel, O. Cointault, D. Ribes, et al., "Hepatitis E Virus and the Kidney in Solid-organ-transplant Patients," *Transplantation* 93 (6) (2012): 617–23.

[65] Dalton et al., "Persistent Carriage of Hepatitis E Virus."

Table 2. Extrahepatic manifestations of hepatitis E

Organ system	Clinical syndrome	Notes
Neurological	• *Neuralgic amyotrophy • *Guillain Barré syndrome • *Meningoencephalitis • Mononeuritis multiplex • Myositis • Bell's palsy, vestibular neuritis, and peripheral neuropathy	See main text
Renal*	• Membranoproliferative and membranous glomerulonephritis • IgA nephropathy	See main text
Haematological	• Thrombocytopenia • Monoclonal immunoglobulin • Cryoglobulinemia • Aplastic anaemia • Haemolytic anaemia	• Mild and common • Twenty-five percent of acute cases • Case reports only • Case reports only • Case reports only
Other	• Acute pancreatitis • Arthritis • Myocarditis • Autoimmune thyroiditis	• Fifty-five cases worldwide. HEV gt 1 only • Case reports only • Case reports only • Case reports only

** There is good evidence to support a causal role for HEV and these associated conditions. For the other extrahepatic manifestations, causality remains to be established. HEV, hepatitis E virus.*

Neurological injury

HEV infection has been described in association with a range of neurological injuries. To date, approximately 150 cases of neurological injury in the context of HEV gt 3 infection have been described, mainly from Europe.[63] HEV-associated neurological injury has also been described in Asia in the context of HEV gt 1 infection. Most (less than ninety percent) cases have been documented in the immunocompetent, but

neurological injury also occurs in the context of chronic infection with HEV gt 3. Neurological pathology that has been described in association with HEV infection includes neuralgic amyotrophy (NA), Guillain Barré syndrome (GBS), encephalitis/myelitis, mononeuritis multiplex, Bell's palsy, vestibular neuritis, myositis, and peripheral neuropathy. The best documented are NA, GBS, and encephalitis/myelitis. [63] [66]

There have been several cohort and case studies of HEV infection in patients with NA. These are almost universally from Europe in the context of HEV gt 3 infection. In an Anglo/Dutch cohort study, five out of forty-seven (10.6 percent) of patients with NA had evidence of HEV infection at the start of their illness.[67] Very recent data, from a multicentre study of 118 patients with NA in Europe, shows that patients with HEV-associated disease have a distinct clinical phenotype, compared to patients with NA, without evidence of HEV infection. Patients with HEV-associated NA were significantly more likely to have bilateral involvement of, and more extensive damage to, the brachial plexus. They were also more likely to have neurological damage outside the brachial plexus, particularly phrenic nerve involvement.[68] Another recent European multicentre study systematically tested over 450 consecutive patients with acute onset of non-traumatic neurological injury prospectively. Evidence of HEV infection was found in 2.4 percent of patients, three of whom had NA with bilateral involvement, which we now know is the clinical phenotype associated with HEV infection.[69] Finally, it is worth noting that in one centre's experience the triad of bilateral shoulder pain in a middle-aged male with abnormal LFTs is highly predictive of HEV infection.[70]

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[66] K. L. Woolson, A. Forbes, L. Vine, L. Beynon, L. McElhinney, V. Panayi, et al., "Extra-hepatic Manifestations of Autochthonous Hepatitis E Infection," *Alimentary Pharmacology & Therapeutics* 40 (11–12) (2014): 1282–91.

[67] J. J. van Eijk, R. G. Madden, A A. van der Eijk, J. G. Hunter, J. H. Reimerink, R. P. Bendall, et al., "Neuralgic Amyotrophy and Hepatitis E Virus Infection," *Neurology* 82 (6) (2014): 498–503.

[68] Van Eijk et al., "Clinical Phenotype and Outcome of Hepatitis E Virus-associated Neuralgic Amyotrophy."

[69] Dalton et al., "Hepatitis E Virus Infection and Acute Non-traumatic Neurological Injury: a Prospective Multicentre Study."

[70] Dalton and Seghatchian, "Hepatitis E Virus: Emerging from the Shadows in Developed Countries."

There have been three case-control studies on HEV infection and GBS from the Netherlands, Bangladesh, and Japan.[71] [72] [73] Collectively, these studies confirm the relationship between HEV infection and GBS, as evidence of HEV infection at the start of the neurological illness was found in five to eleven percent of patients, which is significantly higher than in controls. In addition, in a very recent cohort study from Belgium, six in seventy-three (eight percent) of patients with GBS had evidence of HEV infection.[74]

There have been twelve case reports/small case series on HEV infection and encephalitis/myelitis from Europe, Asia, and the United States. Some cases had features of additional involvement of the peripheral nervous system. Five of the cases were in immunocompromised transplant recipients in the context of chronic HEV gt 3 infection. Several of these patients had a prominent ataxic component to their neurological symptomatology. These patients had poor outcomes, with long-term neurological sequelae and two deaths. [63] In one of these patients, "quasispecies compartmentalisation" was noted, i.e. there was a significant difference in sequence homology in HEV RNA from the serum and cerebrospinal fluid.[75] This raises the question of whether certain strains of HEV might be neurotropic.

In all of the aforementioned studies, the patients with HEV-associated neurological injury generally had only modest abnormalities of liver function and were mostly anicteric. Some patients had normal LFTs. Thus, the neurological symptoms and signs dominated the clinical picture. Pathogenic mechanisms are uncertain, but could be due to molecular mimicry, which would be congruent with current notions in NA and GBS, or due to direct neurotropism. It seems likely that, at least in the case of NA, GBS, and encephalitis/myelitis, the relationship between HEV infection and neurological damage is causal. [63] The evidence to support causality includes the number and homogeneity of cases over time and geographical location; case-control data in GBS; documentation of HEV

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[71] van den Berg, "Guillain-Barre Syndrome Associated with Preceding Hepatitis E Virus Infection".

[72] Geurtsvankessel et al., "Hepatitis E and Guillain-Barre Syndrome".

[73] Fukae et al., "Guillain-Barre and Miller Fisher Syndromes in Patients with Anti-hepatitis E Virus Antibody."

[74] Stevens et al., "Diagnostic Challenges and Clinical Characteristics of Hepatitis E Virus-associated Guillain-Barré Syndrome."

[75] N. Kamar, J. Izopet, P. Cintas, C. Garrouste, E. Uro-Coste, O. Cointault, et al., "Hepatitis E Virus-induced Neurological Symptoms in a Kidney-transplant Patient with Chronic Hepatitis," *American Journal of Transplantation* 10 (5) (2010): 1321–4.

RNA in the serum and cerebrospinal fluid, with quasispecies compartmentalisation in some cases; intrathecal anti-HEV IgM synthesis; resolution of neurological symptoms with viral clearance[76]; *in vitro* data that show HEV can grow on a range of neurological cell lines; and *in vivo* animal studies that show HEV can cross the blood-brain barrier.[77]

Renal injury

HEV can cause glomerulonephritis in both immunocompetent and immunosuppressed patients.[64 78 79 80 81] Renal impairment has been documented in solid-organ transplant recipients during acute HEV infection.[64] Cases of membranoproliferative glomerulonephritis with and without cryoglobulinaemia, as well as cases of membranous glomerulonephritis, have been reported, mainly in immunosuppressed patients infected by HEV gt 3. Cases of membranoproliferative and membranous glomerulonephritis have been documented with HEV gt 1 and 3 in the immunocompetent.[78 81] Renal function improves and proteinuria levels decrease following HEV clearance, either spontaneously or following therapy.[79 80] These data suggest the relationship between HEV infection and the associated renal injury is likely to be causal. Of note, in one case, HEV RNA was isolated from the cryoprecipitate obtained from a patient who developed HEV-associated cryoglobulinaemic glomerulonephritis.[81]

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[76] Dalton et al., "Treatment of Chronic Hepatitis E in a HIV Positive Patient."

[77] X. Zhou, F. Huang, L. Xu, Z. Lin, F. M. S. de Vrij, A. C. Ayo-Martin, et al., "Hepatitis E Virus Infects Neurons and Brains," *Journal of Infectious Diseases* 214 (3) (2017): 361–8.

[78] G. Ali, M. Kumar, S. Bali, and W. Wadhwa, "Hepatitis E Associated Immune Thrombocytopenia and Membranous Glomerulonephritis," *Indian Journal of Nephrology* 11 (2001): 70–2.

[79] B. Taton, K. Moreau, S. Lepreux, T. Bachelet, P. Trimoulet, V. De Ledinghen, et al., "Hepatitis E Virus Infection as a New Probable Cause of De Novo Membranous Nephropathy after Kidney Transplantation," *Transplant Infectious Diseases* 15 (6) (2013): E211–15.

[80] A. Del Bello, C. Guilbeau-Frugier, A. G. Josse, L. Rostaing, J. Izopet, and N. Kamar, "Successful Treatment of Hepatitis E Virus-associated Cryoglobulinemic Membranoproliferative Glomerulonephritis with Ribavirin," *Transplant Infectious Diseases* 17 (2) (2015): 279–83.

[81] D. Guinault, D. Ribes, A. Delas, D. Milongo, F. Abravanel, B. Puissant Lubrano, et al., "Hepatitis E Virus-induced Cryglobulinemic Glomerulonephritis in a Non-immunocompromised Person," *American Journal of Kidney Diseases* 67 (4) (2016): 660–3.

Cryoglobulinaemia

Cryoglobulinaemia has been observed in patients chronically infected by HEV, and disappears following antiviral therapy.[64] [81] Anti-HEV IgG seroprevalence seems to be higher in patients with essential cryoglobulinaemia.[82] [83] Finally, HEV-associated cryoglobulinaemia with arthralgia, myalgia, and rash has been also reported in a liver transplant recipient.[84]

Pancreatitis

Acute pancreatitis episodes have been reported in patients infected with HEV gt 1 from Southeast Asia.[85] [86] [87] However, no cases of acute pancreatitis have been documented in patients with HEV gt 3 or 4 infections.

Haematological disorders

Severe thrombocytopenia has been described in patients with acute HEV gt 1 and 3 infections.[66] [88] [89] [90] [91] HEV infection has been associated with a

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[82] S. Pischke, S. Polywka, F. Haag, C. Iking-Konert, M. Sterneck, M. Lutgehetmann, et al., "Association of Hepatitis E Virus and Essential Cryoglobulinemia?" *Journal of Clinical Virology* 67 (2015): 23–4.

[83] F. Bazerbachi, M. D. Leise, K. D. Watt, M. H. Murad, L. J. Prokop, S. Haffar, et al., "Systematic Review of Mixed Cryoglobulinemia Associated with Hepatitis E Virus Infection: Association or Causation?" *Gastroenterol Rep (Oxf)* 5 (3) (2017): 178–84.

[84] S. Pischke, P. Behrendt, M. P. Manns, and H. Wedemeyer, "HEV-associated Cryoglobulinaemia and Extrahepatic Manifestations of Hepatitis E," *Lancet Infectious Diseases* 14 (8) (2014): 678–9.

[85] S. Sinha, R. Jha, S. Lakhtakia, and G. Narayan, "Acute Pancreatitis Following Kidney Transplantation Role of Viral Infections," *Clinical Transplantation* 17 (1) (2003): 32–6.

[86] S Bhagat, M Wadhawan, R Sud, and A Arora, "Hepatitis Viruses Causing Pancreatitis and Hepatitis: a Case Series and Review of Literature," *Pancreas* 36 (4) (2008): 424–7.

[87] C Deniel, T Coton, S Brardjanian, M Guisset, E Nicand, and F Simon, "Acute Pancreatitis: a Rare Complication of Acute Hepatitis E," *Journal of Clinocal Virology* 51 (3) (2011): 202–4.

[88] N. K. Singh and M. Gangappa, "Acute Immune Thrombocytopenia Associated with Hepatitis E in an Adult," *American Journal of Hematology* 82 (10) (2007): 942–3. 151.

few other haematological disorders, mostly described as single case reports. These include autoimmune haemolytic anaemia, aplastic anaemia, and acute liver failure associated with pure red-cell aplasia.[92] [93] [94] Asymptomatic monoclonal paraprotein has been documented in up to twenty-five percent of patients infected with HEV gt 3. [66] The clinical significance of this observation is uncertain.

Other manifestations

Several other extrahepatic disorders have been described with HEV infection. These include myocarditis,[95] thyroiditis,[96] Henoch-Schönlein purpura,[97] and myasthenia gravis.[98] A causal relationship between these associations has not been established.

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[89] P. Colson, E. Payraudeau, C. Leonnet, S. De Montigny, L. Villeneuve, A. Motte, et al., "Severe Thrombocytopenia Associated with Acute Hepatitis E Virus Infection," *Journal of Clinical Microbiology* 46 (7) (2008): 2450–2;

[90] R. Thapa, D. Mallick, and A. Ghosh, "Childhood Hepatitis E Infection Complicated by Acute Immune Thrombocytopenia," *Journal of Pediatric Hematology/Oncology* 31(2) (2009).

[91] E. Fourquet, J. M. Mansuy, C. Bureau, C. Recher, J. P. Vinel, J. Izopet, et al., "Severe Thrombocytopenia Associated with acute Autochthonous Hepatitis E," *Journal of Clinical Virology* 48 (1) (2010): 73–4.

[92] S. Abid and A. H. Khan, "Severe Hemolysis and Renal Faihire in Glucose-6-Phosphate Dehydrogenase Deficient Patients with Hepatitis E," *American Journal of Gastroenterology* 97 (6) (2002): 1544–7.

[93] P. Mishra, M. Mahapatra, R. Kumar, H. P. Pati, "Autoimmune Hemolytic Anemia and Erythroid Hypoplasia Associated with Hepatitis E," *Indian Journal of Gastroenterology* 26 (4) (2007): 195–6;

[94] S. A. Shah, A. Lal, M. Idrees, A. Hussain, C. Jeet, F. A. Malik, et al., "Hepatitis E Virus-associated Aplastic Anaemia: the First Case of its Kind," *Journal of Clinical Virology* 54 (1) (2012): 96–7.

[95] A. Goyal, D. K. Mishra, R. Kawar, B. C. Kalmath, A. Sharma, and S. Gautam, "Hepatitis E Associated Myocarditis: an Unusual Entity," *The Bombay Hospital Journal* 51 (3) (2009): 361–2.

[96] F. L. Dumoulin and H. Liese, "Acute Hepatitis E Virus Infection and Autoimmune Thyroiditis: Yet Another Trigger?" *BMJ Case Reports* (April 23, 2012).

[97] R. Thapa, B. Biswas, and D. Mallick, "Henoch-Schonlein purpura triggered by acute hepatitis E virus infection," *Journal of Emergency Medicine* 39 (2) (2010): 218–19.

[98] A. Belbezier, A. Deroux, F. Sarrot-Reynauld, S. Larrat, and L. Bouillet, "Myasthenia Gravis Associated with Acute Hepatitis E Infection in Immunocompetent Woman," *Emerging Infectious Diseases* 20 (5) (2014): 908–10.

Recommendations

- EASL recommends HEV testing, irrespective of LFT results, in patients presenting with NA **(B1)** and GBS **(B1)** and suggests HEV testing for patients with encephalitis/myelitis **(C2)**
- EASL suggests testing patients with HEV infection for proteinuria **(C2)**
- Patients with acute or chronic HEV infection who develop new onset proteinuria may be considered for a renal biopsy **(C2)**
- EASL suggests antiviral treatment for patients with chronic HEV infection and associated glomerular disease **(C2)**

Unanswered questions and perspectives

- What are the neurological conditions which are causally related to HEV infection?
- What are the pathogenic mechanisms of HEV-associated extrahepatic injury?
- What is the incidence of HEV-associated glomerulonephritis?
- Are there any other HEV-associated extrahepatic manifestations that remain to be discovered?
- The treatment of most extrahepatic manifestations of HEV infection remains to be determined

Diagnosis

Laboratory diagnosis

The incubation period for hepatitis E is approximately fifteen to sixty days. Around three weeks post-infection, HEV RNA is detected in blood and stool, with viraemia lasting approximately three to six weeks, and the shedding of the virus in stool for approximately four to six weeks. The first appearance of HEV RNA occurs shortly before the onset of symptoms. Around the time of clinical onset, biochemical markers become elevated and antibodies start to appear, with IgM antibodies appearing first, followed soon after by IgG antibodies. The IgM antibodies are relatively short-lived (usually no longer than three to four months but may persist for up to a year). However, the IgG response is long lasting with increasing antibody avidity over time.

Molecular analysis

The detection of HEV RNA in blood or stool is indicative of HEV infection. In immunosuppressed patients with chronic hepatitis E, anti-HEV antibodies are often undetectable, and in such cases NATs are the only reliable means of diagnosis (see Fig. 3 below). Chronic cases of hepatitis E are defined as HEV RNA being detectable for at least three months. In such chronic cases, viral load testing is used to evaluate the response of patients to the modification of immunosuppressive drug treatment or antiviral therapy, as well as to identify relapsing infections.

NATs are used for the detection of HEV RNA. An evaluation of laboratory testing for HEV RNA by NATs revealed wide variations in the performance of different assays[99] and led to the development of the first WHO International Standard (IS) for HEV RNA for NAT-based assays[100] and the first WHO international Reference Panel (RP) for HEV genotypes 1–4. The availability of the WHO IS and RP has facilitated the comparison of the results of diagnostic tests performed by different laboratories, helping to harmonise testing. The WHO IS is an important tool for defining the analytical sensitivity of assays and enables reporting using a common unit, i.e. International Unit (IU). This provides a system of traceability. The analytical sensitivity of NAT-based assays can be lower than 10 IU/ml.

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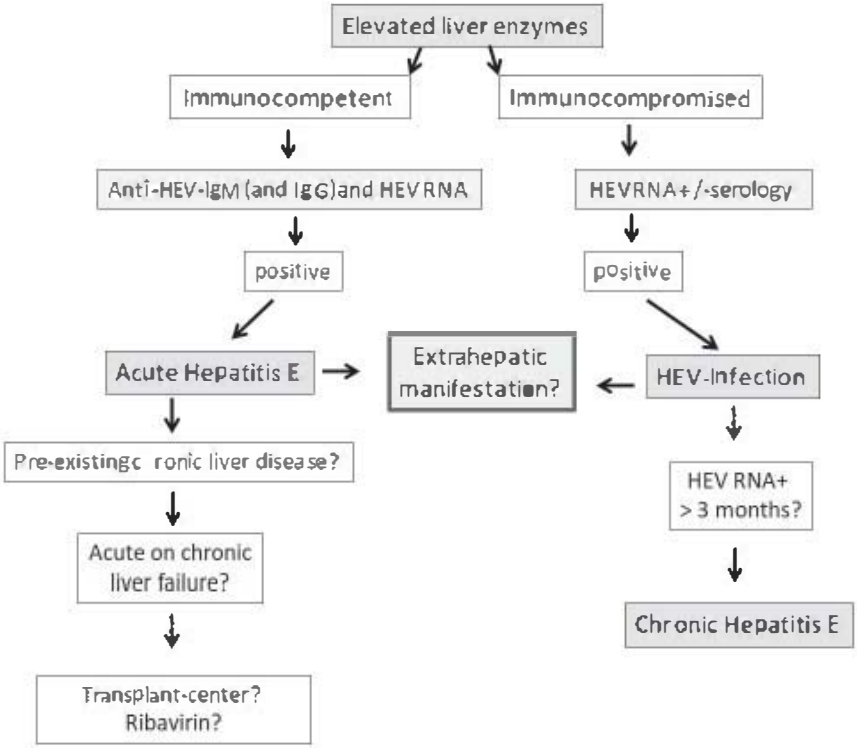
[99] S. A. Baylis, K. M. Hanschmann, J. Blumel, and C. M. Nubling, "Group HEVCS. Standardization of Hepatitis E Virus (HEV) Nucleic Acid Amplification Technique-based Assays: an Initial Study to Evaluate a Panel of HEV Strains and Investigate Laboratory Performance," *Journal of Clinical Microbiology* 49 (4) (2011): 1234–9.

[100] S. A. Baylis, J. Bhunel, S. Mizusawa, K. Matsubayashi, H. Sakata, Y. Okada, et al., "World Health Organization International Standard to Harmonize Assays for Detection of Hepatitis E Virus RNA," *Emerging Infectious Diseases* 19 (5) (2013): 729–35.

Fig. 3. Diagnostic algorithm for HEV infection



Serology and NAT testing are best used in combination, as a negative PCR does not exclude acute infection; serology is sometimes negative in the immunosuppressed patients with chronic infection (HEV: hepatitis E virus; NAT: nucleic acid amplification techniques).

Many different NAT-based assays have been reported for the detection of HEV RNA in serum and plasma or stool samples. These include conventional reverse transcription PCR (RT-PCR) and nested protocols, real-time RT-PCR, and transcription-mediated amplification methods including, for example, reverse transcription loop-mediated isothermal amplification.[99] [100] [101] [102] The most frequently used assays for the

[101] S. A. Baylis, C. Crossan, V. M. Corman, J. Blumel, L. Scobie, and H. R. Dalton, "Unusual Serological Response to Hepatitis E Virus in Plasma Donors Consistent with Re-infection," *Vox Sanguinis* 109 (4) (2015): 406–9.

detection of HEV RNA target highly conserved regions of the genome, in particular the region of ORF2 that overlaps ORF3, and are able to detect all four major genotypes of HEV that infect humans.[103] The sensitivity and specificity of assays depend upon well-designed primer and probe sequences. Occasionally, however, polymorphisms have resulted in false negative results in patients with HEV infection, so improvements have been made to the robustness of existing assays.[104] Sequence analysis is used to determine HEV genotype.

Antibody assays

Acute HEV infection can also be diagnosed by the detection of anti-HEV antibodies (IgM, IgG, or both) by enzyme immunoassays in combination with HEV NAT. Serological testing alone relies upon the detection of anti-IgM and (rising) IgG titres (see Table 3 below), since the specificity of certain assays is not optimal and anti-HEV IgM on its own is not a sufficiently robust marker for diagnosis.[105] Immunoblots are available for confirmatory testing, although they suffer from the same limitations and so have proved ineffective. Occasionally, anti-HEV IgA antibodies are used for the diagnosis of acute hepatitis E. However, such assays are not widely available. Past infection is determined by the presence of anti-HEV IgG.[106] In studies investigating seroprevalence, the sub-optimal performance of certain assays which lack sensitivity has previously resulted in very significant underestimates of populations' exposure to HEV.[106]

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[102] X. Lan, B. Yang, B. Y. Li, X. P. Yin, X. R. Li, and J. X. `Liu, "Reverse Transcription-Loopmediated Isothermal Amplification Assay for Rapid Detection of Hepatitis E Virus," *Journal of Clinical Microbiology* 47 (7) (2009): 2304 6.

[103] N. Jothikumar, T. L. Cromeans, B. H. Robertson, X. J. Meng, and V. R. Hill, "A Broadly Reactive One-step Real-time RT-PCR Assay for Rapid and Sensitive Detection of Hepatitis E Virus," *Journal of Virological Methods* 131 (1) (2006): 65 71.

[104] J. A. Garson, R. B. Ferns, P. R. Grant, S. Ijaz, E. Nastouli, and R. Szypulska, et al., "Minor Groove Binder Modification of Widely Used TaqMan Probe for Hepatitis E Virus Reduces Risk of False Negative Real-time PCR Results," *Journal of Virological Methods* 186 (1 2) (2012): 157 60.

[105] C. Hyams, D. A. Mabayoje, R. Copping, D. Maranao, M. Patel, W. Labbett, et al., "Serological Cross Reactivity to CMV and EBV Causes Problems in the Diagnosis of Acute Hepatitis E Virus Infection," *Journal of Medical Virology* 86 (3) (2014): 478 83.

[106] Bendall et al., "A Comparison of Two Commercially Available Anti-HEV IgG Kits."

Table 3. Laboratory diagnosis of HEV infection

Infection status	Positive markers
Current infection: acute	• HEV RNA • HEV RNA + anti-HEV IgM • HEV RNA + anti-HEV IgG* • HEV RNA + anti-HEV IgM + anti-HEV IgG • Anti-HEV IgM + anti-HEV IgG (rising) • HEV antigen
Current infection: chronic	• HEV RNA (± anti-HEV) ≥3 months • HEV antigen
Past infection	• Anti-HEV IgG

**Patients with re-infection are typically anti-HEV IgM negative, but IgG and PCR positive (HEV: hepatitis E virus)*

Antigen assays

The detection of the HEV antigen by enzyme immunoassays may also be used to diagnose both acute and chronic infections. Older versions of the antigen assays were not as sensitive as NATs.[107] However, newer assays offer improved sensitivity.[108] [109] HEV antigen levels may be lower in patients with acute hepatitis E than in patients with chronic hepatitis E, with an OD450/630 of >15 suggested to discriminate between acutely and chronically infected individuals in one study.[110] Importantly, the HEV antigen may persist for several months after ribavirin-induced HEV RNA clearance of chronic hepatitis E. This observation, and experimental data, suggest that the presence of the HEV antigen does not necessarily correlate with infectious virions. In one recent study, it was suggested that

[107] F. Zhang, X. Li, Z. Li, T. J. Harrison, H. Chong, S. Qiao, et al., "Detection of HEV Antigen as a Novel Marker for the Diagnosis of Hepatitis E," *Journal of Medical Virology* 78 (11) (2006): 1441–8.

[108] G. P. Wen, Z. M. Tang, F. Yang, K. Zhang, W. F. Ji, W. Cai, et al., "A Valuable Antigen Detection Method for Diagnosis of Acute Hepatitis E," *Journal of Clinical Microbiology* 53 (3) (2015): 782–8.

[109] C. Zhao, Y. Geng, T. J. Harrison, W. Huang, A. Song, and Y. Wang, "Evaluation of an Antigen-capture EIA for the Diagnosis of Hepatitis E Virus Infection," *Journal of Viral Hepatitis* 22 (11) (2015): 957–63.

[110] P. Behrendt, B. Bremer, D. Todt, R. J. Brown, A. Heim, M. P. Manns, et al., "Hepatitis E Virus (HEV) ORF2 Antigen Levels Differentiate Between Acute and Chronic HEV Infection," *Journal of Infectious Diseases* 214 (3) (2016): 361–8.

glycosylated forms of ORF2 are excreted in the sera of infected patients at high levels. However, infectious virions are associated with the much less abundant non-glycosylated form of ORF2.[111]

Immunohistochemistry

Immunohistochemistry for HEV ORF2 protein can be used to establish a histopathologic diagnosis of hepatitis E.[112]

Recommendations

- EASL recommends using a combination of serology and NAT testing to diagnose HEV infection **(A1)**
- EASL recommends NAT testing to diagnose chronic HEV infection **(A1)**

Unanswered questions and perspectives

- The role of the HEV antigen in diagnosis remains to be determined.

Differential diagnosis

The differential diagnosis of HEV infection is shown in Table 4 below. An important differential diagnosis of acute hepatitis E is drug-induced liver injury (DILI).[113] In a cohort study of UK patients with "criterion-referenced" DILI, it was found that in thirteen percent the diagnosis of DILI was erroneous, as the patients had acute hepatitis E, caused by gt 3.[114] This is an easy mistake to make as polypharmacy and DILI are both

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[111] C. Montpellier, C. Wychowski, I. M. Sayed, J. C. Meunier, J. M. Saliou, M. Ankavay, et al., "Hepatitis E Virus Lifecycle and Identification of 3 Forms of the ORF2 Capsid Protein," *Gastroenterology* 154 (1) (2018): 211 23, e218.

[112] D. Lenggenhager, J. Gouttenoire, M. Malehmir, M. Bawohl, H. Honcharova-Biletska, S. Kreutzer, et al., "Visualization of Hepatitis E Virus RNA and Proteins in the Human Liver," *Journal of Hepatology* 215 (8) (2017): 1197 1206.

[113] T. J. Davern, N. Chalasani, R. J. Fontana, P. H. Hayashi, P. Protiva, D. E. Kleiner, et al., "Acute Hepatitis E Infection Accounts for Some Cases of Suspected Drug-induced Liver Injury," *Gastroenterology* 141 (5) (2011): 1665 72, e1661 1669.

[114] H. R. Dalton, H. J. Fellows, W. Stableforth, M. Joseph, P. H. Thurairajah, U. Warshow, et al., "The Role of Hepatitis E Virus Testing in Drug-induced Liver Injury," *Alimentary Pharmacology & Therapeutics* 26 (10) (2007): 1429 35.

most common in the elderly, as is acute hepatitis E. Therefore, it is important to note that when making a diagnosis of DILI, particularly in a patient with a predominant aminotransferase elevation, it is key to first exclude HEV infection. Another common diagnostic difficulty is distinguishing between autoimmune hepatitis and acute hepatitis E. It is not uncommon for autoimmune hepatitis to present for the first time in older patients and be associated with non-specific "sticky" cross-reactive antibodies, which can produce false positive HEV serology results. False positive HEV serology can occur in the context of Epstein-Barr virus infection, also due to cross-reactive antibodies. [105]

Table 4. Differential diagnosis of hepatitis E

Infection status	Differential diagnosis
Acute infection*	• Drug-induced liver injury • Autoimmune hepatitis • Acute hepatitis E • Sero-negative hepatitis • EBV hepatitis • Acute hepatitis B • Acute hepatitis A • Acute hepatitis C • CMV hepatitis
Chronic infection in the immunosuppressed	• Graft rejection • Drug-induced liver injury • Recurrence of primary liver pathology in liver transplant recipients • Graft versus host disease • Intercurrent infections, e.g. sepsis • Chronic hepatitis E • EBV and CMV reactivation

** The differential diagnosis is in order of frequency of each condition seen at a rapid-access jaundice clinic in Southwest England. CMV, cytomegalovirus; EBV, Epstein-Barr virus*

Previously, only patients who had travelled to areas in Asia and Africa that are hyperendemic for HEV gt 1 and 2 were considered for HEV testing. We now know that the vast majority of patients with hepatitis E in developed countries have locally acquired infection, so in most countries national diagnostic testing algorithms have been changed. Any patient presenting with biochemical evidence of hepatitis should be considered for

HEV testing, irrespective of travel history. In some countries, patients presenting with hepatitis are only tested for HEV if the "first-line" virological testing (for HAV, HBV, and hepatitis C virus [HCV]) is negative. This is no longer appropriate, as we know that acute hepatitis E is the commonest cause of acute viral hepatitis in many countries. Therefore, all patients presenting with hepatitis should be tested for HEV at presentation (see Table 5 below).

Table 5. Suggested testing for HEV

Immunological status	Patients who should be tested for HEV
Immunocompetent	• Any patient with biochemical evidence of hepatitis • Suspected drug-induced liver injury • Decompensated chronic liver disease* • Neuralgic amyotrophy* • Guillain Barré syndrome* • Encephalitis* • Patients with unexplained acute neurology and a raised ALT**
Immunocompromised (developed countries)	• As above • Persistently abnormal ALT***

** Testing should be done at disease onset, irrespective of ALT results*
*** Testing should be done at disease onset, if ALT is abnormal*
**** If the ALT is above the limit of normal on more than one occasion (ALT: alanine aminotransferase; HEV: hepatitis E virus)*

Recommendations

- All patients with hepatitis should be tested for HEV, as part of the first-line virological investigation, irrespective of travel history **(A1)**
- Patients presenting with suspected DILI should be tested for HEV **(A1)**

HEV and the blood supply

In addition to zoonotic transmission, HEV can be transmitted iatrogenically between humans through infected blood and blood products. Transfusion-transmitted HEV infection has been documented in many countries in Europe (HEV gt 3) and Japan (HEV gt 3 and gt 4). Most cases

of transfusion-transmitted HEV infection are asymptomatic, and only a small minority of recipients of infected blood or blood products develop symptomatic hepatitis. When infected blood or components are given to the immunosuppressed, there is a significant risk that the recipient will develop chronic HEV infection. This is quite easily overlooked, as infected recipients have no symptoms and develop only minor persistent abnormalities in liver function, which may be delayed for months after infection. Transmission of HEV by solvent/detergent-treated plasma has been reported, and in Europe since 2015 solvent/detergent-treated plasma has been tested for HEV by NAT. There are currently no reports of HEV transmission by virally-inactivated fractionated blood products (purified plasma proteins).

Transfusion-transmitted HEV infection has been most well-documented in England and Japan.[29] In a study from 2012–13 in southeast England, 225,000 blood donors were screened for HEV by PCR. Seventy-nine donors were viraemic (gt 3), and sixty-two infected blood components were used prior to identification of donor viraemia.[29] A follow-up of forty-three recipients showed eighteen (forty-two percent) had evidence of infection, which was more likely with high donor viral loads and low levels of donor IgG antibody. Three patients required intervention with reduced immunosuppression (n=1) or ribavirin therapy (n=2) to successfully achieve viral clearance. In this study, the minimum infective dose contained a viral load of 2×10^4 IU HEV RNA, and fifty-five percent of blood components with at least this dose of transmitted infection.[29] In Japan, twenty cases of transfusion-transmitted infection have been documented in recent years. In an analysis of nineteen of these cases, caused mostly by HEV gt 3 and two by gt 4, the minimum infective dose was 3.6×10^4 IU HEV RNA and the rate of infection was fifty percent.[115] The presence of anti-HEV IgG in recipients does not necessarily protect the recipient from transfusion-transmitted infection, as low levels of antibody appear not to prevent re-infection. As zoonotic HEV infection is very common in many developed countries and mostly asymptomatic, it is no surprise that HEV has found its way into the human blood supply. However, what has come as a surprise to many professionals involved in transfusion medicine is the very high frequency of viraemic donors in many countries (see the supplementary table), ranging from 1:600 in the Netherlands to between 1:14,799 and 1:74,131 in Australia. These findings, together with the known adverse outcome of transfusing

[115] M. Satake, K. Matsubayashi, Y. Hoshi, R. Taira, Y. Furui, N. Kokudo, et al., "Unique Clinical Courses of Transfusion-transmitted Hepatitis E in Patients with Immunosuppression," *Transfusion* 57 (2) (2017): 280–88.

infected blood and components outlined above, have made HEV a "hot topic" in the blood transfusion community. Several countries have introduced universal, targeted, or partial screening for HEV in donors, including Ireland, the United Kingdom, France, the Netherlands, and Japan. In Germany, some blood transfusion companies have introduced voluntary HEV screening. In many other countries, donor screening is being considered (see the supplementary table). The screening methodology of choice is NAT, as infected donors usually have normal LFTs and are often anti-HEV IgM and IgG negative. Screening donors for HEV with NATs carries considerable cost, but a recent cost-effectiveness analysis from the Netherlands suggests that screening for HEV compares favourably in this regard to existing donor screening for HBV, HCV, and HIV. In England, it has been estimated that transfusion-transmitted HEV infection comprises less than one percent of all human infections with HEV (the remainder being due to zoonotic transmission), and that the transfusion of thirteen components from different donors equates to the annual dietary risk of HEV exposure in the general population. Thus, although donor screening will be very effective at minimising iatrogenic HEV infection, it will have a relatively minor impact on the numbers of HEV infections in the population as a whole.

Although extremely rare, HEV has been transmitted by liver and kidney grafts from infected donors. There are no current recommendations for organ donor screening.

Recommendations

- Patients with abnormal LFTs after receiving blood products should be tested for HEV **(A1)**
- EASL recommends that blood donor services screen blood donors for HEV by NAT, informed by local risk-assessment and cost-effectiveness studies, both of which may vary considerably by geographical location **(A1)**

Unanswered questions and perspectives

- Does the infective dose of transfusion-transmitted HEV differ by the immunological status of the recipient?
- Should organ donors be screened for HEV?
- Does the clinical phenotype of transfusion-transmitted HEV infection differ from zoonotic infection?
- Can HEV be effectively removed from blood products?

Treatment of acute hepatitis E

Acute HEV infection does not usually require antiviral therapy. In almost all cases, HEV infection is spontaneously cleared. However, some patients may progress to liver failure, so the question of whether hepatic decompensation can be avoided by antiviral treatment arises. Moreover, early therapy of acute hepatitis E may shorten the course of disease and reduce overall morbidity, as has been shown in the treatment of acute hepatitis caused by HBV and HCV.

Very few case reports are available on ribavirin treatment for severe acute HEV infection.[116] Ribavirin therapy was associated with the very rapid normalisation of liver enzymes and HEV RNA became undetectable within a few days. Cases of ribavirin treatment of both HEV gt 3 and HEV gt 1 infection have been published. Liver synthetic function rapidly improved in one case.

Corticosteroids have been used in individual cases of ALF, which were retrospectively identified as being been caused by HEV infection. Steroid therapy was associated with improved liver function parameters in these cases.[48] However, there is currently insufficient evidence to support corticosteroid treatment in patients with ALF due to HEV infection.

Statement

Acute HEV infection does usually not require antiviral therapy **(A)**.

Recommendation

- Ribavirin treatment may be considered in cases of severe acute hepatitis or acute-on-chronic liver failure **(C2)**

Unanswered questions and perspectives

- Does ribavirin therapy reduce morbidity in acute hepatitis E?
- The benefit of ribavirin in patients with severe acute hepatitis E and those with HEV-associated liver failure is uncertain

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[116] J. M. Peron, H. Dalton, J. Izopet, and N. Kamar, "Acute Autochthonous Hepatitis E in Western Patients with Underlying Chronic Liver Disease: a Role for Ribavirin?" *Journal of Hepatology* 54 (6) (2011): 1323–4 (author reply 1324–5).

- The dose and duration of ribavirin therapy in ALF are not defined
- Should corticosteroids be used in patients with HEV-associated ALF?
- Corticosteroid therapy is probably safe in the context of HEV infection, but further data are needed

The treatment of chronic infection in solid-organ transplant recipients

Solid-organ transplant recipients chronically infected with HEV who spontaneously achieve viral clearance have a lower tacrolimus trough level and a lower daily steroid dose compared to those who remain viraemic.[59] This has led to the notion that reducing immunosuppressive therapy, especially drugs targeting T-cells, could be a useful initial therapeutic option. Adopting this approach achieves sustained viral clearance in nearly one-third of chronically infected solid-organ transplant recipients (see Fig. 4 below).[58 59]

In vitro studies show that mTOR inhibitors upregulate HEV replication,[117] while mycophenolate has suppressive effects on HEV.[118] To what extent these *in vitro* findings are clinically relevant remains to be determined. Although in one study of heart transplant recipients the use of mycophenolate was associated with a lower likelihood of developing chronic hepatitis E,[60] mycophenolate-treated patients can still develop chronic hepatitis E.

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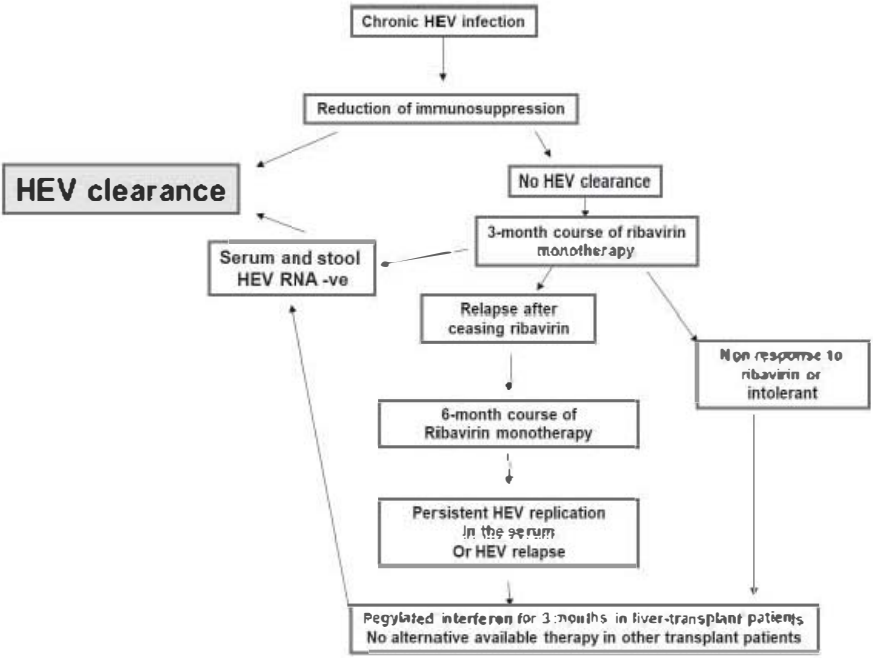
[117] W. Zhou, Wang Y, Metselaar HJ, Janssen HL, Peppelenbosch MP, Pan Q, "Rapamycin and Everolimus Facilitate Hepatitis E Virus Replication." *Journal of Hepatology* 61 (2014):746–754.

[118] Y. Wang Zhou X, Debing Y, ChenK, Van Der Laan LJ, Neyts J, et al. "Calcineurin inhibitors stimulate and mycophenolic acid inhibits replication of hepatitis E virus". *Gastroenterology* 146 (2014); 1775–83.

Fig. 4. Treatment algorithm for chronic HEV infection



The first therapeutic manoeuvre in transplant recipients is to reduce the dose of immunosuppression if possible. This will allow HEV to be cleared in about thirty percent of patients. If this is not possible, or unsuccessful, clinicians should follow the illustrated treatment algorithm. The role of other therapies such as sofosbuvir and immunoglobulins remains to be determined (HEV: hepatitis E virus)

PEGylated-interferon-α has been successfully used to treat a small number of liver transplant recipients and a haemodialysis patient who cleared HEV after a three-month course of therapy.[119] [120] [121] However,

[119] N. Kamar, L. Rostaing, F. Abravanel, C. Garrouste, L. Esposito, I. Cardeau-Desangles, et al., "Pegylated Interferon-alpha for Treating Chronic Hepatitis E Virus Infection After Liver Transplantation," *Clinical Infectious Diseases* 50 (5) (2010): e30–3.

[120] E. B. Haagsma, A. Riezebos-Brilman, A. P. van den Berg, R. J. Porte, and H. G. Niesters, "Treatment of Chronic Hepatitis E in Liver Transplant Recipients with Pegylated Interferon Alpha-2b," *Liver Transplantation* 16 (4) (2010): 474–7

[121] N. Kamar, F. Abravanel, C. Garrouste, I. Cardeau-Desangles, J. M. Mansuy, H. Weclawiak, et al., "Three-monthPegylated Interferon-alpha-2a Therapy for

interferon is generally contraindicated in kidney, pancreas, heart, and lung-transplant recipients because it stimulates the immune system and increases the risk of acute rejection.[122]

Ribavirin monotherapy has been more extensively studied in the treatment of chronic HEV infection in solid-organ transplant recipients, with a number of case reports and case series.[123] [124] [125] [126] Although ribavirin is the treatment of choice, its use is not backed up by any placebo-controlled trials. Several small series have reported high sustained virological response (SVR) rates after a three-month course of ribavirin monotherapy.[126] In a multicentre retrospective study that included fifty-nine solid-organ transplant recipients treated with ribavirin at a median dose of 600 (range, 200–1,200) mg/day for three (range, 1–18) months, the SVR was seventy-eight percent. Relapsers who were retreated with ribavirin for a longer period (six months) cleared the virus and achieved SVR.[126] No difference in SVR was observed between patients who received ribavirin for three months or less and those who were given therapy for more than three months. However, the optimal duration of ribavirin therapy is still unknown.

Ribavirin treatment can be associated with side effects including dose-dependent anaemia, a dry cough, and skin reactions. As patients with chronic hepatitis E frequently suffer from co-morbidities associated with impaired renal function or anaemia, ribavirin should be dosed with caution. Dose adaptations that consider haemoglobin and eGFR levels are strongly recommended.[127]

Chronic Hepatitis E Virus Infection in a Haemodialysis Patient," *Nephrology Dialysis Transplant* 25 (8) (2010): 2792–5.

[122] L. Rostaing, J. Izopet, E. Baron, M. Duffaut, J. Puel, and D. Durand, "Treatment of Chronic Hepatitis C with Recombinant Interferon Alpha in Kidney Transplant Recipients," *Transplantation* 59 (10) (1995): 1426–31.

[123] V. Mallet, E. Nicand, P. Sultanik, C. Chakvetadze, S. Tesse, E. Thervet, et al., "Brief communication: case reports of ribavirin treatment for chronic hepatitis E," *Annals of Internal Medicine* 153 (2) (2010): 85–9;

[124] N. Kamar, L. Rostaing, F. Abravanel, C. Garrouste, S. Lhomme, L. Esposito, et al., "Ribavirin therapy inhibits viral replication in patients with chronic hepatitis E virus infection," *Gastroenterology* 139 (5) (2010): 1612–18.

[125] S. Pischke, Hardtke S, Bode U, Birkner S, Chatzikyrkou C, Kauffmann W, et al. "Ribavirin treatment of acute and chronic hepatitis E: a singlecentre experience". Liver International 33 (2013): 722–726.

[126] Kamar, V. Mallet, and J. Izopet, "Ribavirin for Chronic Hepatitis E Virus Infection," *The New England Journal of Medicine* 370 (25) (2014): 2447–8.

[127] N. Kamar, E. Chatelut, E. Manolis, T. Lafont, J. Izopet, and L. Rostaing, "Ribavirin pharmacokinetics in renal and liver transplant patients: evidence that it

The mechanism of action of ribavirin against HEV is not fully understood. It has been suggested that ribavirin inhibits HEV replication by depleting guanosine triphosphate (GTP) pools.[128] Heart-transplant patients who were treated with mycophenolic acid—an inosine monophosphate dehydrogenase inhibitor that decreases GTP production—had a lower risk of developing chronic hepatitis in one study.[129] *In vitro*, mycophenolic acid and ribavirin have a synergistic anti-HEV effect.[118] Conversely, *in vivo*, in solid-organ transplant recipients, the change in HEV RNA concentration over time did not differ between patients given ribavirin with or without mycophenolic acid.[130] The use of mycophenolic acid as an immunosuppressant does not protect an individual transplant recipient from developing HEV infection.

Deep sequencing has identified several HEV RNA mutations. A recent study showed that ribavirin increases HEV heterogeneity, an effect that seems to be reversible. A G1634R mutation in the HEV polymerase was first described in two cases of ribavirin treatment failure.[131] However, pre-treatment G1634R mutations did not impact on SVR in a series of solid-organ transplant recipients given ribavirin.[132] In another study, the G1634R mutation appeared during therapy in patients who relapsed.[133] Several other variants in the polymerase regions have been described.

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depends on renal function," *American Journal of Kidney Diseases* 43 (1) (2004): 140–6.

[128] Y. Debing, S. U. Emerson, Y. Wang, Q. Pan, J. Balzarini, K. Dallmeier, et al., "Ribavirin Inhibits in Vitro Hepatitis E Virus Replication Through Depletion of Cellular GTP Pools and is Moderately Synergistic with Alpha Interferon," *Antimicrobial Agents and Chemotherapy* 58 (1) (2014): 267–73.

[129] S. Pischke and H. Wedemeyer, "Hepatitis E virus infection: multiple faces of an underestimated problem," *Journal of Hepatology* 58 (5) (2013): 1045–6.

[130] N. Kamar, S. Lhomme, F. Abravanel, Q. Cointault, L. Esposito, I. Cardeau-Desangles, et al., "An Early Viral Response Predicts the Virological Response to Ribavirin in Hepatitis E Virus Organ Transplant Patients," *Transplantation* 99 (10) (2015): 2124–31.

[131] Y. Debing, A. Gisa, K. Dallmeier, S. Pischke, B. Bremer, M. Manns, et al., "A Mutation in the Hepatitis E Virus RNA Polymerase Promotes its Replication and Associates with Ribavirin Treatment Failure in Organ Transplant Recipients," *Gastroenterology* 147 (5) (2014): 1008–11.

[132] S. Lhomme, N. Kamar, F. Nicot, J. Ducos, M. Bismuth, V. Garrigue, et al., "Mutation in the Hepatitis E Virus Polymerase and Outcome of Ribavirin Therapy," *Antimicrobial Agents and Chemotherapy* 60 (3) (2015): 1608–14.

[133] D. Todt, A. Gisa, A. Radonic, A. Nitsche, P. Behrendt, P. V. Suneetha, et al., "In Vivo Evidence for Ribavirin-induced Mutagenesis of the Hepatitis E Virus Genome," *Gut* 65 (10) (2016): 1733–43.

Some of these increase ribavirin sensitivity; others increase HEV replication, while others decrease HEV replication.[134] Hence, the role of HEV RNA variants and their impact on HEV treatment outcome are uncertain.

A high lymphocyte count has been found to be an independent predictor of SVR in solid-organ transplant recipients treated with ribavirin.[135] Persistence of HEV RNA in the stools at the end of ribavirin therapy in patients with undetectable HEV RNA in the serum is associated with an increased risk of HEV viraemia after ribavirin cessation.[136] A decrease in HEV RNA concentration ≥ 0.5 $\log_{10}$ IU/ml at day seven has been shown to predict SVR. Interestingly, in this study no association was observed between SVR and ribavirin trough level, seven days or two months after starting therapy.[130]

At present, no other antiviral therapies are known to be effective in the treatment of patients with chronic HEV infection, other than those outlined.[137] It has recently been reported that sofosbuvir, a specific and potent inhibitor of the hepatitis C virus NS5B RdRp, also has some activity against HEV RNA replication *in vitro* and that the antiviral effect is additive with ribavirin.[138] It is presently unknown if these observations made *in vitro* will translate to clinical efficacy *in vivo*.[137 139]

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[134] Y. Debing, C. Ramiere, K. Dallmeier, G. Piorkowski, M. A. Trabaud, F. Lebosse, et al., "Hepatitis E Virus Mutations Associated with Ribavirin Treatment Failure Result in Altered Viral Fitness and Ribavirin Sensitivity," *Journal of Hepatology* 147 (5) (2016): 1008 11.

[135] N. Kamar, J. Izopet, S. Tripon, M. Bismuth, S. Hillaire, J. Dumortier, et al., "Ribavirin for chronic hepatitis E virus infection in transplant recipients," *The New England Journal of Medicine* 370 (12) (2014): 1111 20.

[136] F. Abravanel, S. Lhomme, L. Rostaing, N. Kamar, and J. Izopet, "Protracted Fecal Shedding of HEV During Ribavirin Therapy Predicts Treatment Relapse," *Clinical Infectious Diseases* 60 (1) (2015): 96 9.

[137] N. Kamar, W. Wang, H. R. Dalton, and Q. Pan, "Direct-acting Antiviral Therapy for Hepatitis E Virus?" *Lancet Gastroenterol Hepatol* 2 (3) (2017): 154 5.

[138] M. van der Valk, H. L. Zaaijer, A. P. Kater, and J. Schinkel, "Sofosbuvir Shows Antiviral Activity in a Patient with Chronic Hepatitis E Virus Infection," *Journal of Hepatology* 66 (1) (2017): 242 3.

[139] M. C. Donnelly, S. N. Imlach, F. Abravanel, S. Ramalingam, I. Johannessen, J. Petrik, et al., "Sofosbuvir and Daclatasvir Anti-Viral Therapy Fails to Clear HEV Viremia and Restore Reactive T Cells in a HEV/HCV Co-Infected Liver Transplant Recipient," *Gastroenterology* 152 (1) (2017): 300 1.

The treatment of chronic HEV infection in other immunosuppressed patients

The treatment of chronic HEV infection in non-transplant immunosuppressed patients, i.e. patients with haematological disorders or HIV, has been documented in a few case reports and small series. PEGylated-interferon-α, ribavirin, or the combination of both was effective for treating HEV infection in patients with haematological disorders[140 141 142] and those with HIV.[76 143 144] Nine out of twelve stem-cell-transplant recipients treated with ribavirin achieved SVR.[142]

Recommendations

- EASL recommends decreasing immunosuppression at the diagnosis of chronic HEV infection in solid-organ transplant recipients, if possible **(B1)**
- In patients with persisting HEV replication three months after detection of HEV RNA, EASL recommends ribavirin monotherapy for a duration of twelve weeks **(B1)**
- At the end of the scheduled period of therapy, HEV RNA should be assessed in the serum and in the stool **(B1)**. If HEV RNA is undetectable in both, EASL suggests stopping ribavirin **(C2)**

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[140] L. Alric, D. Bonnet, G. Laurent, N. Kamar, and J. Izopet, "Chronic Hepatitis E Virus Infection: Successful Virologic Response to Pegylated Interferon-{alpha} Therapy," *Annals of Internal Medicine* 153 (2) (2010): 135–6.

[141] L. Alric, D. Bonnet, O. Beynes-Rauzy, J. Izopet, and N. Kamar, "Definitive Clearance of a Chronic Hepatitis E Virus Infection with Ribavirin Treatment," *The American Journal of Gastroenterology* 106 (8) (2011): 1562–3.

[142] S. Tavitian, J. M. Peron, F. Huguet, N. Kamar, F. Abravanel, O. Beyne-Rauzy, et al., "Ribavirin for Chronic Hepatitis Prevention among Patients with Hematologic Malignancies," *Emerging Infectious Diseases* 21 (8) (2015): 1466–9.

[143] K. Neukam, P. Barreiro, J. Macias, A. Avellon, C. Cifuentes, L. Martin-Carbonero, et al., "Chronic Hepatitis E in HIV Patients: Rapid Progression to Cirrhosis and Response to Oral Ribavirin," *Clinical Infectious Diseases* 57 (3) (2013): 465–8.

[144] H. Hajji, R. Gerolami, C. Solas, J. Moreau, and P. Colson, "Chronic Hepatitis E Resolution in a Human Immunodeficiency Virus (HIV)-infected Patient Treated with Ribavirin," *International Journal of Antimicrobial Agents* 46 (3) (2013): 595–7.

Statement

- The optimal treatment duration in patients who test HEV RNA positive after four or eight weeks of therapy and who are HEV RNA negative after twelve weeks of therapy is unknown **(C)**

Recommendation

- In patients in whom HEV RNA is still detectable in the serum and/or in the stool after twelve weeks, ribavirin monotherapy may be continued for an additional three months (six months therapy overall) **(C2)**

Statement

- The optimal therapeutic approach is unknown in patients who show no response to ribavirin and/or who relapse after retreatment **(C)**

Recommendation

- Liver transplant recipients who show no response to ribavirin can be considered for treatment with PEGylated-interferon-α **(C2)**

Unanswered questions and perspectives

- What is the optimal ribavirin dose and duration of therapy?
- What is the best treatment in patients who show no response to ribavirin and/or who relapse after retreatment?
- What is the mechanism of action of ribavirin?
- Alternative therapies need to be developed for patients who do not achieve viral clearance with (or cannot tolerate) ribavirin or PEGylated-interferon-α

Prevention of HEV infection

Recent evidence from a cell culture model suggests that heating virus stocks for more than two minutes at 70°C eliminates HEV infectivity, while infective HEV could be recovered by storage at room temperature even after twenty-eight days. A temperature of 80°C was required to

prevent HEV infection when heating for one minute.[145] However, it is unclear to what extent these *in vitro* data can be translated into food-preparation practices.

Several case-control studies clearly defined consumption of undercooked meat from pigs, wild boar, and deer as risk factors for HEV infection in Europe.[61] Thus, it is strongly recommended that individuals at risk of severe acute or chronic HEV infection avoid consumption of food products which may contain infectious HEV. However, recommending that the general population avoid undercooked pork is not currently justifiable. Immunocompetent individuals are likely to be able to tolerate exposure to HEV without any significant health threat. However, there is some evidence that consumption of pork is associated with increased mortality.[146] To what extent this increased risk can be attributed to HEV infection remains to be determined. The safety of other food products including strawberries, spinach, shellfish, and camel milk requires further investigation.

The risk of patient-to-patient transmission of HEV is poorly defined. Sexual transmission of HEV has been described in men having sex with men,[147] [148] but in another study of a cohort of patients with HIV, no evidence of sexual transmission was found.[149] As stool contains high amounts of infectious HEV particles, and as stool-derived HEV has been shown to be more infectious than plasma-derived HEV,[150] [151] strict

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[145] R. Johne, E. Trojnar, M. Filter, and J. Hofmann, "Thermal Stability of Hepatitis E Virus as Estimated by a Cell Culture Method," *Applied and Environmental Microbiology* 82 (14) (2016): 4225–31.

[146] H. R. Dalton, R. P. Bendall, C. Pritchard, W. Henley, and D. Melzer, "National Mortality Rates from Chronic Liver Disease and Consumption of Alcohol and Pig Meat," *Epidemiology and Infection* 138 (2) (2010): 174–82.

[147] F. Montella, G. Rezza, F. Di Sora, P. Pezzotti, and O. Recchia, "Association Between Hepatitis E Virus and HIV Infection in Homosexual Men," *The Lancet* 344 (8934) (1994): 1433.

[148] B. A. Payne, M. Madhi, S. Ijaz, M. Valappil, E. J. Savage, O. N. Gill, et al., "Hepatitis E Virus Seroprevalence Among Men who Have Sex with Men, United Kingdom," *Emerging Infectious Diseases* 19 (2) (2013): 333–5.

[149] F. Keane, M. Gompels, R. Bendall, R. Drayton, L. Jennings, J. Black, et al., "Hepatitis E Virus Coinfection in Patients with HIV Infection," *HIV Medicine* 13 (1) (2012): 83–8.

[150] I. M. Sayed, L. Verhoye, L. Cocquerel, F. Abravanel, L. Foquet, C. Montpellier, et al., "Study of Hepatitis E Virus Infection of Genotype 1 and 3 in Mice with Humanised Liver," *Gut* 66 (5) (2017): 920–9.

hygienic recommendations should be considered to prevent the spread of HEV by contaminated stool, e.g. in hospitals or nursing homes. HEV RNA can also be detected in urine.[152] It is unclear if HEV can be transmitted by saliva, sweat, semen, or breast-milk.

A vaccine against HEV was licensed in China in 2011. This vaccine showed an efficacy of ninety-seven percent for preventing episodes of symptomatic acute hepatitis,[153] with its long-term efficacy proved during further follow-up.[154] The vaccine is based on a protein containing 239 amino acids of HEV ORF2 protein (aa 368–606), derived from HEV gt 1. Surface protrusions, formed by dimerisation of HEV 239, correspond to a protruding domain of the virus capsid responsible for eliciting neutralising antibodies. Cellular immune responses are also involved in the control of HEV infection and these include both natural killer cells as well as HEV-specific T-cells.[155] The vaccine prevented symptomatic HEV gt 4 infections, suggesting cross genotype efficacy, but the vaccine does not provide sterilising immunity, and subclinical infections can still occur. While the vaccine seems to be safe in pregnant women,[156] the long-term efficacy and safety in patients with chronic liver disease and the immunosuppressed remain to be determined. A major role of the vaccine could be to prevent HEV outbreaks, e.g. in African refugee camps or other emergency settings. However, the vaccine is currently not licensed for this

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[151] L. Allweiss, S. Gass, K. Giersch, A. Groth, J. Kah, T. Volz, et al., "Human Liver Chimeric Mice as a New Model of Chronic Hepatitis E Virus Infection and Preclinical Drug Evaluation," *Journal of Hepatology* 64 (5) (2016): 1033–40.

[152] Y. Geng, C. Zhao, W. Huang, T. J. Harrison, H. Zhang, K. Geng, et al., "Detection and Assessment of Infectivity of Hepatitis E Virus in Urine," *Journal of Hepatology* 64 (1) (2016): 37–43.

[153] F. C. Zhu, J. Zhang, X. F. Zhang, C. Zhou, Z. Z. Wang, S. J. Huang, et al., "Efficacy and Safety of a Recombinant Hepatitis E Vaccine in Healthy Adults: a Large-scale, Randomised, Double-blind Placebo-controlled, Phase 3 Trial," *The Lancet* 376 (9744) (2010): 895–902.

[154] J. Zhang, X. F. Zhang, S. J. Huang, T. Wu, Y. M. Hu, Z. Z. Wang, et al., "Long-term Efficacy of a Hepatitis E Vaccine," *The New England Journal of Medicine* 372 (10) (2015): 914–22.

[155] A. Brown, J. S. Halliday, L. Swadling, R. G. Madden, R. Bendall, J. G. Hunter, et al., "Characterization of the Specificity, Functionality, and Durability of Host T-Cell Responses Against the Full-Length Hepatitis E Virus," *Hepatology* 64 (6) (2016): 1934–50.

[156] T. Wu, F. C. Zhu, S. J. Huang, X. F. Zhang, Z. Z. Wang, J. Zhang, et al., "Safety of the Hepatitis E Vaccine for Pregnant Women: a Preliminary Analysis," *Hepatology* 55 (6) (2012): 2038.

purpose in countries other than China, but efforts are currently underway to obtain WHO "prequalification" for use in emergency settings.

Recommendations

- Immunocompromised individuals and those with chronic liver diseases should avoid consumption of undercooked meat (pork, wild boar, and venison) and shellfish **(B1)**
- EASL suggests that immunocompromised patients consume meat only if it has been thoroughly cooked to temperatures of least 70°C **(B2)**

Unanswered questions and perspectives

- The risk of HEV transmission to animals by potentially contaminated animal feeds is unknown
- The HEV infection dynamics in farm-reared animals need to be better defined
- What is the risk of patient-to-patient transmission by exposure to contaminated body fluids/close personal contact?
- The efficacy and safety of an HEV vaccine needs to be defined in immunocompromised patients, patients with end-stage organ disease awaiting transplantation, and patients with chronic liver disease
- The efficacy of an HEV vaccine against HEV gt 3 remains to be determined
- The efficacy of an HEV vaccine in farm-reared animals is unknown
- How long does immunity (both natural immunity and immunity after vaccination) against HEV last?

Conclusions

Our understanding of HEV infection has completely changed in the last decade. There are still many knowledge gaps, and it is likely that as answers to these questions become available, these CPGs will require amendment in a few years' time.[42 157 158 159]

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[157] S. A. Baylis, O. Koc, S. Nick, and J. Blumel, "Widespread Distribution of Hepatitis E Virus in Plasma Fractionation Pools," *Vox Sanguinis* 102 (2) (2012): 182 3.

Conflict of interest

H. R. Dalton reports grant support from the BMA, consultant/advisory roles with Roche, Gilead, Wantai, and Merck, and the delivery of sponsored lectures for the Gates Foundation. Co-holder of patent Kernow CP6 with NIH and others. H. Wedemeyer reports grant support from Abbott, Roche diagnostics, Abbvie, and Gilead, consultant/advisory roles for Abbott, Roche diagnostics, Abbvie, and Gilead, and the delivery of lectures sponsored by Abbott, Abbvie, and Gilead. All other panel members report no conflicts of interest.

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Supplementary table: HEV viraemia in blood donors and donor screening status

Country	Blood donors HEV RNA positive	Reference	Blood donor screening for HEV
Austria	1:8416	Fischer et al. (2015)[1]	No screening
Australia	1:14799 1:74131	Shrestha et al. (2016)[2] Hoad et al. (2017)[3]	No screening
Canada	1:13993	Fearon et al. (2017)[4]	No screening
China *	1:1000	Zhang et al. (2016)[5]	No screening
Denmark	1:2330	Harrishøj et al. (2016)[6]	Screening has been deemed unnecessary
England	1:1365 1:2848 1:7000	Domanović et al. (2017)[7] Hewitt et al. (2014)[8] Ijaz et al. (2012)[9]	Targeted screening in donors for high risk recipients 2016. Universal screening from April 2017
France	1:2218	Gallian et al. (2014)[10]	Screening under consideration. Plasma for high-risk recipients screened for HEV since 2013
Germany	1:616 1:1200 1:4525	Müller et al. (2015)[11] Vollmer et al. (2012)[12] Baylis et al. (2012)[13]	Some donor centres started voluntary screening 2016
Ireland	1:2778 1:4997	Domanović et al. (2017)[14] O'Riordan et al. (2016)[15]	Universal screening from 2016
Japan (Hokkaido)	1:8173	Matsubayashi et al. (2011)[16]	Donors screened in Hokkaido since 2005
Japan (excluding Hokkaido)	1:15075	Minagi et al. (2016)[17]	No screening
Netherlands	1:612 1:2671	Zaaijer (2015)[18] Slot et al. (2013)[19]	Universal screening to be introduced July 2017

Poland	1:1033	Gdowska et al. (2016)[20]	Screening under consideration
Scotland	1:1250 1: 2481 1:14520	Domanović et al. (2017)[21] Thom et al. (2018)[22] Cleland et al. (2013)[23]	Targeted screening in donors for high-risk recipients 2016. Universal screening from April 2017
Spain	1:3333	Sauleda et al. (2015)[24]	Screening under consideration
Sweden	1:7986	Baylis et al. (2012)[25]	No screening
USA	Nil Nil* 1:9500 1:42673**	Baylis et al. (2012)[26] Xu et al. (2012)[27] Stramer et al. (2016)[28] Roth et al. (2017)[29]	Screening under consideration
Wales	1:2280	Domanović et al. (2017)[30]	Targeted screening in donors for high-risk recipients 2016. Universal screening from April 2017

Genotype 3 was found in all countries except China where only genotypes 1 (fifty-eight percent) and 4 (forty-two percent) were observed. In the Hokkaido region of Japan, genotype 4 was also reported.

* Only 1,939 donors tested;

** Pooled plasma donations. Rates of viraemic donations have been observed to fluctuate considerably over time within countries where screening has been implemented (O'Riordan: Ireland donor screening results. Oral presentation, 23rd IPFA/PEI Workshop, Zagreb, Croatia, 2017; R.Tedder: The introduction of universal HEV Screening. Oral presentation, 23rd IPFA/PEI Workshop, Zagreb, Croatia, 2017).

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INDEX

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"If this island belonged to me I would bury my all books here and never leave"

He died the next year, aged thirty-six