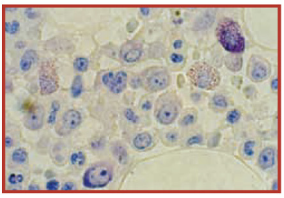
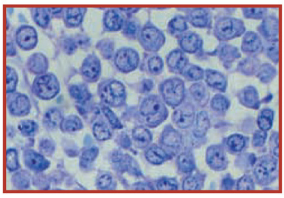
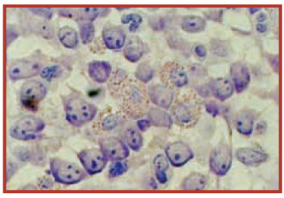
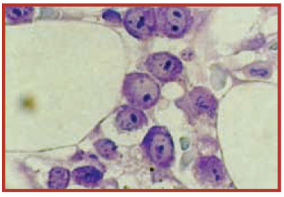
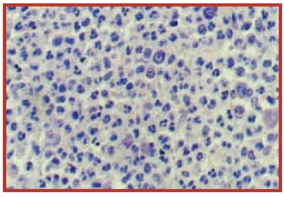
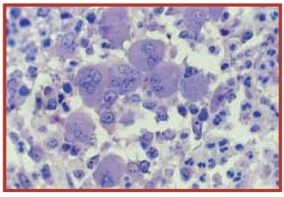
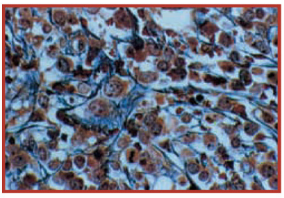
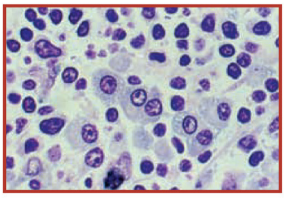
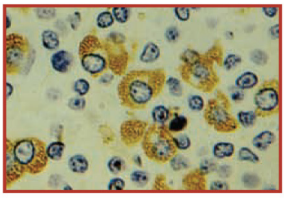


Manual of Bone Marrow Examination

Anwarul Islam

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Manual of Bone Marrow Examination

By

Anwarul Islam

Cambridge Scholars Publishing



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Manual of Bone Marrow Examination

By Anwarul Islam

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To my parents, my wife Shelley, sons Dimitri and Pierre
and to my mentors
Professor Daniel Catovsky
Hammersmith Hospital
London, England
and
Late Professor Rolf Burkhardt, Munich, Germany, Late Professor Bertha Frisch, Tel Aviv, Israel
Late Professors D. A. G. Galton, and John M Goldman
Hammersmith Hospital
London, England

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PREFACE

The purpose of this manual is to present a systematic approach to the methods of procurement and examination of bone marrow (aspiration and trephine biopsy) samples which play a crucial role in the diagnosis and management of hematological as well as non-hematological conditions. The manual is designed for medical students, house officers, physicians and other health professionals with an interest in hematology and oncology. It can also be used as a readily available, contemporary reference source for technologists and nurses who are involved in assisting in bone marrow aspiration, biopsy procurement and processing of marrow for cytological, immunological and histological examination. Although most practicing hematologists are familiar with bone marrow sampling techniques for diagnostic evaluation there is a growing body of information that merits review, critical analysis and consolidation in one working reference.

The manual is organized into two major sections. The first is directed towards an appreciation of the advantages, disadvantages and limitations of bone marrow aspiration biopsies specimens. The selection of biopsy site(s) and the diagnostic value of the derived Romanowsky stained dry film smears are discussed. The second section of the text addresses the trephine or solid core bone marrow biopsy specimens. Particular attention is directed to the new and improved instrumentation that has been introduced into the field. In addition to comparing the trephine/core biopsy with the aspiration biopsy technique the particular advantages of the former procedure are evaluated in detail. Finally, considerable attention has been given to the stepwise bedside technique of obtaining ideal bone marrow aspiration and trephine/core biopsy specimens and their processing.

It is recognized that bone marrow aspiration and trephine/core biopsy are specialized clinical procedures. It is associated with well recognized requirements as well as potential problems and pitfalls that are less well known. These considerations and their resolution from a clinical hematologist's viewpoint are specifically included in this text.

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PREFACE TO THE SECOND EDITION

On a vacation in 1943, Edwin Land snapped a photo of his three-year-old daughter, Jennifer, who asked why she could not see the picture *right* now. Land wondered the same thing. He later recalled that by the end of that same day he had pretty much figured out the solution-"except for those details that took from 1943 to 1972."

Land's created "Polaroid" Readers Digest

Readers Digest

Almost fifteen years have passed since the first edition of this book was published. During this time there has been considerable improvement in the technique of procuring bone marrow, particularly the core biopsy sample and it's processing into plastic—methyl or glycol methacrylate. The loss of bone marrow core samples during its extraction, in other words, failure to retain the complete biopsy sample within the lumen of the needle after the needle is withdrawn from the patient's body has been a serious continuing problem. Although the importance and significance of this particular problem, i.e. the loss of biopsy sample during the process of its extraction was recognised many years ago and was successfully addressed by a new Islam bone marrow biopsy needle with the 'core retention device'. But until now, this needle had not been available in a disposable form because of the complicated nature and high cost involved with the production of such a needle. In recent years, new technology has emerged by which such needles can be made economically and in large numbers. Taking advantage of this new technology, a new Islam single-use bone marrow biopsy needle that retains the original principle of core retention device has now been produced which has been detailed in this book.

Although the problem of core loss by the conventional bone marrow biopsy needles is now universally recognized and to overcome this problem several different single-use needles have recently been introduced. Each of these needles features different methods of securing a core sample during withdrawal of the needle from the patient's body. Unfortunately, in the process of doing this, all of these needles significantly complicate the procedure by introducing multiple steps and a

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nearly unmanageable assortment of extra parts and components. In some cases, these needles contain up to six or more additional parts. Furthermore, these core-capturing devices as they grasp the biopsy specimen may also cause a crush artefact and reduce the amount and quality of marrow tissue available for histological examination.

The advantage of the new Islam single use bone marrow biopsy needle lies in its simplicity and also in the reduced number of parts and steps required to complete the procedure. This new needle essentially contains only three parts—the needle, spacer guide and the stilette. In this new system, the same stilette is used as a pusher to extrude the biopsy sample out of the needle. In addition, the distal cutting end of the needle, which bears the *internal* core retention device, has been fitted with multiple small outside serration's/flutes which enhance the force of boring through the hard cortical bone and facilitate the entry of the main wider portion of the hollow needle into the marrow cavity. Although it now sounds very simple, it took over 30 years to develop the Islam single use bone marrow biopsy needle. In that respect the same analogy (quoted above) that applied to Land is also applicable to Islam.

In general bone marrow aspiration and bone marrow core biopsies are now routinely obtained for the investigation, diagnosis and management of various haematological, non-haematological and various other diseases. The procedure usually involves aspiration of a fluid suspension of bone marrow from the sternum, or from the posterior iliac crests using a sternal puncture or similar needles. The bone marrow core biopsies are usually obtained from the posterior iliac crest with a bone marrow biopsy needle. Since the aspirate and core biopsy provide complimentary and useful information, both specimens are routinely obtained at the same time and usually from the same site in a large majority of cases. Posterior iliac crest is most commonly the site of choice. However, because of the extra time required and the inconvenience of using two needles—one for aspiration and one for core biopsy, and the additional cost involved in using the two needles, some investigators use a single bone marrow biopsy needle for both purposes. The technique of aspiration and obtaining a core biopsy at the same time using the same needle and at the same site has inherent technical problems and other disadvantages which has been highlighted in Chapter 5 and proper method of doing so but without sacrificing the quality of the specimens have been recommended. In addition the book has now been produced in colour and several coloured illustrations of mostly plastic embedded bone marrow biopsy sections in normal and diseased condition have been added.

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PREFACE TO THE THIRD EDITION

In preparing this third edition I have made corrections to a number of minor errors and have improved the text and exposition. This edition has left intact the material of most chapters and added several new chapters including the one on myelodysplastic syndromes depicting the author's perspective and introducing a considerable amount of detailed information concerning the future directions of bone marrow techniques and analysis.

I have tried to emphasize the value of the procedure of obtaining a bone marrow aspiration with an aspiration needle *first*, followed by deriving a trephine (core) biopsy specimen using a separate bone marrow trephine (core) biopsy needle. I have also tried to impart the importance of making fresh, bedside smears from the *first pull* (0.5 ml) of marrow rather than makings them from a diluted marrow sample (the aspirated large amount of marrow obtained in one single pull) which could remain standing at length (even hours) before the marrow suspension is transported to the laboratory. In addition, I have discussed the pros and cons of currently available bone marrow trephine (core) biopsy needles that require extra steps and additional parts (such as core-capturing/core trapping devices) to capture a biopsy specimen such as the Jamshidi, Ranfac and OnControl needles and compared them with the *Islam* bone marrow trephine (core) biopsy needle that has an smooth internal core retention device that avoids the need for any extra components or parts and any additional steps or maneuvers (which may elicit additional pain) to capture the biopsy specimens. Unlike the Islam needle system, the other core-capturing/trapping devices are hard to push over the biopsy specimens and not only cause fragmentation of the biopsy specimens but also inflict considerable damage to the biopsied tissue, particularly to the edge of biopsy specimens.

Finally I wish to add that if any reader of this text, particularly my colleagues in hematology/oncology, interventional radiology and pathology can enhance their knowledge and skill in procuring, processing, analyzing and reporting bone marrow I would consider the effort and journey of writing this text worthwhile.

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I am indebted to Professor Chester Glomski, for his enthusiasm and help in writing this book. I am also grateful to Mrs. Janet O'Bryan of Cardinal Health for her unparalleled personal interest in the development of the core retention bone marrow instruments. I am further very thankful for Mrs. Sarah Rettig's (Moeller Medical, Germany) input into the design and production of the bone marrow needles. Sincere thanks are owed to Mrs. Rebecca Gladders, Commissioning Editor and Amanda Millar, Cambridge Scholars Publishers, Newcastle Upon Tyne, UK for their professional efforts. I am thankful for Neil Halstead's excellent art work and Samuel Destefano's help with technical help. I personally appreciate my patients and technicians who imparted clinical relevance to the text. I am indebted to Dr. Pierre Islam for his support with the layout and editorial presentation. Finally without Shelley this volume would never have been accomplished.

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CHAPTER 1

INTRODUCTION

Introduction to bone marrow and its examination

Bone marrow is housed within the inner fixed confines of bone and is the hematopoietic organ responsible for the production of the blood cellular elements that perform vital functions of oxygen transport, protection against bacterial and viral pathogens, control of inflammatory responses, and participation in endothelial repair as well as clot formation. The importance of bone marrow examination in any hematological disorder cannot be overemphasized. In its absence the investigation of any hematopoietic disorder, unless otherwise well defined, documented and prognostically evaluated, is incomplete. Even in many cases where the diagnosis is clinically and pathologically established an examination of the bone marrow remains an integral part of the practice of effective, scientific, hematologic medicine.

Cytologic and histologic analysis

There are two methods available for diagnostic access to the bone marrow, cytologic and histologic. In the former approach, i.e. bone marrow aspiration, a sample of marrow is withdrawn from a bone via an aspirating needle and a syringe delivering a mixture of free hematopoietic cells, small aggregates or clusters of marrow cells and fat (often termed bone marrow particles, fragments or units), and a variable amount of sinusoidal blood. This material is utilized to prepare dry film smears which are typically stained with a Romanowsky type dye (Leishman, Giemsa etc.). Conversely in the histologic analysis of bone marrow, a biopsy is obtained which provides an undisturbed segment of marrow tissue with its cellular, vascular and osseous *in situ* relationships intact. This tissue is then fixed in a suitable fixative and prepared for paraffin or plastic embedding, sectioning, staining, and subsequent analysis.

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Access to bone marrow

Marrow Aspiration and Biopsy Sites

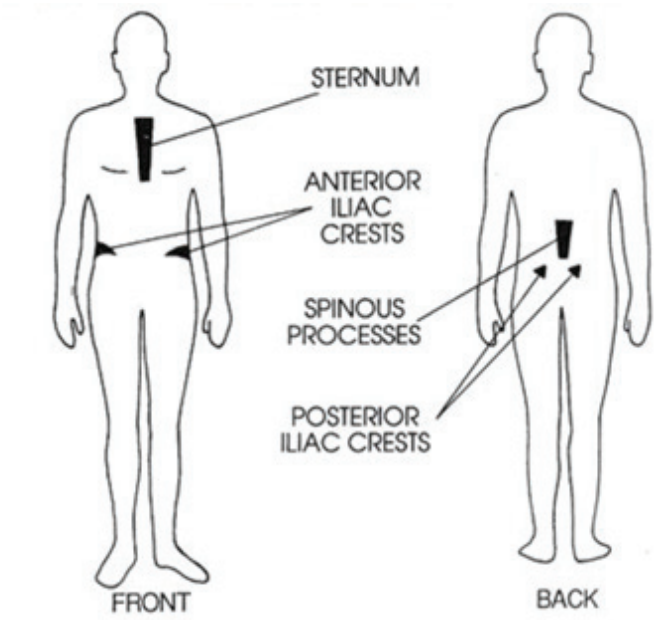


Figure 1.1 Access to bone marrow

Various sites are available for the access of hematopoietic bone marrow in humans. Satisfactory samples can be routinely aspirated from the sternum, the iliac crest(s) in the region of the anterior or posterior iliac spines and the spinous processes of the lumbar vertebrae (Figure 1.1). A bone marrow aspirate sample can also be obtained from ribs, vertebral bodies or any other bones which show radiologic or other evidence of osseous lesion. The region of the tibial proximal epiphysis is an excellent safe site for sampling bone marrow in children but is not appropriate for adults because of the replacement of its red marrow with adipose cells (inactive yellow marrow). Sternal puncture has historically been the most commonly used technique of aspirating bone marrow. In recent years, however, due to the availability of improved, more durable bone marrow aspiration instruments the region of the posterior iliac spine has become more frequently the site of choice. Bone marrow histologic (solid tissue) biopsies, often termed needle or core biopsies, are usually performed at the anterior or posterior

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iliac crests. Again, as a result of technological improvements as well as ease of access the posterior locus is becoming more frequently utilized.

Quantitative requirements for aspiration and sectioned tissue sampling

For routine bone marrow cytology the amount of marrow required to be aspirated is minimal. Usually 0.3-0.5 ml is sufficient to prepare several dry film smears. Small volumes are also cited as advantageous because this prevents a dilution of the hematopoietic cells with circulating blood and its cellular contents. Larger volumes may be necessary when cytogenetic and and/or fluorescent flow cytometric analyses are required. For solid tissue (core/trephine) biopsies a 15-20 millimeter-long core of marrow tissue should be obtained to insure the retrieval of adequate, histlogically representative, undisturbed specimens. Sections of variable, limited usefulness are also sometimes obtainable by collecting excess bone marrow units from an aspirate, allowing them to aggregate in a plasma/thromboplastin clot and submitting this mass to the embedding and sectioning process.

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CHAPTER 2

BONE MARROW ASPIRATION

Sternal Puncture

Introduction

In 1929, Mikhail Innokent'evich Arinkin (figure 2.1) a Russian physician first introduced the technique of bone marrow aspiration from the sternum when he used a lumbar puncture (spinal tap) needle to obtain a marrow aspirate from this site. Since then sternal puncture has become one of the most common intraosseous diagnostic procedures used in the field of hematology. Although the structure in adult humans which yields the largest quantity of bone marrow is the posterior ilium, the sternum has remained one of the most commonly used sites for obtaining aspirates for hematological diagnosis. This preferential selection may be due to the fact that this locus of hematopoietic marrow is near the surface of the body and is easily accessible.



Figure 2.1 Profile of Mikhail Arinkin (Courtesy of Kilinicheskaia Meditsina).

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Site

Sternal puncture is normally performed in the upper part of the body of the sternum, below the sternal angle of Louis and opposite the second intercostal space, midway between the midsternal line and the right or left sternal border (figure 2.2). This particular site is chosen because the needle enters one of the previous centers of ossification where the red marrow is usually more abundant than in the midsternal line. The sternum is most stable at this level and least likely to move or fracture under applied pressure. This area is also separated from the underlying great vessels by a distance of 2-3 cm, while at the levels of third and fourth intercostal spaces, the sternum lies in close proximity to the pericardium and heart.

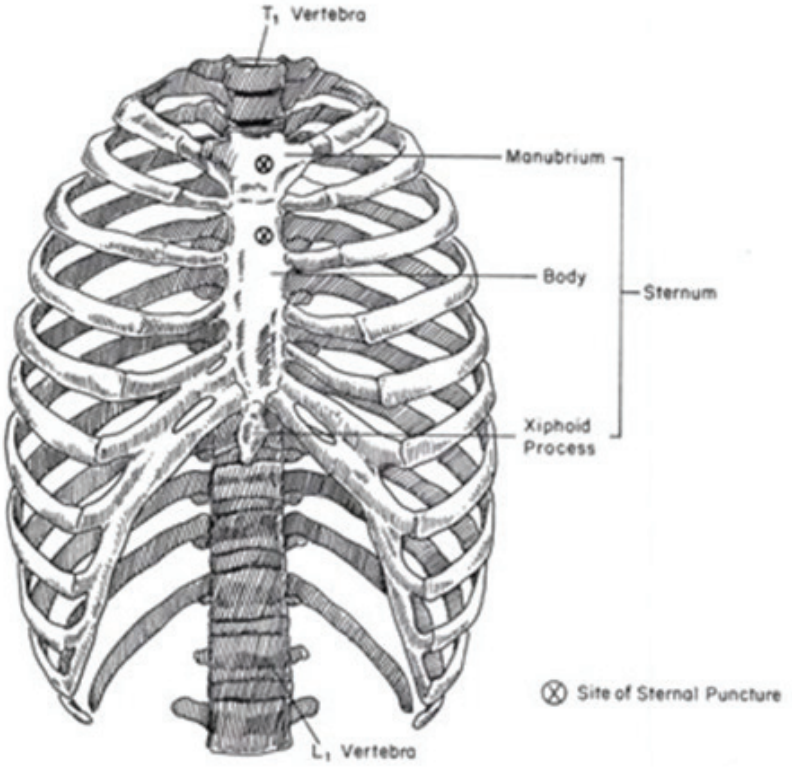


Figure 2.2 Anterior view of the thorax showing anatomical sites of sternal puncture.

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The manubrium of the sternum can also be used as a site for obtaining bone marrow aspirates and is perhaps the safest area of this bone to puncture. But as a rule, particularly in elderly subjects, the manubrium contains more adipose cells than the sternal body and as a result an aspiration at this site may yield an inadequate or non-representative marrow sample. However, completely satisfactory samples are obtained more often than not from the manubrium. If the manubrium is selected for aspiration, the appropriate site for the puncture is about 1 cm above the sterno-manubrial angle and slightly lateral to the mid-line.

Instrumentation

The needles most commonly used for obtaining bone marrow aspirate samples from the sternum are the Salah and Klima needles (figure 2.3) or their modifications.

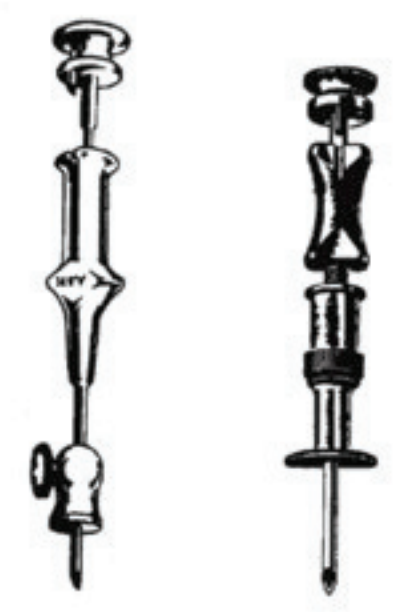


Figure 2.3 Salah (left) and Klima (right) sternal marrow-puncture needle. (Reproduced from Disorders of the Blood by Whitby and Britton (1957), Churchill, London.)

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They were designed in the 1930's and except for the introduction of various kinds of stops and guards there has been very little change over the years in their basic construction and design. These instruments are small, do not conveniently fit the operator's hand, and the lack of a T-bar handle in most instances often makes them difficult to maneuver during the sternal puncture procedure. The recently introduced Islam sternal puncture needle (figure 2.4) overcomes these disadvantages. The domed handle of its stilette rests comfortably in the operator's hand while the T-bar handle provides a firm grip and precise control of the needle movement. An important feature of the Islam sternal puncture needle is the short length of the penetrating segment which is almost half the length of a conventional sternal puncture needle (figure 2.5).

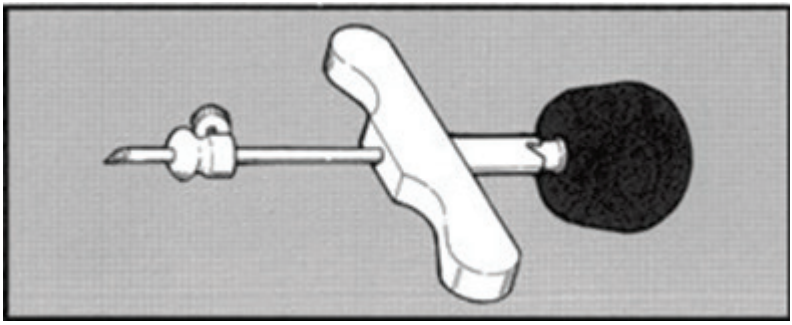


Figure 2.4 The Islam sternal puncture needle.

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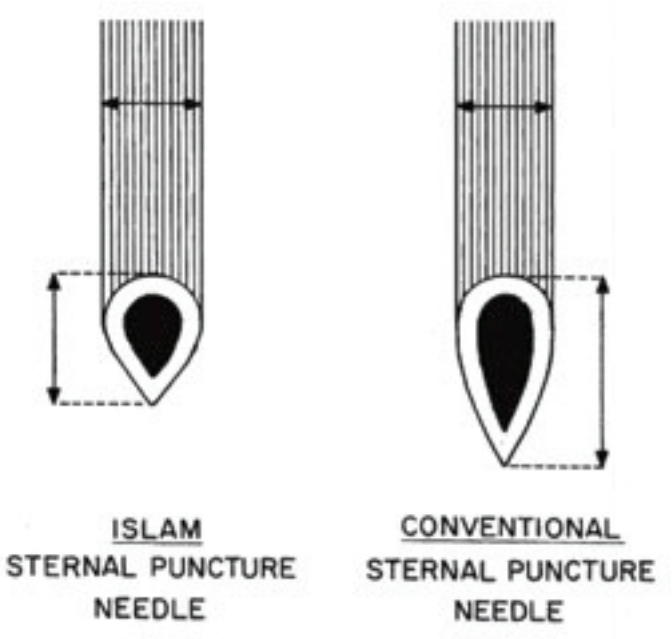


Figure 2.5a Schematic representation of the penetrating segment of the Islam (left) and conventional (right) sternal puncture needle. (See text for details)

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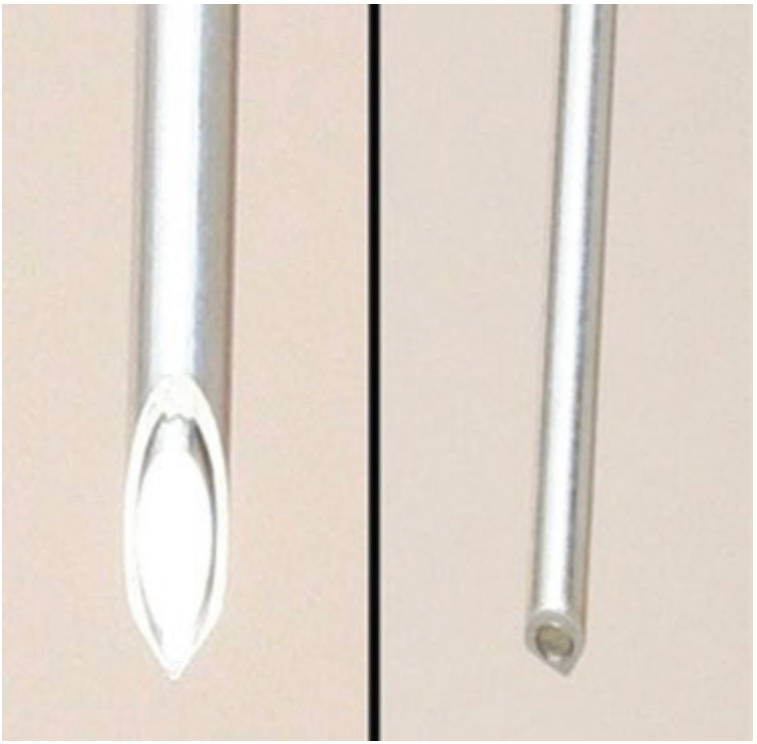


Figure 2.5b Actual picture of the penetrating segment of the conventional (left) and Islam (right) sternal puncture needle.

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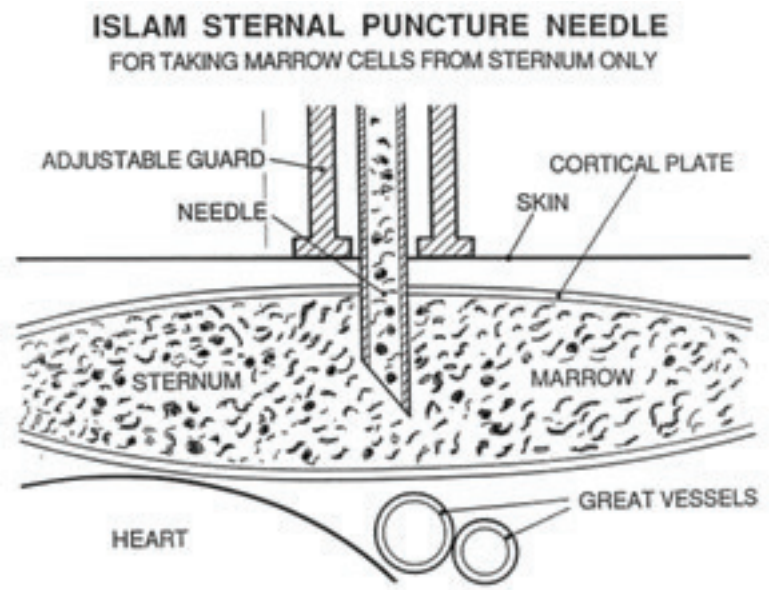


Figure 2.6 Schematic representation of the Islam Sternal puncture procedure with respect to the posterior wall of the sternum and the great blood vessels that lie underneath.

This reduces the possibility of accidental penetration of the inner cortex (posterior wall) of the sternum and injuring the great blood vessels that lie underneath (Figure 2.6). Further it also has an adjustable guard to prevent accidental over penetration and a sloped stop at its expanded proximal end for easy fitting and withdrawal of the stilette.

The Islam Sternal Puncture Needle

The instrument

The instrument[1] (figure 2.7) consists of three parts. The standard size *needle* has an overall length of 45 mm, a uniform external diameter of 2.0 mm and a constant internal diameter of 1.25 mm except for the 2-3 mm distal portion where it is beveled to produce a tip (cutting edge) very similar to hypodermic needles but much shorter in configuration. The proximal end of the needle has been fitted with a large *metal bar*

[1] The instrument is available in several different sizes (bore diameters) and lengths.

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specifically shaped to insure a firm grip and a standard female luer-lock to receive the nozzle of a syringe and to fit the male luer-lock of the stilette.

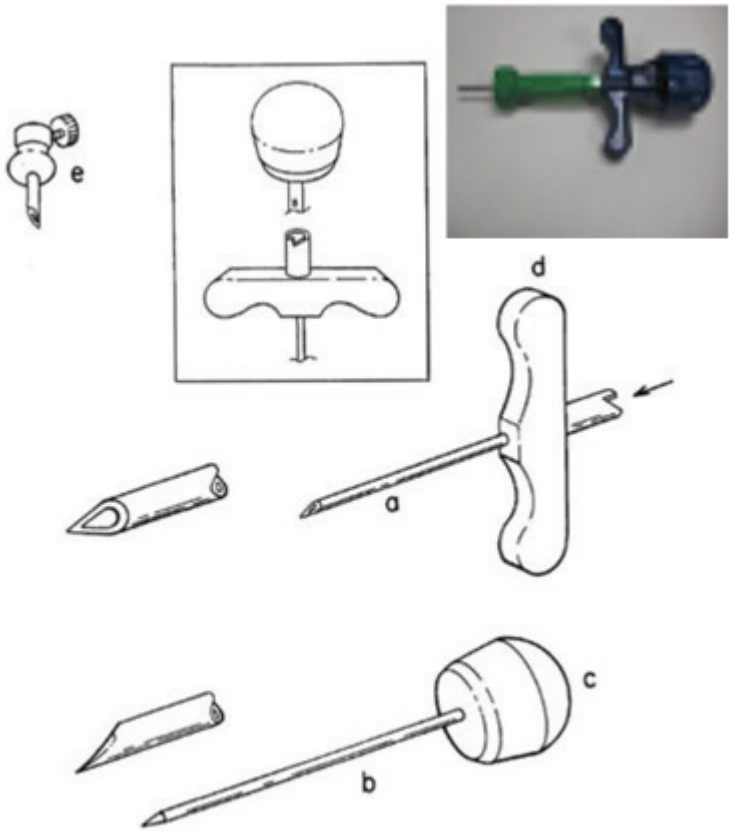


Figure 2.7. Needle [a], stilette [b], dome handle [c], the T-bar handle [d], and the guard [e]. The upper center inset shows the details of the luer-lock attachment of the needle and the handle. The sloped stop at the proximal end of the needle is shown by an arrow. The upper right inset shows a Islam single use sternal/iliac puncture needle.

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The female luer-lock of the needle also has a sloped stop for easy positioning and resting of the metal stud attached to the male luer-lock of the stilette. This arrangement makes it possible to automatically position the cutting edge of the stilette and needle in the same plane. This design also facilitates the easy unlocking and withdrawal of the stilette (by gentle anti-clockwise rotary motion) during the sternal puncture procedure. As has been mentioned the tip of the needle has been specially designed to make it short (figure 2.5 a&b) considering the narrowness of the space between the inner and outer plates of the sternum but sharp enough to easily penetrate the overlying soft tissue and bony cortex. The overall length (from the tip to the base, figure 2.5a) of the penetrating portion of the needle is approximately one half of a conventional needle, thus reducing the fear of accidental penetration of the inner plate of the sternum and injuring the pericardium or heart. The *stilette* is a solid shaft of 1.24 mm in diameter except for the distal portion where it ends in a 2-3 mm beveled tip to fit the beveled tip of the needle to provide means of easy penetration of the soft tissue and bony cortex. The proximal end of the stilette has been fitted with a male luer-lock mounted on the inner side of the dome handle to fit the female luer-lock of the needle. It also has a metal stud which fits the sloped stop at the proximal end of the needle and help automatically align the penetrating end of the stilette and needle in the same plane. The proximal end of the stilette is capped with a *smooth dome-shaped solid nylon handle* 25 mm in diameter and 15 mm deep with 5 mm lightly milled edge. It rests snugly in the operator's hand and the two together (the dome and the T-bar handle) provides a uniquely designed instrument to carry out the sternal puncture procedure with efficiency. The metal *guard* is adjustable and can be fixed at any point over the needle by tightening the screw. The adjustable guard is provided mainly to control the depth of penetration during the sternal puncture and also as a precaution and protection against accidents. In obese patients it may be necessary to adjust the guard to a higher level before attempting to enter the sternum. In such circumstances the positioning of the index finger over the shaft (Figure 2.8) of the needle helps stabilize the needle and permits adequate control during the sternal puncture procedure. If the sternal puncture needle is used for bone marrow aspiration from sites other than the sternum the adjustable guard may be removed before attempting to penetrate the bone and aspirating the marrow.

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Figure 2.8 Demonstrates the actual holding of the Islam sternal puncture needle. The arrow shows the position of the index finger over the shaft of the needle which helps stabilize the needle and permits adequate control of the needle during the aspiration procedure.

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Procedure:

1. Position of the patient: Place the patient on his/her back with the head and neck comfortably resting on a soft low-lying pillow. In men it may be necessary to shave the skin over the sternum prior to puncture.



2. Site: In adult the sternal puncture is usually performed in the proximal region of the body of the sternum, at the level of the second intercostal space, half way between the midsternal line and the left or right sternal border.



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3. Identify the area of sternal puncture by palpating the angle of Louis at the junction of the manubrium and body of the sternum. Mark the location with an indelible marker or digital pressure. Surgically prepare the area down to the fourth intercostal space with alcohol and iodine and then drape the site.



4. First withdraw 3-5 ml of anesthetic (2% lignocane) through a 21 gauge 1 1/2" needle into a 5 ml syringe. Then substitute the 21 gauge needle for a 25 gauge 5/8" hypodermic needle and make an intradermal injection producing a 5 mm papule. Replace the 25 gauge with a 21 gauge needle and pass it through the papule infiltrating the subcutaneous tissue with the local anesthetic. Then with the needle still in place also inject about 1.0 ml directly into the periosteum. Give ample time for the anesthetic to take effect.



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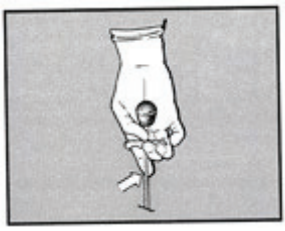
5. It is useful to probe the site with a 21 gauge, one and a half inch needle (with or without an attached syringe) to roughly assess the effect of the anesthetic and the depth at which the sternum will be struck. Using this as a guide, adjust and firmly fix the guard on to the shaft of the bone marrow aspiration needle.



6. No skin incision is necessary for this procedure.



7. Hold the needle assembly with the domed handle in the palm, the middle and fourth fingers over the transverse handle, and the index finger against the shaft of the needle. The position of the index finger against the shaft (arrow) helps stabilize the needle and controls it during the sternal puncture procedure.

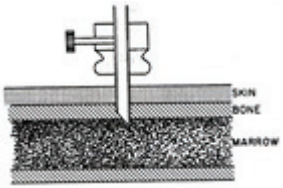


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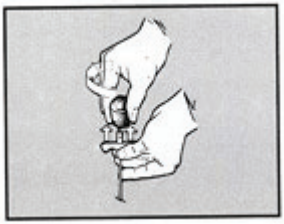
8. After skin sterilization and local anesthesia of the skin, subcutaneous tissue and periosteum the needle with its stilette in place is slowly and gently advanced towards the sternum so as to hit the bone at a right angle (or at 45°). When the sternum is reached it is then penetrated by gentle rotary (clockwise/ counterclockwise) motion of the needle.



9. Entrance into the sternal marrow cavity is recognized by a “sudden” give of the needle which indicates that the outer table of the sternum has been perforated. Once the cortex is penetrated advance the needle only few millimeters into the marrow cavity with gentle, reciprocal clockwise/counterclockwise rotary motion.



10. Once the needle is in place — hold it in position with the left hand, (as shown in the illustration), unlock the stilette and domed handle by anticlockwise twist and gently remove it.

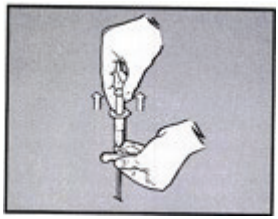


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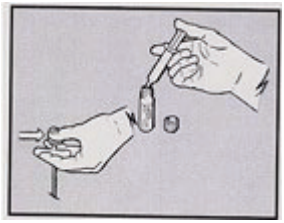
11. Attach a syringe to the needle mount.



12. Apply a negative pressure and aspirate the required amount of marrow sample from the sternum.



13. Following aspiration of the required amount marrow remove the syringe from the needle mount and using sterile technique, close the proximal opening of the needle (arrow) to prevent any loss of marrow or blood from the wound while the marrow specimen collected in the syringe is being delivered into a bottle containing EDTA (or other anticoagulant) for processing and examination.

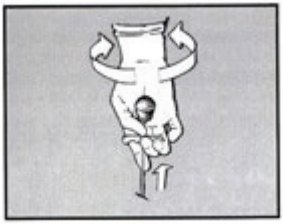


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14. Replace and lock the stilette with domed handle by a twisting clockwise motion.



15. Slowly withdraw the needle with the right hand with a gentle alternating rotary motion while fixing the sternum with the index and middle fingers of the left hand.



16. After withdrawal of the needle, apply firm pressure for one or two minutes over the site of the puncture to prevent any bleeding and then cover the wound with a small dressing.



Note: To protect the marrow aspiration needle and obtain the desired results the needle should never be introduced or withdrawn without the stilette in place.

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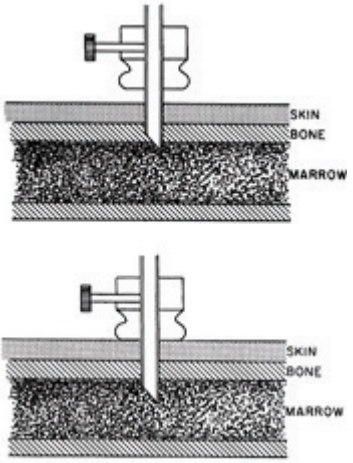


Figure 2.9 Schematic representation of the sternal puncture procedure using the Islam sternal puncture needle.

Schematic Representation of the Sternal Puncture Procedure Using the Islam Sternal Puncture Needle

1. The sternal puncture needle, with the stilette and handle in place and the guard firmly secured at a proper distance from the distal end of the needle, is slowly advanced through the skin and subcutaneous tissue towards the sternum so as to hit the bone at 90°. When the sternum is reached, it is gently penetrated by clockwise and counterclockwise rotary motion of the needle (figure 2.9, upper).

2. Once the outer table of the sternum is penetrated the needle is advanced slowly a few millimeters in the marrow cavity by the same rotary motion of the needle (figure 2.9, lower).

3. Once the needle is in place within the marrow cavity, the stilette is removed with an anticlockwise twisting action, a syringe is attached, and the aspiration performed.

4. Following aspiration of the desired amount of bone marrow, the stilette is promptly replaced and adequately secured and the whole needle assembly is withdrawn with a rotary motion.

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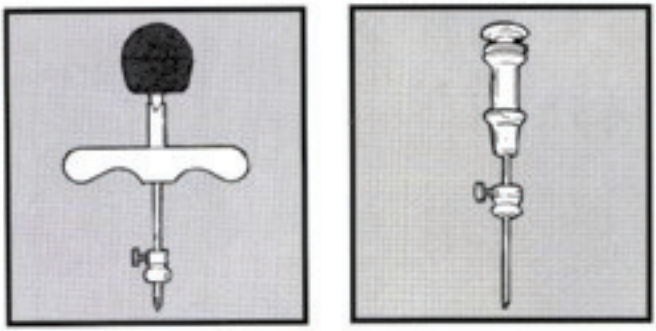


Figure 2.10. Islam (left) and conventional (right) sternal puncture needle.

Difference Between Conventional and Islam Sternal Puncture Needle

Conventional sternal puncture needles (figure 2.10, right) are small, do not fit properly in the operator's hand, and due to the absence in most instances, of a T-bar handle, are often difficult to maneuver during the sternal puncture procedure.

The recently introduced Islam sternal puncture needles (figure 2.10, left) are larger, stronger and more effective in obtaining bone marrow aspirate samples from the sternum than the conventional sternal puncture needles. The large T-bar handle permits a secure and firm grip and the smooth dome shaped handle rests snugly in the operator's hand providing a comfortable cushion during the sternal puncture procedure. These two important features (the T-bar and the dome handle) are lacking in the conventional sternal puncture needles. In addition, in the Islam sternal puncture needle the penetrating end of the needle has been designed to make it sharp and relatively broad but not overtly long to ensure the penetration of the outer but not the inner lamina of the sternum while retaining the aspirating end of the needle within the narrow medullary space of the sternum.

Precaution

Although the technique of sternal puncture is a safe and very effective method of diagnostic marrow aspiration, care must be taken while performing this procedure on elderly patients, particularly elderly women

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who may have severe osteoporosis.

Bone manifesting this pathology lacks normal density and may permit a diagnostic needle to penetrate deeper than desired even with normal pressure. The sternum should never be punctured below the second intercostal space, because, at the level of the third and fourth intercostal spaces, the sternum lies in close proximity to the pericardium and heart.

During sternal puncture procedure the patient may become apprehensive as the needle is being introduced into the chest. It is advisable to inform the patient fully about the entire procedure (including the momentary and fleeting suction pain) before it is undertaken in order to reduce the fear and anxiety. It is also advisable to practice on cadavers to obtain confidence and experience in this procedure.

Iliac Puncture

The ilium (figure 2. 11) is another site from which hematopoietic marrow may be withdrawn. The ilium can be penetrated without much difficulty in a variety of places; the crest, however, offers too great resistance for it to be a practical site for routine penetration except perhaps in infants and children in whom the compact bone is less hard. Usually the site near the anterior superior iliac spine (anterior iliac puncture) or the area near the posterior superior iliac spine (posterior iliac puncture) is chosen for aspirating bone marrow samples from this bone. It should be noted that the Ileum offers greater resistance to penetration than the sternum and consequently stronger needles are required for this approach.

Anterior Iliac Puncture (Figure 2.12)

For puncture of the anterior iliac crest, the area just posterior to the anterior superior iliac spine is utilized. Some hematologists prefer the area about 1-2 cm inferior to the crest and 1-2 cm posterior to the anterior superior iliac spine. Others have found more success with an area about 1 cm below the crest and about 1 or 2 cm posterior to the anterior gluteal line. At the anterior iliac crest the compact bone frequently proves to be exceedingly hard, so that the entire aspiration needle sometimes bends and is also inclined to slip off the site.

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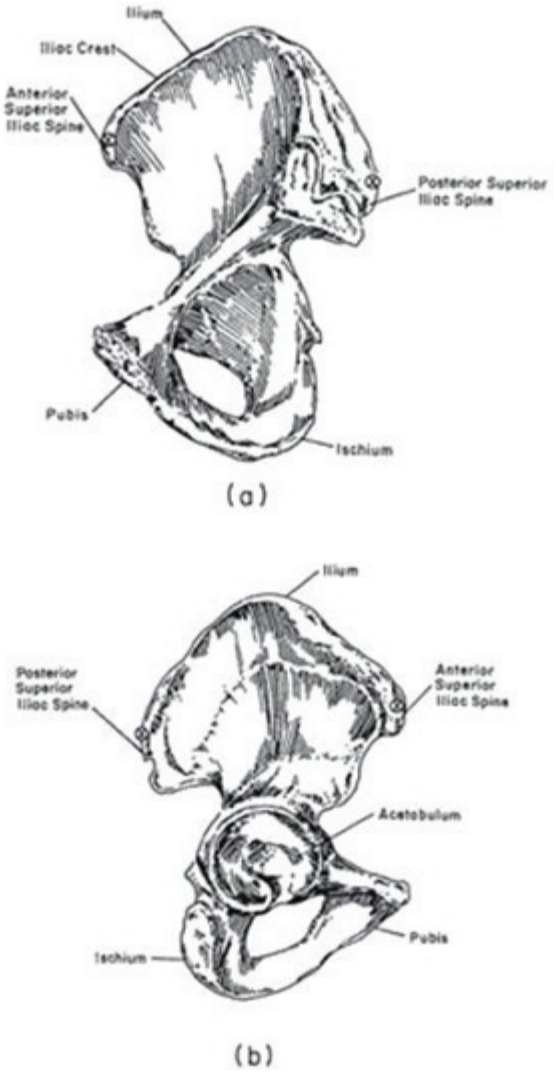


Figure 2.11 Illustrations of the ilium: (a) internal surface, (b) external surface, and the usual sites of bone marrow aspiration. ⊗ = site of aspiration.

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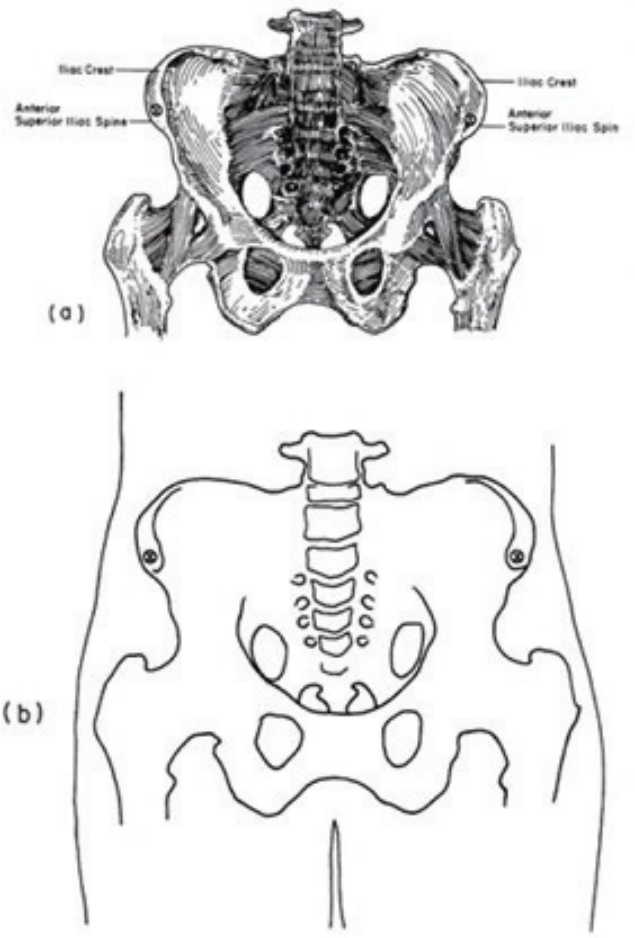


Figure 2.12 [a] Anterior view of the pelvis, (b) pelvis *in situ.* ⊗ = site of aspiration.

Instrumentation

Both the Salah and Klima needles as well as the Islam sternal puncture needle can be used for obtaining bone marrow aspirate samples from the anterior iliac crest. The Salah and Klima needles however, were originally designed for the sternum, a much softer bone. They are potentially weaker

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and less suitable for puncture of the harder ilium where the needle may be at risk. The Islam sternal puncture needles are much sturdier and due to the presence of a T-bar and dome handle they are easier to hold and maneuver during puncture of a hard bone. Depending on the operator's preferences the Islam needle may well be the needle best suited for anterior iliac puncture.

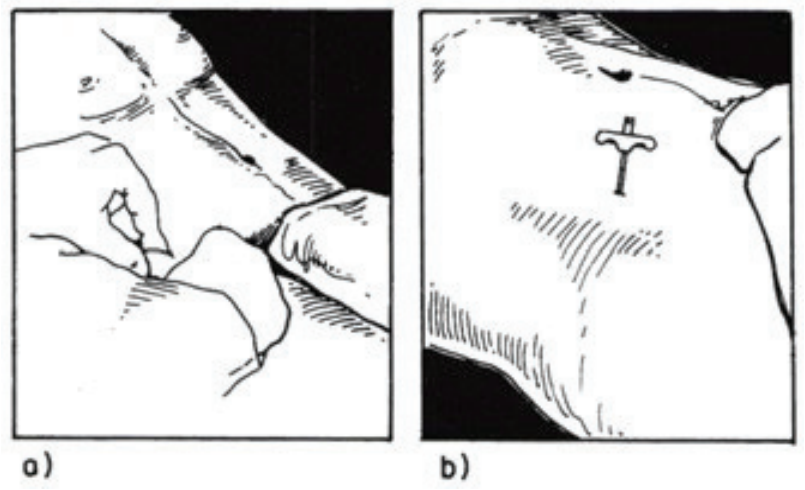


Figure 2.13 [a] The oval protuberance near the anterior superior iliac spine is located between the thumb and forefinger, [b] The needle is introduced perpendicularly (or pointing slightly cephalically) into the ilium.

Procedure

The patient should lie flat on a reasonably firm surface. The site typically punctured is just behind the anterior superior iliac spine. It is located by palpation with the fingers as an oval protuberance (Figure 2.13a). Using sterile technique the skin is prepared with an antiseptic and draped. The skin, subcutaneous tissue and periosteum are infiltrated with a local anesthetic. Ample time should be given for the anesthetic to take effect. It is useful to probe the site with a 21 gauge, 11 inch needle to roughly outline the borders of anterior iliac crest and to ascertain the effect of the anesthetic. This also gives an indication of the depth at which the bone will be struck and also permits determination of the proper angulation of the needle. With the patient in the supine position as indicated, and the anterior iliac crest properly secured by the thumb and forefingers of the

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left hand, the needle is introduced perpendicularly (or pointing slightly cephalically) into the ilium (figure 2.13b). If the Islam sternal puncture needle is used, the guard should be removed and the needle assembly held with the domed handle in the palm, the middle and fourth fingers over the transverse handle, and the index finger over the shaft of the needle (figure 2.14). The position of the index finger over the shaft (arrow) helps stabilize the needle and facilitates positive control of its movements.

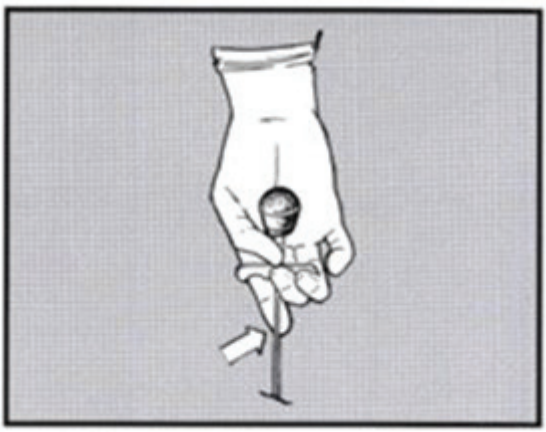


Figure 2.14 Demonstration of the holding of the Islam sternal puncture needle during anterior iliac puncture.

Posterior Iliac Puncture (Figure 2.15)

The area of the posterior iliac spine is the thickest region of the ilium and houses the largest volume of hematopoietic (red) marrow both in the child and in the adult. It is easily accessible and large amounts of red marrow are readily aspirated. This segment of the ilium is distant from any vital structure and hence complications are unlikely. The patient also cannot observe the procedure and the anxiety often associated with a sternal puncture is thus avoided. An additional favorable feature is the fact that the cortical bone at this region is also appreciably less dense than it is in the area of the anterior iliac spine and thus more easily penetrable.

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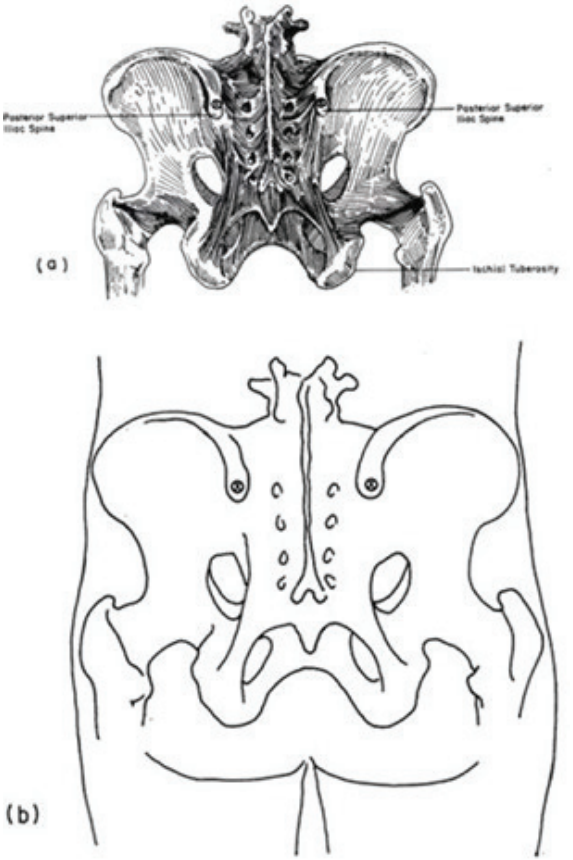


Figure 2.15 [a] Pelvis, posterior view (b) pelvis *in situ.* ⊗ = site of aspiration.

Instrumentation

The Salah and Klima needles have been commonly used for posterior (as well as anterior) iliac bone marrow aspiration. As indicated, they were initially designed to obtain sternal samples of marrow and are not particularly suited for iliac puncture where the configuration of the bone is different and the thickness of the cortex is greater.

The Islam posterior iliac puncture needles (figure 2.16) have been specifically designed to obtain bone marrow aspirate samples from the posterior iliac crests.

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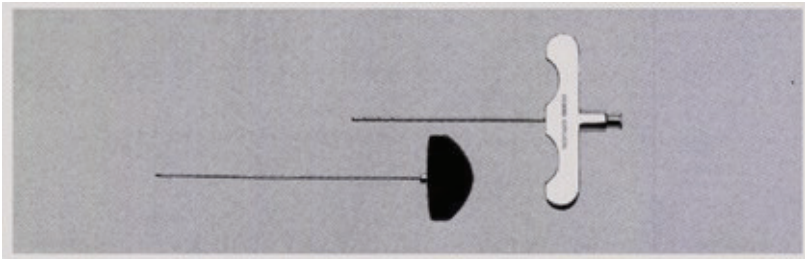


Figure 2.16 The Islam posterior iliac puncture needle. (This needle is also available with side holes near the frontal opening).

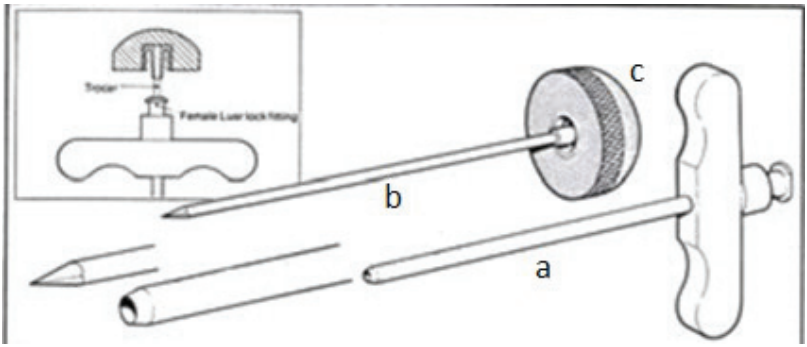


Figure 2.17 Illustration of the details of the Islam posterior iliac puncture needle without side holes. The needle (a), stilette (b) and the dome handle (c). The inset shows the details of the luer lock attachment of the needle and the handle.

These instruments are longer and stronger than the conventional aspiration needles, and the presence of a T-bar and domed handle makes them much easier to hold and maneuver during the aspiration procedure.

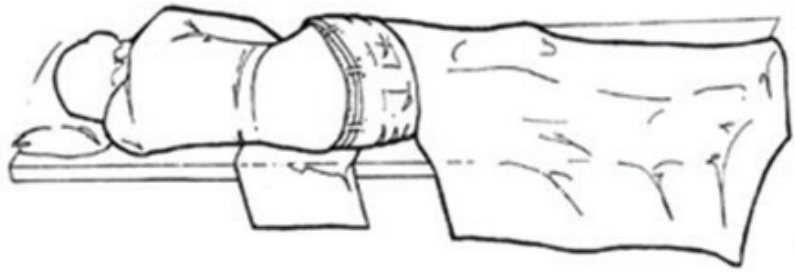
The Standard size steel instrument[2] (figure 2. 17) consists of two parts, (a) *The needle* has an overall length of 80 mm, a uniform external diameter of 2.35 mm and a constant internal diameter of 1.78 mm except for the 1.25 mm distal portion where it is beveled to 18°. The proximal end of the needle has been fitted with a large metal bar specially shaped for firm grip and a female luer lock to receive the nozzle of a syringe and to fit the male luer lock of the stilette and domed handle, (b) *The stilette* is a solid shaft 1.62 mm in diameter except for the distal portion where it ends with a 3.0 mm long, three faceted, sharp-pointed cutting tip which projects beyond

[2] Other sizes (bore diameters) and lengths are also available.

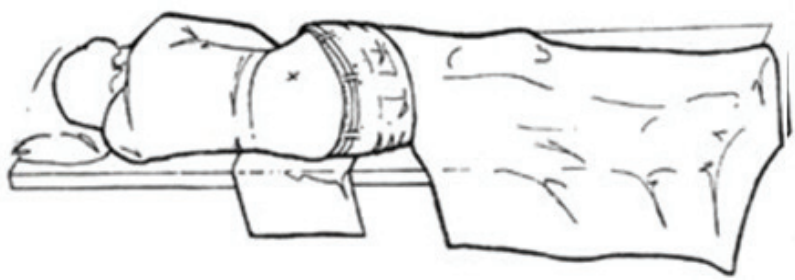
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the distal end of the needle to provide a means of easy penetration of the soft tissue and bony cortex. The proximal end of the stilette has been mounted into a male luer lock buried inside the dome handle to fit the female luer lock of the needle. The proximal end of the stilette has been capped with a hemispherical smooth dome-shaped solid nylon handle (c) 30 mm in diameter and 15 mm deep with a 5 mm lightly milled edge. It has been designed to rest snugly in the operator's hand and to provide comfort if and when forceful thrusting is necessary.

Aspiration Procedure

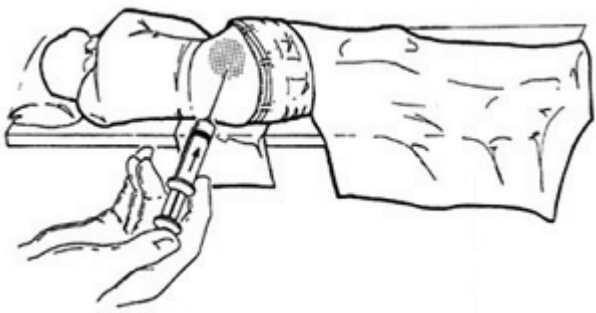


1. Position of the patient — The patient is placed in a right or left lateral decubitus position, with the knees drawn up and back comfortably flexed, or in the prone position with pillow beneath the hips.

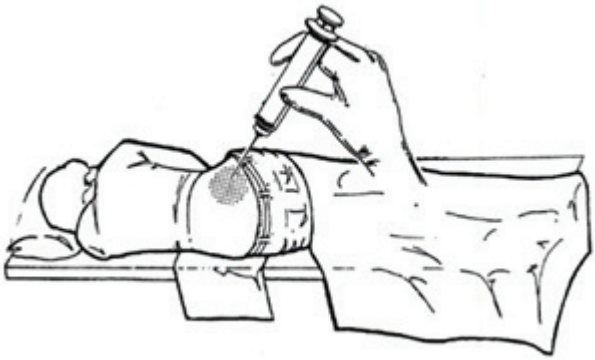


2. Locate the posterior iliac crest by palpation and mark the area with indelible marker or thumbnail pressure. With the use of sterile technique prepare the skin with an antiseptic and drape.

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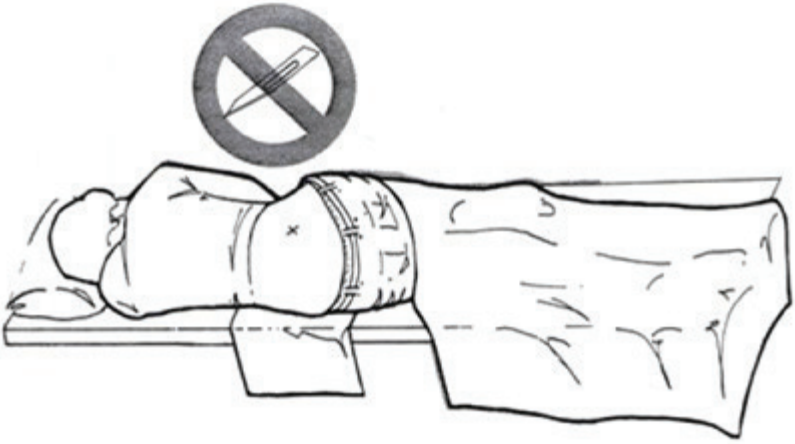


3. First infiltrate the skin with the anesthetic using a small 25 gauge 5/8" hypodermic needle. After few seconds infiltrate the subcutaneous tissue, muscle and periosteum with the same local anesthetic entering the tissue through the same puncture wound but using a larger 21 gauge 1½" hypodermic needle. Provide ample time for the anesthetic to take effect.

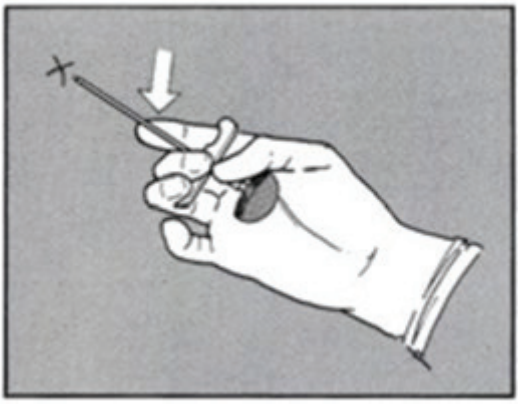


4. It is always useful to probe the aspiration site with a 21 gauge 1 ½ needle to establish whether the anesthetic has taken affect and to roughly outline the borders of posterior iliac crest. This technique also gives an indication as to the depth at which the bone will be struck and also permits determination of the proper angulation of the needle.

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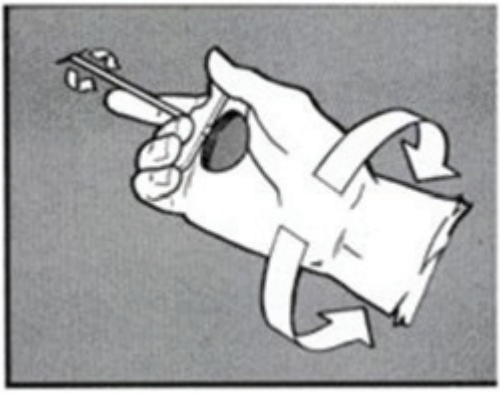


5. No skin incision is usually necessary for this procedure. However, if a solid tissue bone marrow biopsy is also to be performed at the same site following aspiration of the marrow, a skin incision would be preferable.

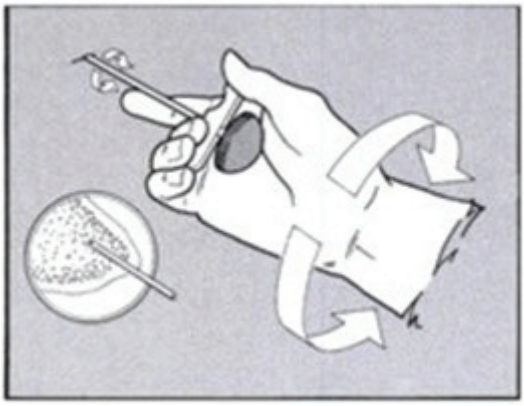


6. Holding of the needle — Hold the needle assembly with the domed handle in the palm, middle and fourth fingers over the transverse handle, and the index finger against the shaft of the needle. The position of the index finger over the shaft (arrow) helps stabilize the needle and permits adequate control during penetration of the soft and bony tissues.

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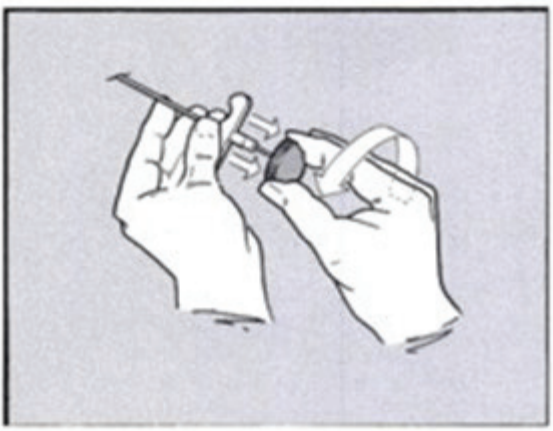


7. With the stilette and domed handle in place — introduce the needle through the skin and slowly advance it towards the surface of the posterior ilium pointing the needle in the direction of the anterior superior iliac spine. When the posterior iliac crest is reached, penetrate the cortical bone with gentle rotary motions of the needle.

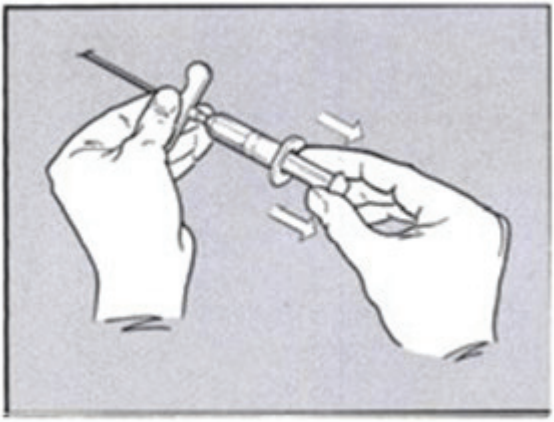


8. Once the cortex is penetrated (which can be felt by decreased resistance) — slowly advance the needle into the marrow cavity with gentle clockwise- anticlockwise rotary motions until an adequate depth (0.5-1.0 cm) is reached.

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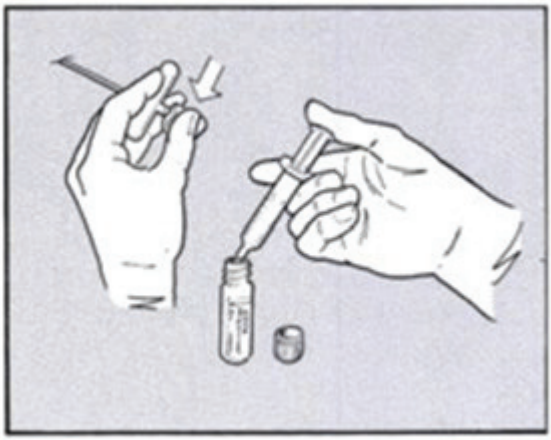


9. Once the needle is in place — hold it in position with the left hand (as shown in the illustration), unlock the stilette and domed handle by anticlockwise twist and gently remove it.

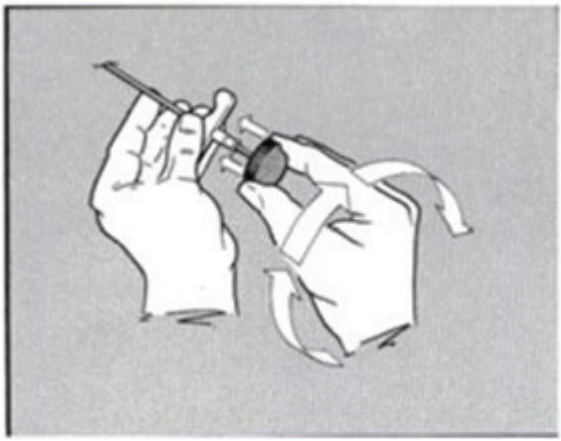


10. Attach a syringe on to the needle mount. Apply a negative pressure and aspirate the required amount of marrow sample.

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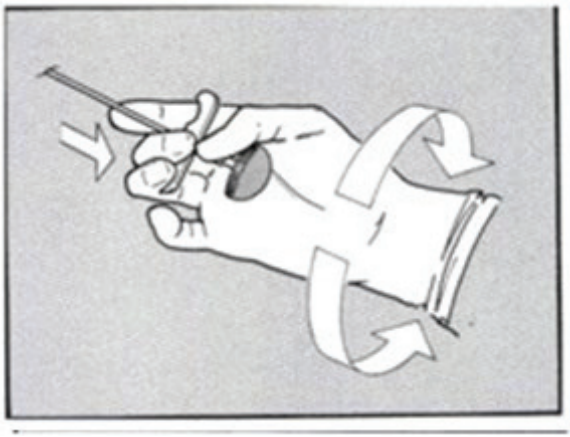


11. Following aspiration of the marrow remove the syringe from the needle. Using sterile technique close the proximal opening of the needle (arrow) to prevent any exudation of marrow from the patient while the collected sample in the syringe is delivered into a container with anticoagulant (e.g. EDTA) or other receptacle(s) for processing and examination. It is during these maneuvers that an assistant is particularly helpful.

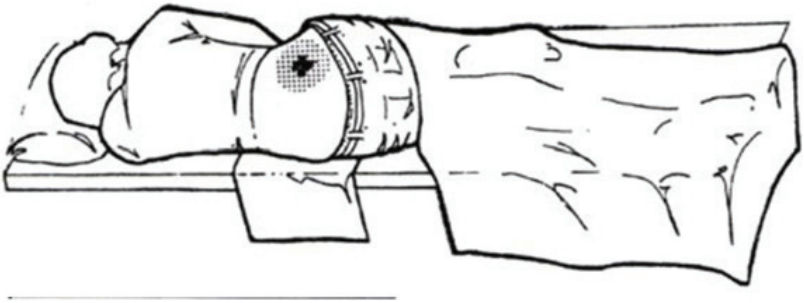


12. Once the aspiration is complete replace the stilette with domed handle and lock it with the needle by twisting clockwise.

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13. Then slowly withdraw the needle by gentle alternating rotary motions. Firmly hold the shaft, T-bar and domed handle together during the withdrawal.



14. After withdrawal of the needle apply firm pressure for one or two minutes at the puncture site to prevent any bleeding and then cover the wound with a small sterile dressing.

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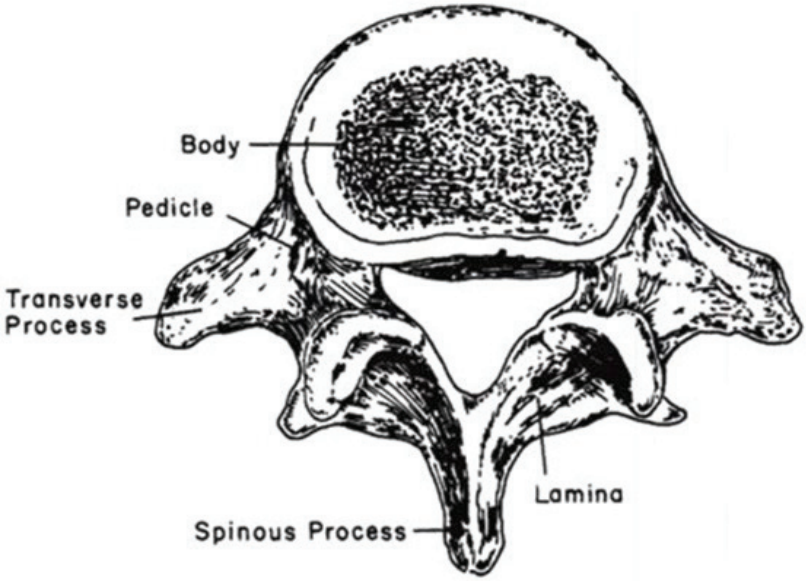


Figure 2.18 A lumbar vertebra showing its spinous process.

Puncture of Spinous Processes of Lumbar Vertebrae (Figures 2.18, 2.19. 2.20)

Adequate samples of marrow may be obtained from adults by puncturing the spinous processes of lumbar vertebrae. Although punctures are not too difficult at the spinous process(es) because of their superficial location and ease of identification, the volume of marrow available for aspiration is limited. The sternum and posterior ilium, thus remain the most generous sites for obtaining samples of hematopoietic (red) marrow.

Instrumentation

Any of the available sternal puncture needles can be used for puncturing the spinous processes of lumbar vertebrae. Conventional needles however are rather small and thus can be inconvenient to hold and maneuver with precision. The Islam sternal puncture needles are an optimal choice for this approach. The T-bar and domed handle facilitate a comfortable grip and positive, accurate penetration of the bone. They are also available in several different sizes (bore diameters) and lengths. Thus depending on the

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physical size of the patient an appropriate size and length of the needle may be selected.

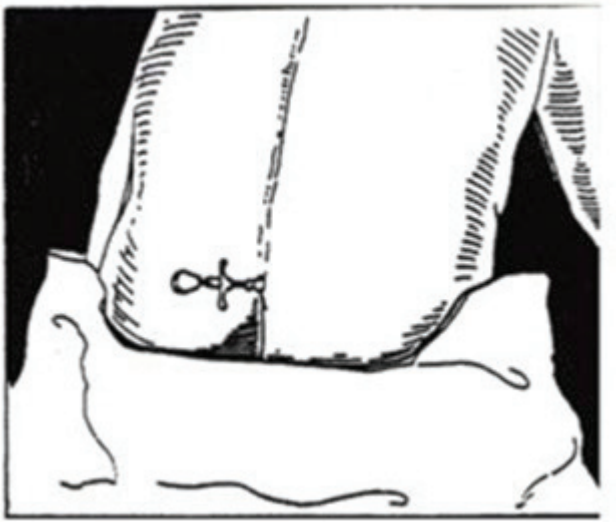


Figure 2.19 Demonstrates lumbar spinal process puncture. The patient is in a sitting position with the back comfortably flexed. An Islam sternal puncture needle is fixed in the spinous process of a lumbar vertebra.

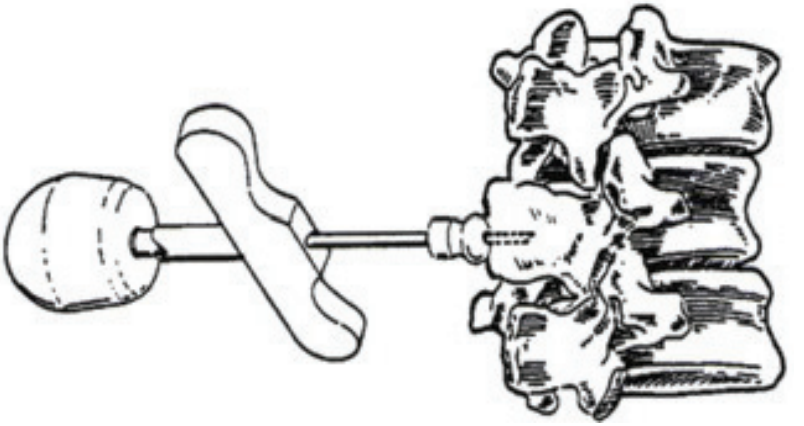


Figure 2.20 Lumbar vertebrae 2, 3 and 4 with an Islam sternal puncture needle fixed in the spinous process of L3.

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Procedure

The patient is placed in a right or left lateral decubitus position with the knees drawn up and back comfortably flexed or in a sitting position as for a lumbar puncture (figures 2.19). The lumbar spinous process to be punctured is located and marked with an indelible pen or thumb nail pressure. Following the usually accepted precautions of skin sterilization and local anesthesia, the needle with its stilette in place is slowly advanced through the skin and subcutaneous tissue in the mid-line and at right angles to the skin surface pointing towards the spinous process. Once the spinous process is reached the needle is introduced into the spine with gentle rotary motions. When the needle is in place the stilette is removed, a syringe is attached, and the aspiration is performed. Following aspiration, the stilette is promptly replaced and the needle is withdrawn firmly holding the shaft and T-bar together. After withdrawal of the needle local pressure is applied to prevent any bleeding and then a small sterile dressing is applied.

Puncture of the Tibia (Figure 2.21 and 2. 22)

Site

The tibia contains active marrow at its proximal (epiphyseal) end throughout the entire childhood. Hematopoietic marrow has been successfully aspirated from the tibia in children at the age of 10 years. It is the accepted practice to select the tibia as the preferred site of puncture in all children under the age of 2 years.

Instrumentation

Any of the available sternal puncture needles can be used for puncturing the tibia. Salah, Klima or similar needles may be used. The Islam sternal puncture needles are ideally suited for this purpose because of their improved design, ease of holding and manipulation.

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Figure 2.21 Diagram of the tibia in later childhood, indicating the optimal site for tibial (marrow) puncture.

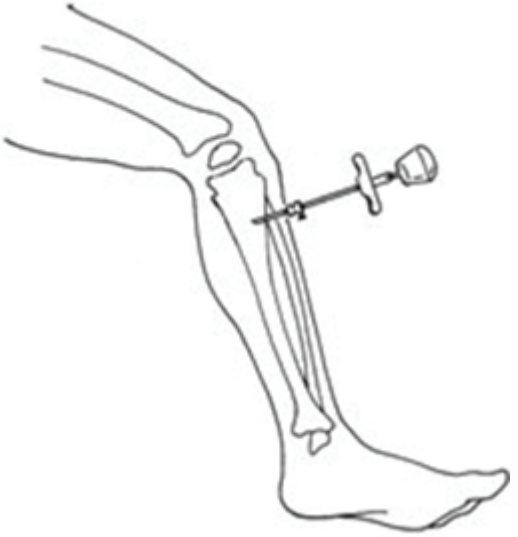


Figure 2.22 Schematic demonstration of a tibial puncture procedure.

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Aspiration Procedure

The flat triangular, non-muscular area on the medial aspect of the proximal end of the tibia is the site usually selected for aspiration of hematopoietic bone marrow from this long bone (figure 2.22). The best point for the insertion of needle appears to be medial to the insertion of the patellar tendon at the tibial tuberosity. This site is often the only certain, dependable landmark in an obese infant. If the needle is inserted lower in the shaft, difficulty is likely to be experienced due to thickening of the bony cortex and narrowing of the lumen of the medullary cavity.

Aspiration from Other Sites

As previously mentioned, almost any area of functioning marrow near the surface of the body may be utilized for obtaining a bone marrow aspirate. The two most commonly used sites are the sternum (at the level of the second intercostal space), and the posterior iliac crest. However, other bones such as ribs, vertebral bodies, tibia and femur (or other bones if accessible by an aspirating needle) may be used particularly when there is radiologic evidence of a bony lesion. In such circumstances aspiration of marrow from a lesion may be aided by prior localization of the site ("hot spots") with radionuclide or other imaging techniques. This is particularly true in certain hematologic and non-hematologic malignant conditions (e.g. multiple myeloma and metastatic breast carcinoma respectively).

Choice of Puncture Site(s)

In general, the overall composition (cellularity, myeloid-erythroid ratio, cytomorphology) of marrow withdrawn from a bone containing hematopoietic marrow is usually similar regardless of the bone selected for study. Which site is used is a matter of personal preference. It should be noted, however, there can be considerable variation even in adjacent sites particularly under pathologic conditions. Such cellular manifestations are more likely to be recognized when aspiration biopsies are accompanied by concomitant histologic sections.

The sternum is probably the easiest bone to puncture and does indeed yield very satisfactory samples. As a result the sternum remains one of the most commonly utilized aspiration sites. It does nevertheless have disadvantages. First, the patient is aware of the activities surrounding him or her and can observe the entire procedure. Apprehension, especially when the needle is introduced into the sternum is to be expected. Second, deaths have been

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reported due to cardiovascular penetration (such risks are extremely small in adults when the procedure is performed carefully and with a guard firmly in place on the shaft of the needle). With these precautions the incidence of serious risk should be reduced to zero. Third, the sternum contains a relatively small volume of marrow which, though usually sufficient for most diagnostic requirements, may not be adequate when large amounts of aspirate are desired.

The advent of improved needles designed for the aspiration of marrow from the posterior ilium has permitted this site to be ideal and perhaps even preferable to sternum. It is readily accessible, large amounts of marrow can be obtained, and is distant from any vital structures. Complications are unlikely and as the patient cannot observe the procedure, anxiety is avoided.

The Multiport Aspiration Needle

The technique of examination of bone narrow aspirates obtained via conventional marrow aspiration needles is widely used in the diagnosis of malignant and benign, hematologic and non-hematologic conditions. Inherent in the structure of such needles, though almost totally unappreciated, is the fact that marrow fragments are only obtained from a limited volume of tissue near the open front end (mouth) of the needle.

Bone marrow has patchy, random involvement in many pathological processes, a feature documented by multiple marrow aspiration studies in selected patients. Conventional aspiration needles have only one opening for the access and sampling of marrow. Their sampling may or may not include cells near to or distant from the point of aspiration (figure 2.23). To help eliminate the uncertainty of obtaining cells from distant and separate loci of pathology a multi pore aspiration needle has been designed. The use of this instrument reduces the risk of failure to sample small focal infiltrates in conditions as lymphoma, leukemia, preleukemia (MDS), and metastatic malignancy (Figure 2.24). Experience has further indicated this needle is particularly useful in posterior ilial (posterior ilium) aspirations because of the enhanced depth of penetration afforded by this bone.

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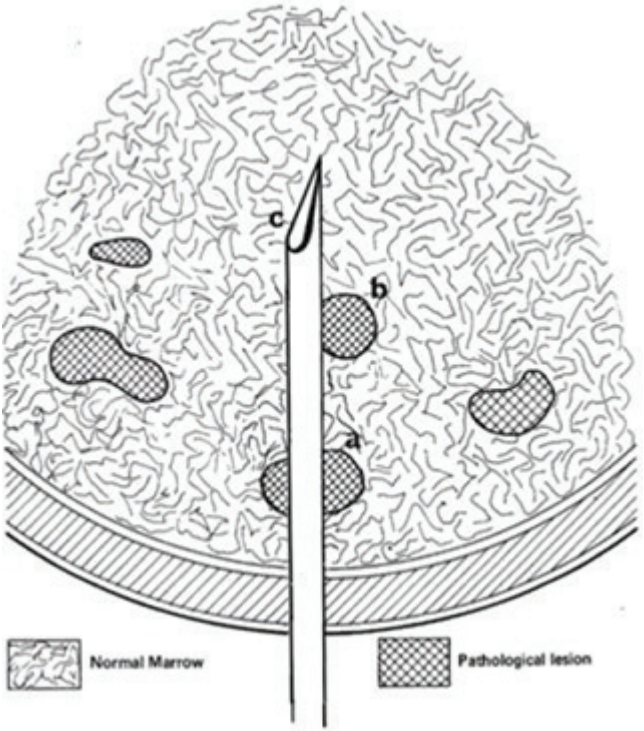


Figure 2.23 Schematic representation of the aspiration procedure by a conventional aspiration needle which has only one opening at the front end. It shows that the needle with the stilette in place, has gone through a lesion during insertion (a), by-passed a lesion (b) and lodged its frontal opening into an area of normal marrow (c).

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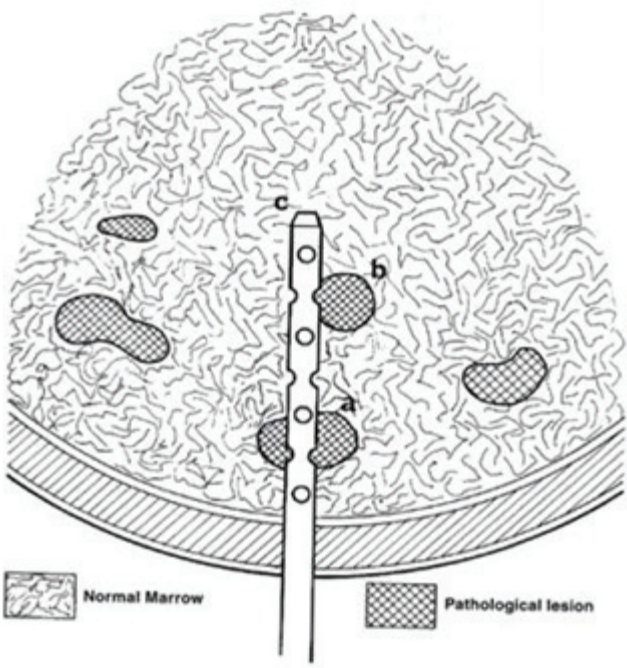


Figure 2.24 Schematic representation of the aspiration procedure performed with a multiple port bone marrow aspiration needle. It shows that the needle with the stilette in place has gone through a lesion during insertion (a), by-passed another lesion (b) in the same manner as the conventional needle in Figure 2.23 with the terminal opening lodged in an area of normal marrow (c). However, because of the multihole configuration of the needle it has gained access to both lesions (a) and (b) in addition to the area of normal marrow.

Instrumentation[*]

The construction and design of this instrument is identical to that of the Islam posterior iliac puncture needle but has multiple side holes in addition to the one frontal opening (figure 2.25). The 17.5 mm distal portion of the needle has 14 lateral ports, 4 rows of 8 holes in one plane and 3 rows of 6 holes in another. The rows of apertures are 2.5 mm apart and drilled in a spiral fashion to avoid any weakness which would appear if the drilling for any two ports were executed on the same transverse

[*] This instrument is also available in different sizes (bore diameters) and lengths.

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plane. The first row of holes is made 3.0 mm from the end of the beveled point and the diameter of each hole is approximately 1.0 mm.

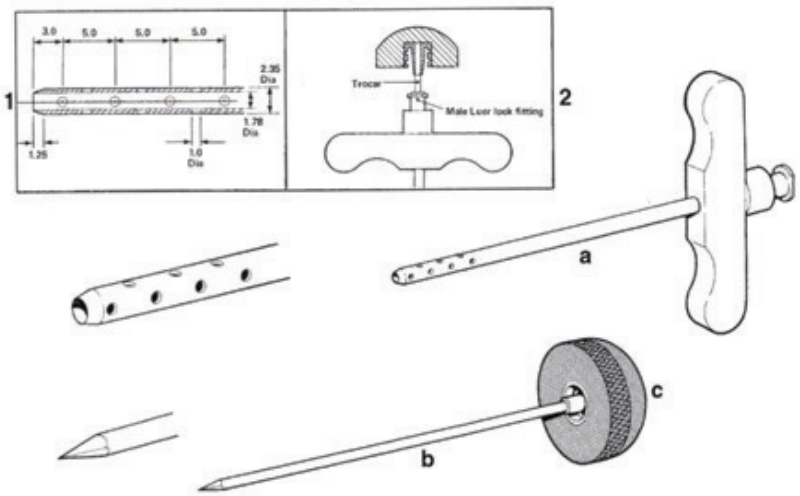


Figure 2.25 The Islam multiport bone marrow aspiration needle. The needle (a), stilette (b) and the handle (c). The inset 1 shows the details of distal 17.5 mm portion of the needle and the inset 2 illustrates the details of the luer lock attachment of the needle and the handle.

Aspiration Procedure

The aspiration procedure with this needle is the same as for any posterior iliac puncture. In this case however, care must be taken to insure that the entire perforated segment of the needle is introduced into the medullary cavity and away from the cortical entry site. This avoids the potential aspiration of air and soft tissue adherent to the externum of the ilium.

Processing of Specimens

Preparations of Aspirate Smears

Following aspiration of marrow, smears should be made without much delay. This can be done in several ways. (1) A large drop of marrow with enough fragments can be placed on a slide usually directly from the aspirating needle (figure 2.26 A) or from the syringe after it has been dislodged from the needle (Figure 2.26B). Several smears are made by

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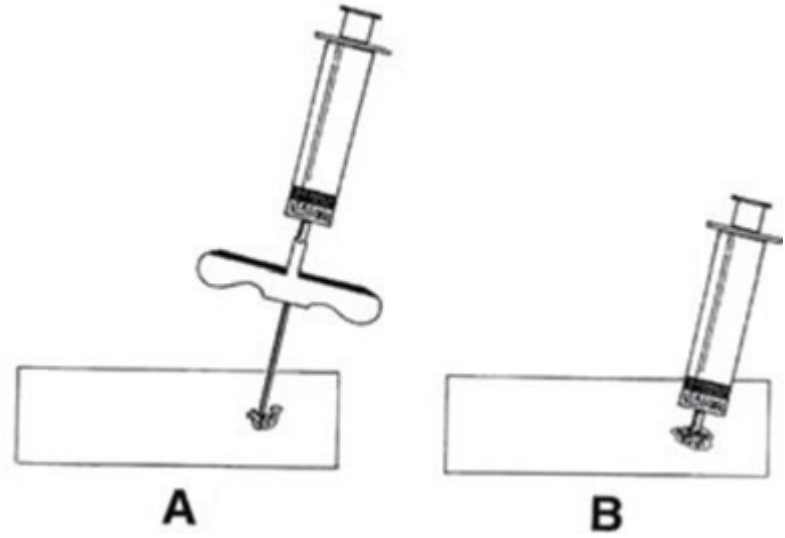


Figure 2.26 Marrow smear preparation. A small amount of aspirated marrow is delivered directly from the aspirating needle (A) or directly from the syringe after it has been dislodged from the needle (B).

repeatedly collecting the marrow from the slide above and making dry film smear using the edge of the spreader slide as Shown in figure 2.27. (2) Alternatively, a single drop of marrow can be placed on several slides, the excess blood (but not the fragments) is sucked out with a fine pasteur pipette and then smears are made from the remaining samples (figure 2.28). (3) A small amount of marrow can be delivered directly into a cuvet (perhaps lined with a non wetable material as Teflon or paraffin) containing a suitable anticoagulant. Fragments are then retrieved with a pasteur pipette, delivered on to a slide and smears made in a usual manner (figure 2.29). (4) A drop of marrow can be placed in the center of a slide (extra blood may be removed by a fine pasteur pipette) and smears are made by squashing the marrow particles by putting another slide on the top of it and pulling the slides in opposite direction as shown in the illustration (figure 2.30). (5) Smears can also be made by putting a drop of marrow or isolated fragments between two cover-slips, and applying slight digital pressure to the “sandwich” and then gently pulling them apart (figure 2.31). Some workers routinely add the aspirated marrow to an anticoagulant, e.g. EDTA, in a tube and prepare films at leisure upon return to the laboratory. While this technique is convenient, it requires

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special care as it is all too easy to use an excessive quantity of the anticoagulant which may then affect the quality of the stained smears. Vacuolization of the cytoplasm and deformation of the nuclei (e.g. cloverleaf shapes) are also a potential problem if the preparation of the smears is delayed too long. Regardless of the technique of dry film preparation, the smears should be air dried as rapidly as possible to derive the best cytologic presentation. In some circumstances, particularly on days with a high level of humidity, fans can be used to direct a stream of air over the smears or they may be waved in the air to insure rapid drying.

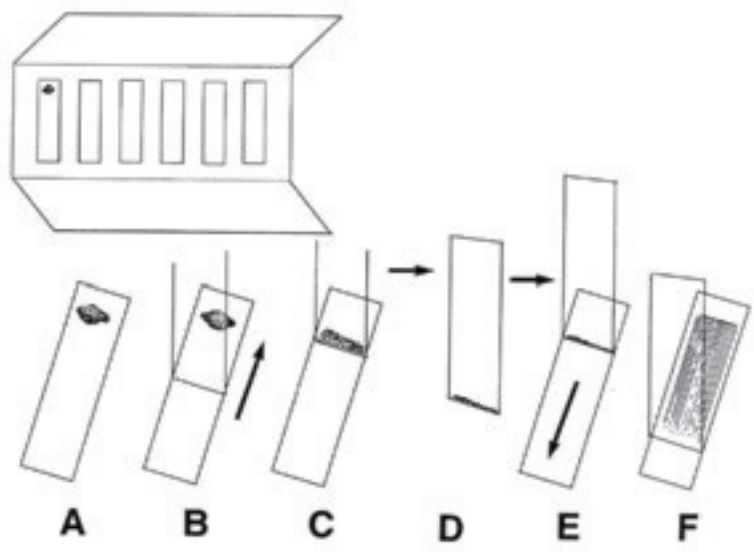


Figure 2.27 An illustration of the method of preparation of several smears from an original sample of marrow by repeatedly collecting the marrow particles with a spreader and making smears using the usual method of smear preparation. (A) Slide with small amount of marrow aspirate, (B) the spreader slide is placed in front of the marrow specimen, (C) the spreader slide is then pulled back towards the marrow sample to collect enough marrow particles at its edge which is then lifted-up (D) and placed on another clean slide (E) and a smear is made. Completed slide (F). The inset shows the arrangement of glass slides for the preparation of such smears. Note that a small amount of marrow is placed at the end of one slide only.

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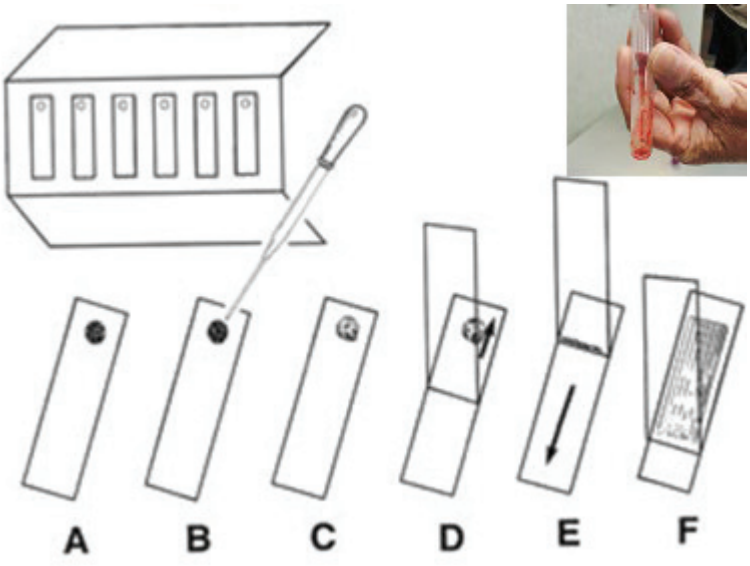


Figure 2.28 An illustration of the method of preparation of marrow smears by placing a drop of marrow aspirate on several glass slides. (A) slide with a small drop of marrow aspirate, (B) excess blood is sucked out with a fine pasteur pipette, (C) slide with the remaining marrow sample containing mostly marrow particles, (D) the spreader slide is pulled back over the remaining marrow sample, (E) spreader slide is advanced in smooth motion, (F) completed slide. The arrangement of the glass slides are shown in the upper left hand corner. Note the drop of marrow on each slide. The inset shows withdrawal of aspirated marrow from the *first pull* (0.5 ml) by a pasture pipette from a lavender (EDTA) tube for the preparation of marrow smears as depicted above.

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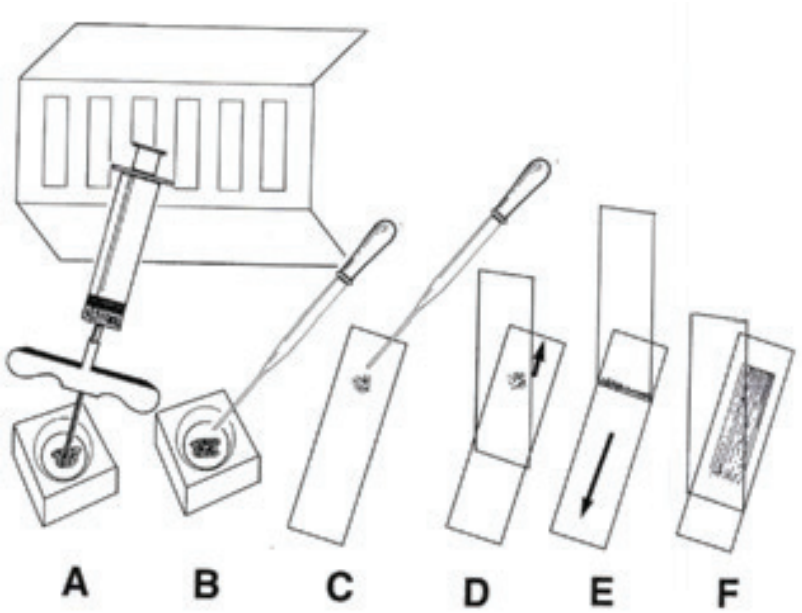


Figure 2.29 Illustration of the method of preparation of marrow smears by first placing a small amount of aspirated marrow into a cuvette containing a suitable anticoagulant. (A) Aspirated marrow being delivered into a cuvette, (B) excess blood (but not the fragments) is sucked out with a fine pasteur pipette and discarded, (C) a drop of marrow sample with the fragments is now withdrawn from the cuvette and placed at one end of a glass slide, (D) the spreader is pulled back over the drop of marrow sample, (E) the spreader slide is gently advanced in smooth motion, (F) completed slide. The cuvettes with marrow sample and the arrangement of slides for the preparation of smears by this method is shown on the left side of the illustration.

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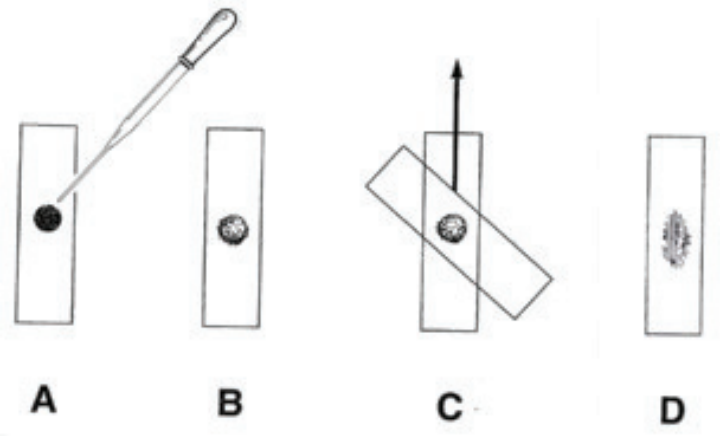


Figure 2.30 Illustration of the method of making squash preparation. (A) A drop of marrow is first placed in the center of a clean glass slide, (B) excess blood is sucked out leaving mostly the marrow particles, (C) another clean glass slide is placed over the marrow fragments and pulled in the direction of the arrow while holding firm the slide with marrow fragments, (D) completed slide.

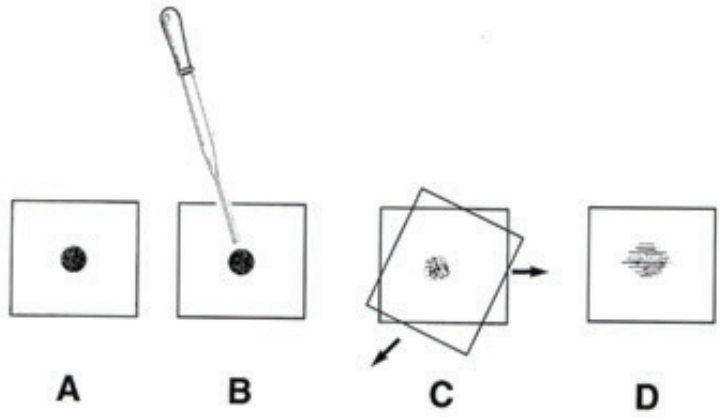


Figure 2.31 Illustration of the cover slip method of making squash preparation. (A) A drop of marrow is placed in the center of a cover slip, (B) excess blood is sucked out with a fine pasteur pipette, (C) a second cover slip is placed over the remaining marrow fragments and the cover slips are pulled in directions of arrows, (D) completed smear (squash).

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Usually the first or second method of preparation of aspirate smears proves quite satisfactory. It is preferable to select the third method when there is a possibility of rapid clotting of the aspirated marrow as in cases of hyper granular promyelocytic leukemia. Squashing and smearing of the particles not only causes disruption of the marrow units but also can cause considerable distortion of cells. This technique also tends to produce regionally thick preparations which are difficult to stain well. Although some workers prefer the squash preparations most likely because of prior training and/or long term usage, but this approach has no advantages over the first three described methods. Cover slip preparations require delicate handling because of the fragility of these small thin glass plates. Staining them involves additional work since they are not the dimensions of conventional microscope slides and hence require special holders. They do not readily lend themselves to some automated stainers. They must also be mounted on regular microscope slides after staining to be efficiently examined under a light microscope. Other than the possible advantage of yielding excellent results with minimal sized samples no specific benefits are attributable to this technique.

Concomitant with the preparation of dry film smears, the remainder of the aspirated marrow is delivered into a suitable anticoagulant for flow cytometric and cytogenetic studies and/or into a fixative for the preparation of histological sections (clot sections). Some of the films should be fixed in absolute methanol as soon as they are dry for staining with one of the Romanowsky type stains (e.g. May-Grunwald-Giemsa, Wright-Giemsa, Leishman) or by the periodic acid Schiff reaction or for marrow iron stores. Additional films should be fixed in formol- ethanol when other cytochemical staining is desired. The staining with the Romanowsky type dyes should be conducted immediately after fixing with methanol.

When no marrow sample is obtained from the aspiration procedure (dry tap) the stilette should be inserted into the needle to push out any material from inside the lumen of the needle on to a slide. This material should be spread into a film and stained. Occasionally in some cases of lymphoma or carcinoma a small but sufficient amount of the malignant tissue is nevertheless drawn into the needle from which a definite diagnosis can be made.

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Preparation of Sections from Aspirated Specimens

A number of methods of preparing histologic sections from aspirated fragments of marrow (clot sections) have been published. They all differ to some extent in the details of handling and concentrating the fragments, fixation and embedding. The method described by Lukes and Tindle yields an adequate concentration of the marrow particles and is simple to carry out. It is summarized below.

Method

Following preparation of the smears, and setting aside a portion of the aspirate for flowcytometric and cytogenetic study, the remainder of the marrow (1-3 ml) present in the syringe is expelled into a specimen jar (60 ml) containing 3 ml of EDTA (7 mg/ml) (ethylenediamine tetra acetic acid) for anticoagulation. After thorough mixing, Zenker's fixative solution (half strength) is added, completely filling the container to avoid drying of marrow particles adherent to the sides of the container. Fixation is usually complete within 1-2 minutes. The specimens may be allowed to stand for up to 48 hours without apparent harm using a modified Zenker's solution (FU 48, Technicon Instruments Corp., Tarry town, N.Y.). The latter does not harden the tissue excessively upon standing, nor does it require washing of the specimen after fixation. The marrow is then filtered through a plastic funnel containing a circular stainless steel foundation mesh No. 120 (United Surgical Supplies Co., Inc., Port Chester, N.Y.) which provides the grid upon which the tissue particles are collected. This filtration technique not only eliminates the erythrocytes but also concentrates the marrow tissue particles. The filtration process may be assisted by negative pressure by placing the funnel with the attached grid on the top of a vacuum bottle. After filtration is complete, the particles on the grid are cautiously lifted off with a scalpel and placed on a clean slide. Fluid is removed with blotting paper applied at the margins of the area of the particles. The marrow particles are aggregated according to the examiner's requirements and covered with a 2% agar suspension previously maintained at 46°C. Upon cooling it forms a tissue mat and holds the particles in place. Sections are cut at 3 to 5 μm in thickness and routinely stained with hematoxylin and eosin (H & E) and/or the periodic acid Schiff method (PAS) with a hematoxylin counter stain. The Prussian blue method is also used to stain and quantitate hemosiderin. The PAS method serves as an excellent differential stain.

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Special considerations

The fragments of bone marrow aspirated by puncture technique are typically small (less than 1 mm in diameter) and usually free of bone. As a result the marrow architecture and the relationships that exist between bone and bone marrow cells cannot be studied. In a satisfactory preparation however, the relationship between the hematopoietic and adipose cells is well preserved, hypoplasia or hyperplasia if present can be evaluated, and tumor cells and granulomata can be identified. The usefulness of such sections is limited by their small dimensions making it uncertain how representative they are of the total bone marrow. A more significant disadvantage of histologic sections of aspirated marrow is that when no bone marrow units are obtained, as in some cases of aplasia, myelosclerosis, packed marrow of acute or chronic leukemia, or replacement by tumor cells, this procedure fails to provide any definitive diagnostic information. A trephine biopsy consequently becomes mandatory when aspiration of the marrow fails to deliver the required tissue. Currently since many hematologists perform bone marrow aspirations at the posterior iliac crest they also simultaneously use the same puncture wound to perform a trephine biopsy, sometimes using the same biopsy needle. As a result the request for histologic sections preparation from aspirated marrow fragments has been reduced considerably. This is quite appropriate since histologic sections of aspirate fragments cannot provide the extent of information that is available from histologic sections of a marrow core.

Clinical (bedside) assistance with biopsy procurement

In many hospitals (outpatient department, doctors surgery) hematologists tend to perform the entire bone marrow examination (bone marrow aspiration and bone marrow biopsy) procedure single handedly without the help of an assistant. The entire procedure, as is quite apparent, entails multiple steps some of which require speed, accuracy and clinical skill (e.g. preparing the patient, administering the anesthesia, making the smear etc.). Further potential complications are the immediate clotting of the sample in some patients and/or bleeding at the puncture site if the wound is not attended and pressure applied after the needle is withdrawn. Therefore help from an assistant/hematology technician can facilitate the procedure considerably. He or she can stand by the side of the bed, lay out slides on a tray while the haematologist prepares and drapes the patient. He/she can also help the clinician withdraw the local anesthetic into a syringe and following aspiration can receive the aspirated material,

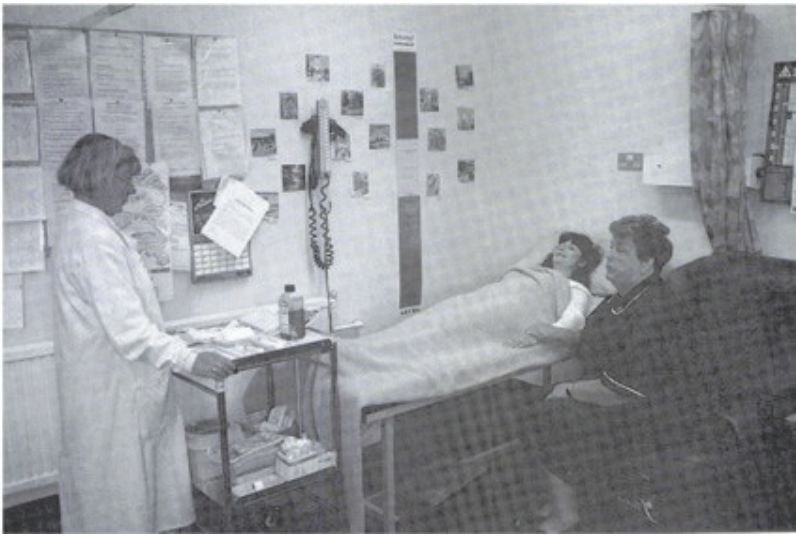
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prepare the smears, and transfer the marrow into vials for further tests while the clinician tends to the wound and prepares himself/herself to perform the marrow (core) biopsy procedure. See photograph 1-7 demonstrating the in-clinic bone marrow aspiration and biopsy procedure.



Photograph 1. Note the adjustable bed for the patient placed in a private setting. A technician's tray containing needles, syringes, gauze, antiseptic, bone marrow aspiration and biopsy needles etc. is placed adjacent to the bed.

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Photograph 2. Shows a patient lying in the bed, a technician who will assist in the process standing in front of the tray and the sister in charge (holding the hand of the patient).



Photograph 3. Shows tending of the wound by the operator. Pressure is being applied with the left hand to the sternal bone marrow aspiration site.

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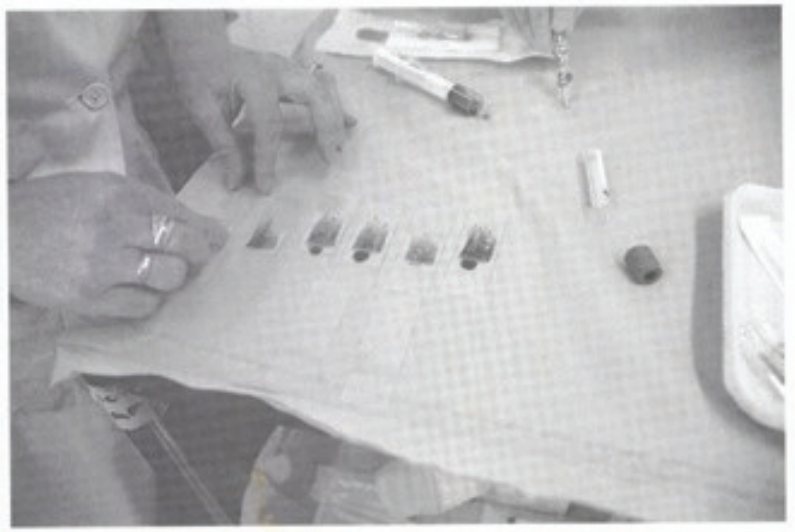


Photograph 4. Shows delivery of the aspirated marrow to the technician for the preparation of smears and utilization of the remainder of the marrow for other uses.

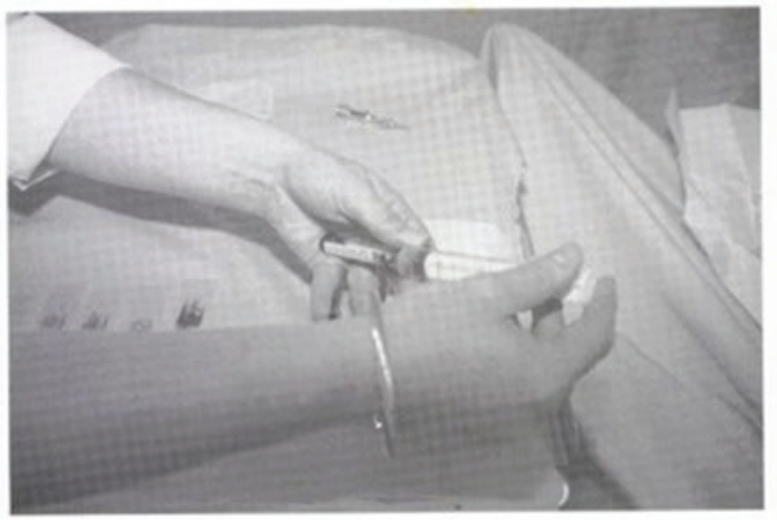


Photograph 5. Shows putting a drop of marrow on to a slide by the technician.

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Photograph 6. Shows careful preparation of the smears by the technician.



Photograph 7. Shows residual marrow being delivered into a bottle containing EDTA for additional uses.

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Methods of Staining Smears

The films are first dried in air (rapidly), then fixed by immersing the slides in a Coplin jar containing absolute methanol for 5-10 minutes. They are then transferred (according to one well recognized technique) to a staining jar containing May-Grunwald stain freshly diluted with an equal volume of Sorensen's phosphate buffer pH 6.8 and filtered through a Whatman filter paper No. 1. After the films have been allowed to stain for 15-20 minutes, they are then immediately transferred (without washing) to another jar containing Giemsa stain freshly diluted with 9 volumes of Sorensen's phosphate buffer pH 6.8 and filtered through a No.1 Whatman filter paper. After staining in the Giemsa stain for 10-15 minutes, the slides are dipped ("washed") several times in Sorensen's phosphate buffer pH 6.8 and then allowed to stand undisturbed in water for 2-5 minutes for differentiation to take place. This may be controlled by inspection of the wet slide under the low power of the microscope; with experience the color of the film as observed by the naked-eye is often a good guide. During staining the slides should be transferred from one staining solution to the other without being allowed to dry. The intensity of the staining is also affected by any variation in the thickness of a film and as a result it is often not easy to obtain uniform staining throughout a film's length. This is the rationale for exercising care in selecting the proper region (where morphology and staining characteristics of marrow cells are at their best) of a smear for morphologic assessment.

After staining the smears are air dried and mounted with a cover-glass using diatex or permount as the mounting medium. The cover slip prevents the film becoming scratched during subsequent handling and also facilitates microscopy at less than oil immersion magnifications. However if desirable the slides need not be cover slipped. They can be examined under immersion oil which can be removed by gently wiping the slide with tissue or dipping it into xylol. Such films will retain their usefulness and will not deteriorate for an indefinite period.

Most laboratories presently use automated staining machines (Figure 2.32) and if properly employed they provide good quality staining for both peripheral blood and bone marrow films. However, smears containing obvious, readily recognizable bone marrow fragments are more likely to lose these structures when stained by machine rather than the more gentle staining in a Coplin jar or by the flooding method. Bone marrow smears should also be routinely stained by Perl's reaction (Prussian blue technique) to evaluate non-haem iron stores (haemosiderin, ferritin) and to

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establish the presence or absence of sideroblasts.

Examination of Smears

Careful preparation of films from aspirated marrow is essential. The hematologist's dependence on good staining to derive a correct interpretation of a marrow smear cannot be over emphasized. A preparation can be considered satisfactory only when an adequate number of marrow particles as well as enough free marrow cells are present (figure 2. 33). In order to effectively analyze an aspirate at least two or more slides should be examined. The initial reading should begin with an overall assessment of the marrow film with an examination under low power (10x objective). This insures that large cells as megakaryocytes, osteoclasts, clusters or aggregates of metastatic cells or macrophages or even erythroblastic islets will not be missed or overlooked because of an inadequate survey.

The differential counts should be made in the trails of cells commencing from a marrow fragment in the distal end (feather edge) of the smear and working back towards the head (beginning) of the film (figure 2 . 33). The morphology of hematopoietic cells that are close to the fragments from which they originated is most likely to be optimal. Cells that are more distal or near to the origin of the smear reside in the thicker region of the film and are less likely to be morphologically ideal. Trails of several marrow fragments in one or several bone marrow aspirate smears should be examined to make an adequate reading. Megakaryocytes are often dragged along with the fragments. Consequently before reporting that megakaryocytes are either reduced or absent areas close to the marrow fragments should be thoroughly examined and searched for their presence.

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Figure 2.32 An automated staining machine.

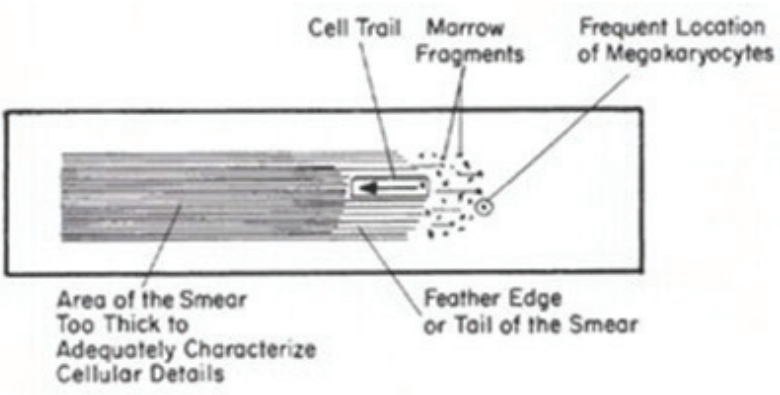


Figure 2.33 Schematic drawing of a bone marrow aspirate smear. The smear has been spread from left to right.

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Interpretation and Reporting

The reporting of a bone marrow should begin with an analysis of the marrow particles to assess the marrow cellularity. The degree of cellularity can be assessed within broad limits as increased, normal or decreased by careful inspection of several marrow fragments in one or more stained films. The bone marrow is considered normocellular when the volumetric ratio between hematopoietic cells and fat is about 50%/50%. The cellularity of the marrow is affected by age and this physiological variation has to be taken into account in one's evaluation of the tissue. In adults, a relatively smaller portion of the marrow cavity is occupied by haemopoietic marrow than in children and the proportion of fat cells to active marrow is increased. In subjects aged 60 or more the marrow tends to become still more fatty; this is particularly true for the manubrium sterni. It is known that the marrow undergoes slight to moderate hyperplasia in pregnancy.

Following assessment of the cellularity the evaluation of the bone marrow should address the qualitative and quantitative aspects of erythropoiesis, granulopoiesis, thrombopoiesis and the presence or absence of any abnormal cells. This is ideally done in the cell trails. Megakaryocytes are most visible near the fragments. Then an assessment of iron stores and presence or absence of ring sideroblasts should be made. Finally a comment should be made as to the reviewer's overall impression of the marrow.

An Effective, Useful Bone Marrow Report Should Comment on the Following

1. **Site**: bone marrow aspirate obtained from the sternum, right or left posterior iliac crest etc, under local anesthesia.

2. **Overall cellularity**: normal, increased or decreased. The increase or decrease can further be qualified by a prefix as either mild, moderate or marked. Bone marrow cellularity cannot be adequately assessed if few or no fragments are available in the aspirate.

3. **Erythropoiesis**: activity—normal, increased or decreased; maturation sequence (normoblastic vs megaloblastic); cytologic abnormalities such as dyserythropoietic changes, etc.

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4. **Granulopoiesis**: activity—normal, increased or decreased; maturation sequence (i.e. whether all stages of maturation are represented or if there is a maturation arrest); cytologic abnormalities such as dysgranulopoiesis (giant metamyelocytes, Pelger-Huet forms etc.); the presence and number of myeloblasts and promyelocytes.

5. **Megakaryopoiesis**: numerical assessment (increased, normal or decreased); maturation sequence, platelet production, pleomorphism; cytologic abnormalities such as dysmegakaryopoiesis (multinucleated forms etc.).

6. **Plasma cell series**: numerical assessment (expressed in percentage), maturation, inclusion bodies, any abnormalities or neoplastic changes.

7. **Lymphocyte series**: lymphoid aggregates, germinal centers, numerical assessment (expressed in percentage), morphologic abnormalities (large, small, cleaved, character of nucleoli), malignancies.

8. **Eosinophils and basophils**: numerical assessment (expressed in percentage), any abnormalities.

9. **Iron stores**: content (normal, increased or decreased), the presence or absence of ring sideroblasts.

10. **Miscellaneous**: presence of macrophages, mast cells, granulomas, amyloidosis, gelatinous transformation of fat, pathologic lesions of the bone, osteoblasts, osteoclasts and metastatic neoplasms etc.

11. **Differential cell count**: a detailed differential count (myelogram) is not always necessary but sometimes they may be useful. The normal ranges for differential counts on aspirated bone marrow are given in Table 1.

12. **Comment/conclusion**: overall impression of the marrow as being normal or abnormal. If abnormal— identify the abnormality, any further investigations such as vit. B12 and/or folic acid assays for megaloblastic anemias; serum iron, TIBC etc. for iron deficiency anemia and any other studies that are recommended to be performed.

Common Problems and their Resolution

Although a satisfactory sample of bone marrow can be aspirated without much difficulty from the sternum or from the posterior iliac crest (the most

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commonly used sites), occasionally it may be necessary to re-insert the stilette and advance the needle a little further or to reinsert the needle into the bone in a slightly different position in order to access the tissue. Sometimes, however, no marrow can be aspirated resulting in a dry tap. In such circumstances the stilette, as indicated previously should be inserted into the needle to push out any material within the lumen of the needle on to a slide to examine the tissue lodged therein.

Table 1. Normal ranges for differential counts on aspirated bone marrow

Reticulum cells	0.1-2%
Myeloblasts	0.1-3%
Neutrophil promyelocytes	0.1-5%
Neutrophil myelo and metamyelocytes	17-41%
Neutrophil bands and segmented form	15-32%
Eosinophils and precursors	1-5%
Basophils and precursors	0-1%
Monocytes	0-4%
Lymphocytes	7-23%
Plasma cells	0.1-3.5%
Proerythroblasts	0.1-2%
Basophilic erythroblasts	0.1-4%
Polychromatophilic erythroblasts	5-20%
Orthochromatic erythroblasts	2-10%
Myeloid/erythroid ratio	2.5-10:1

An optimal myelogram requires the enumeration of a minimum of 200-500 cells.

Needle breakage during aspiration procedure

Rarely, a bone marrow aspiration needle (particularly of the older generation of Salah or Klima type needles when they are used for posterior iliac crest aspiration) may break while being inserted into or withdrawn from the bone. In such circumstances an attempt should be made to keep the distal broken portion of the needle exposed and always in view of the operator (that is to keep the needle visible and avoiding the possibility of its loss in a mass of depressed and then rebounded soft tissue mass). This is accomplished by pressing the tissue surrounding the needle with fingers of the left hand while trying to clamp or secure the needle with a needle holder. Hemostats like artery forceps are usually unsatisfactory for this

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purpose. Once the needle is secured it is then removed by gentle alternating rotary motion of the needle holder. If however, for some reason the broken needle is retained within the flesh then the patient should be reassuringly informed of the mishap, the site of the aspiration properly marked, a roentgenogram obtained, and a surgeon notified for consultation.

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CHAPTER 3

DRY TAP AND THE DIAGNOSTIC VALUE OF PREPARING BONE MARROW SMEARS FROM THE SMALL AMOUNT OF TISSUE LEFT WITHIN THE ASPIRATION NEEDLE FOLLOWING A DRY TAP

Bone marrow aspirations are routinely used in the diagnosis and management of patients with hematological disorders. Cytological examination of the hematopoietic marrow is viewed as not possible when the aspiration is a dry tap. A dry tap during bone marrow aspiration typically means a failure to obtain any sample (little or no sample) of hematopoietic tissue. A dry tap is not uncommon when the marrow is packed with malignant hematopoietic cells, carcinoma or when the marrow is fibrosed (myelofibrosis).

Cytomorphological evaluation of a bone marrow aspirate sample is essential to make an accurate diagnosis and the management of patients with leukemia, lymphoma, multiple myeloma, myelodysplastic syndrome and other hematological disorders. A dry tap can therefore interfere with the initial diagnostic evaluation of a hematopoietic condition or evaluation of marrow following therapy with respect to residual disease, relapse and resistance. In such circumstances smears prepared from the small amount of material left within the lumen of the aspiration needle following a dry tap may help making an accurate diagnosis which might otherwise be missed if only simultaneously obtained hematoxylin and eosin stained sections of the bone marrow core biopsy specimens are examined. A dry tap may also fail to demonstrate or establish the status of marrow following treatment or transplantation. In such circumstances smears produced from the material left in the needle following a dry tap can provide valuable information either to complement or even make an accurate diagnosis.

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If the dry tap is genuine and not due to technical reasons (see below) it usually indicates significant marrow pathology which is usually associated either with marrow fibrosis or hypercellularity (packed marrow), or both. The predominant conditions associated with a dry tap usually include leukemias, particularly chronic myelogenous leukemia and hairy cell leukemia; metastatic solid tumors, and idiopathic myelofibrosis. The topic of dry taps has received very little attention and the diagnostic value of making smears from the material left in the needle has largely been ignored. It has been reported that in about 80% of the dry taps there is retained material within the lumen of the bone marrow aspiration needle. When this material is expelled on to a slide and smears are made and stained, the resulting microscopic image can reveal not only useful information complimentary to a simultaneously obtained bone marrow core biopsy specimen but may provide the only material available to yield correct diagnostic information.

In a recent case study the diagnostic value of preparing bone marrow smears from a small amount of marrow left within the aspiration needle following the dry tap proved to be essential in making an accurate diagnosis. The patient a 67 year-old white female was referred to a hospital for the evaluation and management of transfusion-dependent anemia and high WBC count. She did not have any major complaints except tiredness and generalized weakness particularly in her legs. Her physical examination was unremarkable except for pallor and slight splenomegaly as evidenced by CT scanning. Her laboratory values were: WBC 25.4 x 10^9/L, hemoglobin 7.2 g/dl, an elevated MCV at 122.4 fl, a raised MCH at 39.3 pg, and a normal platelet count of 254 x 10^9/L. Her iron studies were mostly normal except for the serum iron level which was modestly raised at 168 mcg/dl (n 20-135). Her folate level was normal at 5.2 ng/ml but her B12 level was raised at >2000 pg/ml (although she was not taking any vitamin B12). The LDH was slightly raised at 283 unit/L (n 95-265). Her complete metabolic profile was normal but her erythropoietin level was increased, 79.4 milliUnit/ml (n 2.6-18.5). The reticulocyte count was normal at 3.6%. Her serum intrinsic factor antibody was normal at 1.0 Au/mL (n 0.0-1.1) and parietal cell antibody was negative (<1:20). Her stool occult blood test was negative X3 and a colonoscopy and esophagogastroduodenoscopy did not reveal any source of bleeding. She was positive for the JAK–2 mutation, but negative for the BCR–ABL translocation. A solid core bone marrow biopsy revealed a highly cellular marrow (cellularity of 95-100%) with a markedly increased amount of granulopoietic cells (Figure 3.1), occasional atypical megakaryocytes (Figure 3.1 arrows) and a few scattered erythroid precursors. The bone

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marrow aspirate was a dry tap. However, smears prepared from the small amount of material left within the aspiration needle following the dry tap clearly revealed marked myeloid hyperplasia with rare blast cells (<1%). Red cell maturation was megaloblastoid and showed dysplastic features (Figure 3.2 A). Myeloid maturation was progressive and dysplastic (Fig 3.2 B). Megakaryocytic atypia was clearly evident (Figure 3.2 C&D). Ring sideroblasts were not observed. These bone marrow aspirate findings lead to a diagnosis of myelodysplastic/myeloproliferative neoplasm (MDS/MPN). The patients vitamin B12 level was high which was consistent with a diagnosis myeloproliferative disorders.

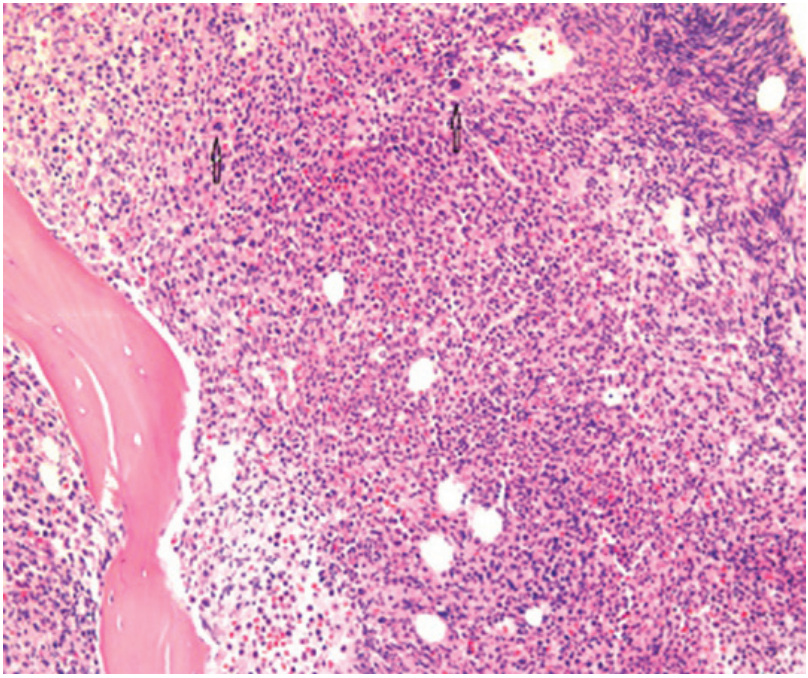


Figure 3.1 H & E stained section of a bone marrow biopsy specimen demonstrating a markedly hypercellular marrow with massive infiltration by myeloid precursor cells. Note occasional atypical megakaryocytes (arrows).

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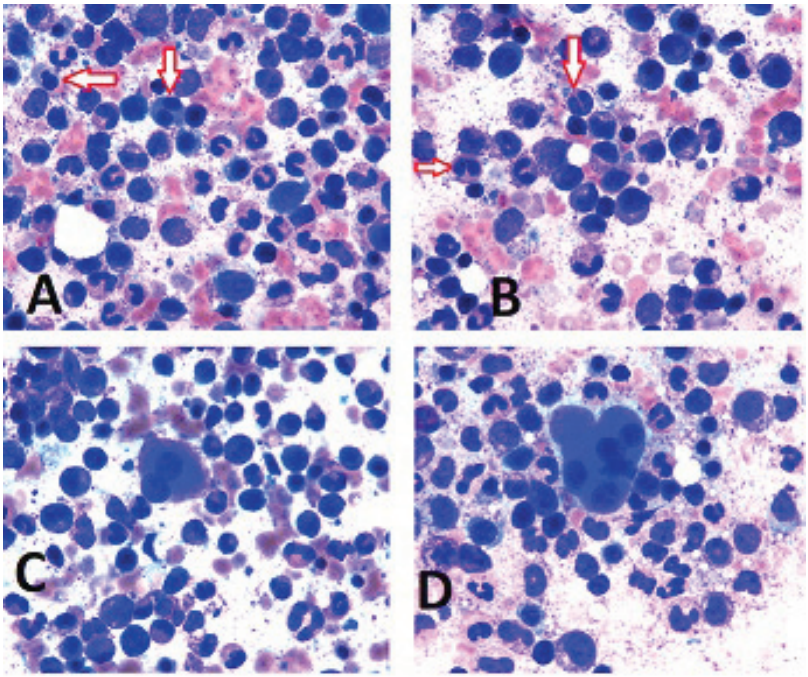


Figure 3.2 Wright-Giemsa stained smear of the material obtained from the needle following a dry tap demonstrating dysplastic features in the erythroid precursors (bilobed nuclei and nuclear budding-arrows) (A), granuloid cells (nuclear hypolobation and pseudo-Pelger Huet cells - arrows) (B), and megakaryocytic cells [bi and multinuclear (separate nuclear lobes) megakaryocytes) (C & D).

In 2008 the WHO introduced a new disease entity termed the myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN). It is considered to be a rare *de novo* myeloid neoplasm that exhibits hybrid dysplastic and proliferative features at presentation. The dysplastic features of the maturing hematopoietic cells are an important criterion for a diagnosis of MDS/MPN. Unlike H & E stained sections of bone marrow core biopsy specimens, dysplastic features in developing hematopoietic elements are best visualized in the May-Grunwald or Wright-Giemsa stained smears of aspirated marrow. When no marrow is obtained (dry tap) a diagnosis of MDS/MPN can be difficult to establish and may be easily missed if only H & E stained sections of bone marrow core biopsy specimens are available for examination.

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In the case discussed above a solid core bone marrow biopsy revealed an extremely hypercellular marrow (cellularity over 90%) with predominant myeloid hyperplasia (Figure 3.1), occasional erythroid precursors and a few megakaryocytes. When considered in conjunction with the CBC findings and the JAK-2 mutation a diagnosis of myeloproliferative neoplasm was not in question. On the other hand, with only an examination of the H and E stained sections of the bone marrow biopsy it was not possible to appreciate the dysplastic features of the hematopoietic cells which were clearly evident in the smears produced from the material left within the aspiration needle following the dry tap. As a result a diagnosis of MDS/MPN could be accurately established.

During bone marrow aspiration occasionally no material enters into the syringe causing a dry tap. The frequency of dry tap is about 5%, although it has been reported to vary from 1.6% to 6.8%. The etiology of a dry tap can vary with the type of disease as well as faulty technique and operator experience. While attempting a bone marrow aspiration from the posterior ilium if the aspiration needle is introduced tangentially the tip of the needle may remain completely buried in the solid cortical bone and may never reach the hematopoietic spongy bone (figure 3.3, needle 1). Alternatively, the tip of the needle may traverse the cortical bone, pass through spongy bone and re-enter the cortical bone of the contralateral wall of the ilium. As a result the procedure will obviously be a dry tap (figure 3.3 needle 2).

When a bone marrow aspiration procedure is performed and no marrow is obtained on the first attempt the operator should withdraw the needle a few millimeters with the stilette/stylet in place and re-introduce the needle into the bone at a different angle (figure 3.4). Hopefully this step will reach a site of spongy bone with aspiratable marrow. On the other hand, if this second attempt fails to yield an aspirate and the operator is confident that the tip of the needle is in spongy bone, this status can be considered a verified dry tap. At this point the needle is withdrawn from the patient and its potential contents should be expelled from the needle with the use of a stilette/stylet on to a glass slide. Dry film smears are then prepared, stained and carefully studied. It is recommend that in case of a dry tap one should routinely try to make smears from the material left within the lumen of the needle.

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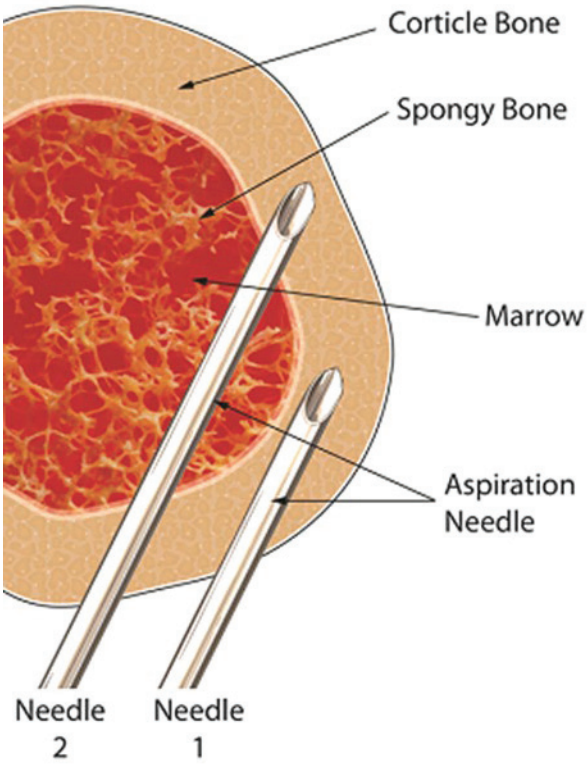


Figure 3.3 Schematic representation of the aspiration biopsy technique from the ilium: needle 1 has been introduced tangentially through the cortical bone but the needle tip has not entered the spongy bone containing the marrow and as a result the aspiration will be a dry tap. The needle 2 has also been introduced tangentially and has traversed through the spongy bone but the tip of the aspiration needle has lodged in the distal cortical bone and as a result no marrow will be aspirated (dry tap).

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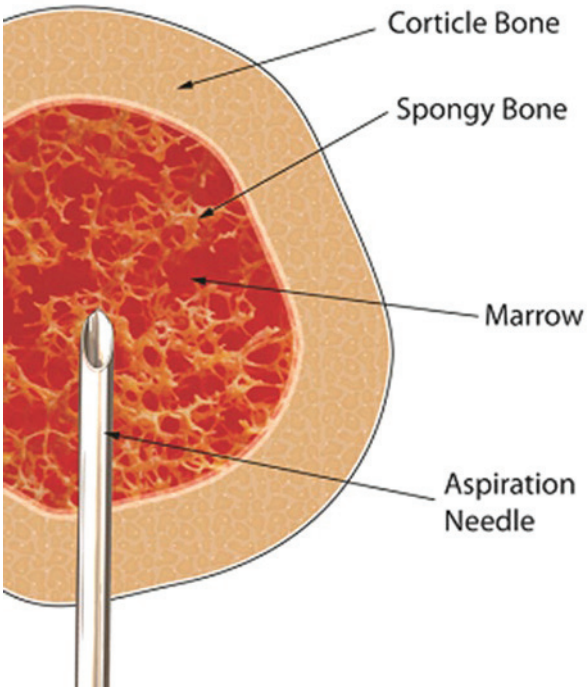


Figure 3.4 Schematic representation of the aspiration biopsy technique from the ilium demonstrating introduction of the needle at a correct angle. Here the tip of the needle has entered the spongy bone containing the marrow and as a result the aspiration will most likely be successful.

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CHAPTER 4

BONE MARROW TREPHINE (CORE) BIOPSY

Introduction

The technique of bone marrow trephine biopsy was first introduced by Ghedini of Genoa in 1908 when he performed a surgical bone marrow biopsy on a patient to aid in the diagnosis of a hematologic disease. He obtained a sample of bone and marrow from the upper end of the tibia of an adult using a manual trephine. Although the value of bone marrow biopsy in the diagnosis of bone and bone marrow disorders have long been recognized, it is only fairly recently that the technique has become popular and gained some acceptance among hematologists and oncologists. This is specifically due to two reasons; (1) development of new needles ensuring that the biopsies can be carried out with virtually no discomfort to the patient while imposing little or no damage to the biopsied tissue (figure 4 .1), and (2) improvements in the technique of processing bone marrow biopsies in plastic (methyl and glycol-methacrylate) which require no decalcification. This approach provides thin (1-2 *μm)* sections of high histological quality that are stainable with Romanowsky type stains (Giemsa or May-Grunwald & Giemsa) providing excellent cytomorphologic detail of the haemopoietic tissue (figure 4. 2 a&b). It has also become apparent that much more diagnostic and prognostic information can be obtained from adequately processed and properly stained bone marrow biopsy sections than from dry film smears alone.

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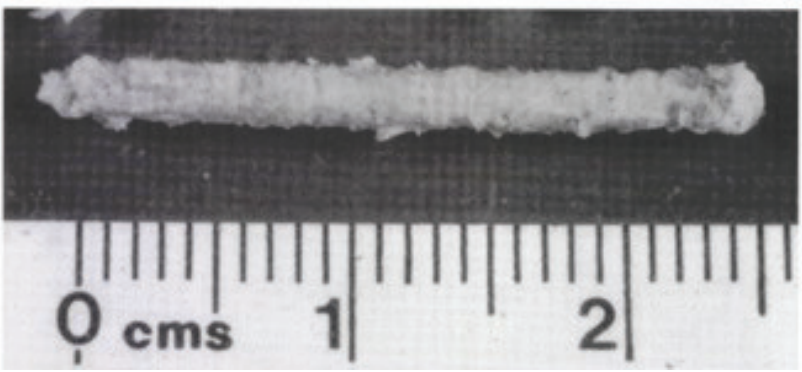


Figure 4.1 A bone marrow biopsy specimen obtained from the right posterior iliac crest using a (standard size) Islam bone marrow biopsy needle. Note the long and uniform core of marrow tissue obtained by the procedure.

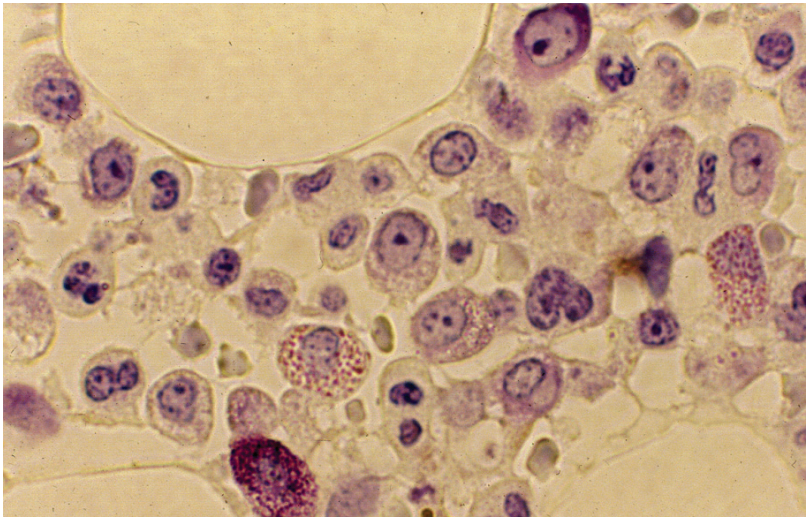


Figure 4.2a Bone marrow biopsy section from a normal adult showing elements of granulopoiesis. Note a myeloblast, two eosiniphilic granulocytes, a basophil granulocyte, a few neutrophilic myelocytes and their segmented forms. (The section was processed in methyl-methacrylate (MMA) and stained with May-Grunwald-Giemsa stain).

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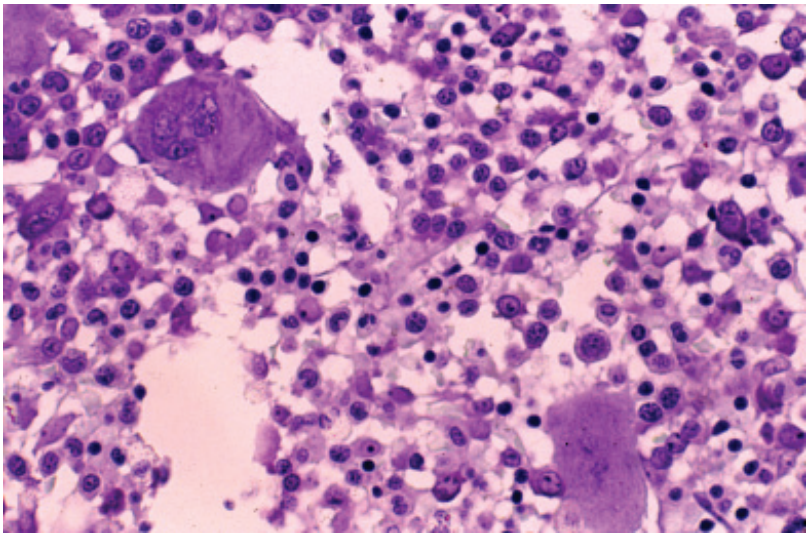


Figure 4.2b Bone marrow biopsy section from a normal adult showing elements of erythropoiesis in different stages of maturation. Two megakaryocytes and a mast cell are also present. (The section was processed in MMA and stained with May-Grunwald-Giemsa stain).

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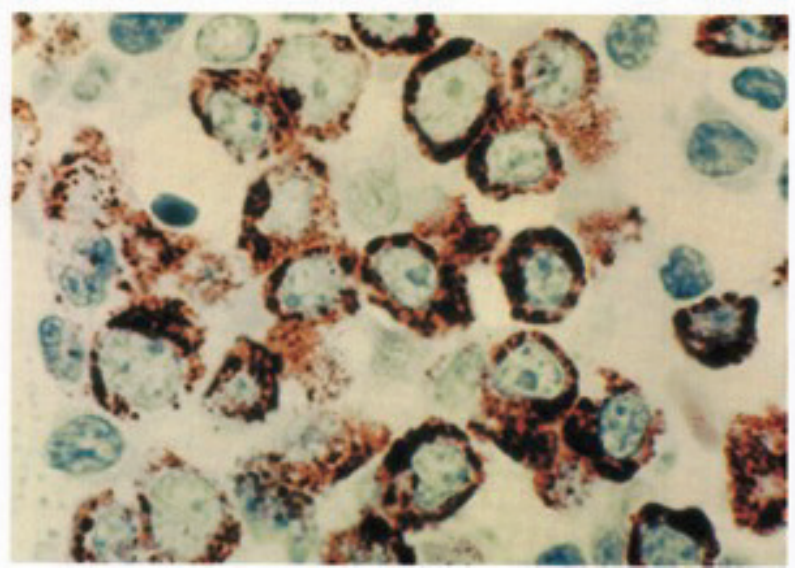


Figure 4.3a Bone marrow biopsy section from a patient with acute myeloid leukemia showing myeloperoxidase-positive blast cells. The specimen was processed into glycol-methacrylate (GMA) and stained for myeloperoxidase by Hanker's method.

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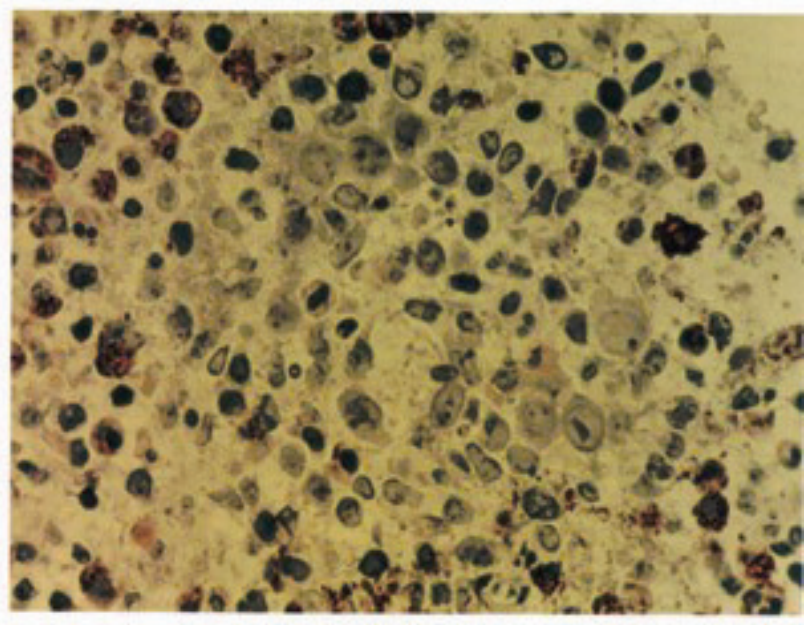


Figure 4.3b Bone marrow biopsy section from a patient with CML in lymphoblastic transformation. It presents a cluster of myeloperoxidase-negative blast cells. Note the peroxidase positive mature granulocytic cells at the periphery of the lesion. The specimen was processed into GMA and stained for myeloperoxidase by Hanker's method.

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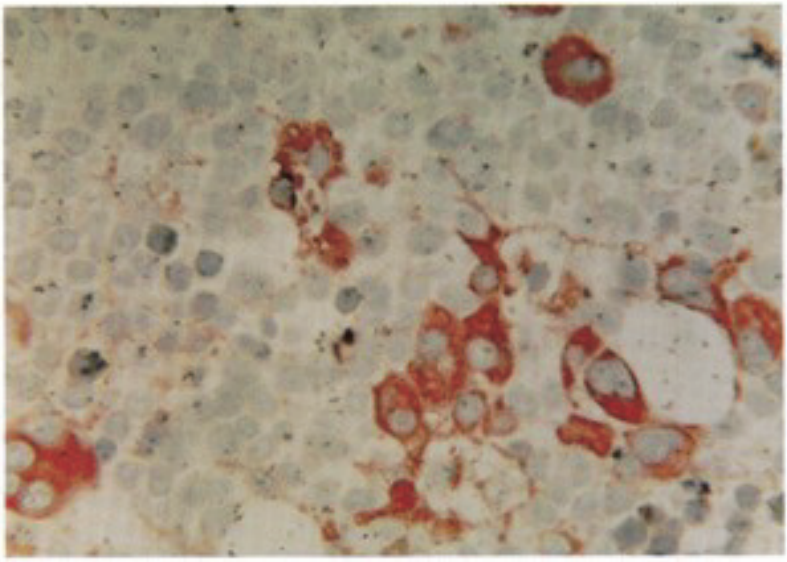


Figure 4.3c Bone marrow biopsy preparation from a patient with chronic granulocytic leukemia in megakaryoblastic transformation. The section was stained for factor VIII—related antigen with an indirect immunoperoxidase method and counterstained with Mayer's haematoxylin. The reaction product was demonstrated by using AEC as substrate. Note the strong positive reaction throughout the cytoplasm of the megakaryocytes including the megakaryoblasts.

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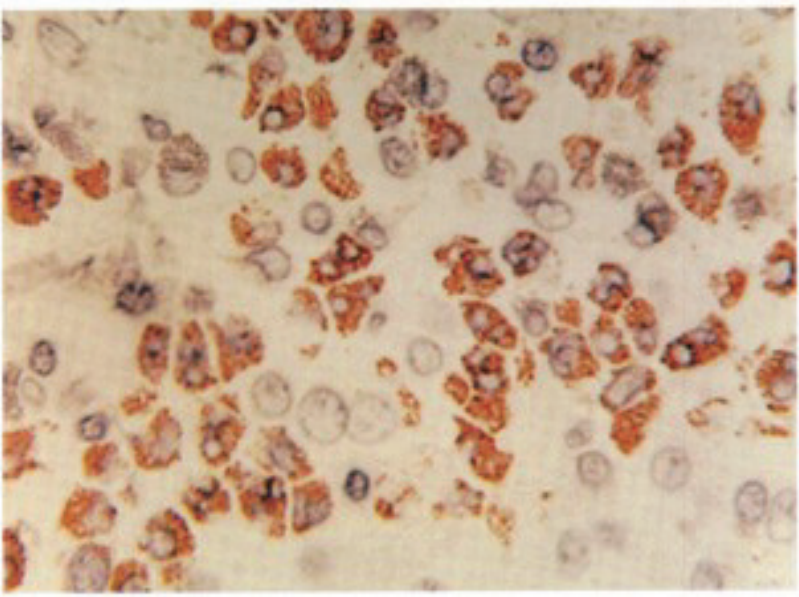


Figure 4.3d Bone marrow biopsy preparation from a patient with chronic granulocytic leukemia in chronic phase. The section was stained with monoclonal antibody L12-2 (a marker for mature granulocytes) with an indirect immunoperoxidase method and counterstained with Mayer's haematoxylin. The reaction product was shown by using AEC as substrate. Note strong positive reaction for L12-2 among all mature granulocytic cells.

The ability to perform enzymatic and immunohistological analyses on decalcified (paraffin-embedded) and undecalcified (plastic-embedded) bone marrow biopsies (Figure 4.3a-d) has added additional impetus and new dimensions to the diagnostic evaluation of bone marrow.

Furthermore, the molecular genetic techniques, such as *in situ* mRNA hybridization, interphase cytogenetics and PCR amplification of DNA for evaluation of minimal residual leukemia/lymphoma in bone marrow biopsies are opening new frontiers in the diagnostic and aetiologic evaluation of bone marrow biopsies in hematologic and non-hematologic malignant conditions. These techniques are particularly useful in cases where attempts at aspirating bone marrow fails and no malignant cells are available from peripheral blood (for example in certain leukemias with densely packed marrow or marrows associated with considerable fibrosis and peripheral pancytopenia).

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Traditionally bone marrow has been examined in Romanowsky stained smears of aspirated marrow. Although such preparations provide excellent cytomorphologic details of haemopoietic tissue, they are unable to detect, in most instances, focal pathological lesions that may be present in the bone marrow. They are also unsatisfactory in cases of inadequate, unsatisfactory or failed aspirations. In addition they do not reveal any characteristic or spatial localization of particular cell types [such as abnormal localization of immature precursors (ALIP's) in myelodysplastic syndromes and paratrabecular clustering of immature myeloid precursors observed in the accelerated and blastic phase of chronic myeloid leukemia] and structural and vascular histologic organization of the marrow.

Bone marrow trephine biopsy on the other hand not only overcomes most (if not all) of the disadvantages associated with bone marrow aspiration while in addition sections of the tissue thus obtained can be studied as an organ with its architecture and cellular components both presented in their own natural environment. A bone marrow biopsy thus offers a broader basis for the comprehension of marrow function in health and in disease.

Site(s)

As in bone marrow aspiration, bone marrow trephine biopsies can also be obtained from many different sites. A satisfactory sample of marrow core can be obtained from the anterior or posterior iliac crest. Other sites such as ribs, vertebral bodies, tibia, femur, humerus, Ischial tuberosity etc. can also be used. These additional sites for bone marrow biopsy are used only in the presence of radiologic or other evidence of osseous lesions to obtain diagnostic material.

At present most bone marrow trephines biopsies are performed at the posterior iliac crest. This is because of the advent of newer needles which are easier to manipulate and thereby making their access to the posterior iliac crest much easier. In most instances an adequate biopsy sample can be obtained from this site. The bone of the anterior iliac crest, however, is too thick and is difficult to penetrate with standard bone marrow biopsy needles. It is possible to obtain satisfactory specimens from this locus with manually operated boring trephines and electric drills but they require an open surgical procedure, and in most instances, the procedure cannot be repeated on the same site for at least 4-6 months. Conversely, the posterior iliac crest is comparatively less dense than the anterior iliac crest and presents the largest readily accessible area of marrow-rich bone in the body. This area is also distant from any vital structure thus serious accidents

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or complications are unlikely. With brief training and minimal experience biopsies of adequate size can be easily obtained from this site with an appropriate bone marrow biopsy needle. More importantly perhaps, this region can be re-biopsied as often as every four to six weeks as required for monitoring the marrow following chemotherapy or other therapeutic modalities.

Method

There are several different ways that a bone marrow trephine biopsy sample can be obtained e.g. by an open surgical biopsy, with electric myelotomy drills, with manually operated boring trephines, and with hand held bone marrow trephine biopsy needles. Each technique has its limitations, advantages and disadvantages.

Open surgical biopsy

The sole advantage of an open surgical marrow biopsy is that it allows a larger segment of bone and marrow to be obtained and examined. This method on the other hand has several disadvantages. It has to be carried out in an operating theatre under general anesthesia and with full aseptic procedure. It may be risky if the patient has a bleeding disorder or granulocytopenia, while in leukemic patients the incision may fail to heal. One of the significant drawbacks of an open surgical biopsy is that the procedure can seldom be repeated at the same site. Surgical bone marrow biopsy is rarely, if ever, required in hematological problems.

Electric myelotomy drill (Figure 4.4)

This technique was pioneered by Rolf Burkhardt of Munich, Germany in the 1970's. This is the superior (or vertical) approach for anterior iliac crest biopsy (Figure 4.5). In this technique the patient lies in the supine position and the anterior iliac crest area is prepared; 10 to 15 ml of 1% lignocane is used to anaesthetize the skin, subcutaneous tissue and periosteum. A 1 to 2 cm long incision is made directly over the border of the iliac crest, about 2 to 3 cm posterior to the anterior superior iliac spine (figure 4.6a). The guide funnel is introduced through the incision by a to and fro twist around its vertical axis until it touches the periosteum. An assistant then holds the funnel which is anchored to the periosteum by pressure leverage of its sharp- toothed lower end. The punch is introduced through the funnel, the tissues are cut circularly at the base of the funnel

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Figure 4.4 Components of Burkhardt's electric myelotomy drill, (a) Low voltage drive motor and gearing in sterilizable casing, (b) Guide funnel with lower sharp-toothed edge, (c) Punch for the removal of tissue external to the periosteum (disassembled), (d) Concave cutter with sharp-toothed, slightly inward-drawn, edge and spiral cutting grooves on the outside, (e) Pincers with spring leaves to appose their free ends by counter rotating the outer sleeve, which is conically narrowed at the bottom. The interior contains an ejector pin (disassembled). (Reproduced from *Bone Marrow and Bone Tissue: Color Atlas of Clinical Histopathology by* Rolf Burkhardt (1971), Springer-Verlag, New York, Heidelberg, Berlin.)

by rotating the handle within the punch. Soft tissue remnants and blood are cleaned from the periosteum with splinter forceps and swab. The motor driven cutter (electric myelotomy drill) is then introduced along the funnel until it touches the pelvic wing in a longitudinal direction (Figure 4.6b). Once an adequate length of marrow is cored, the cutter is withdrawn and

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the pincers are gently inserted over the reamed tissue cylinder. The leaves of the pincers are closed by gently turning the sleeve, and they are levered out by a short pull after two lateral movements. The leaves of the pincers are opened and the biopsy sample is extruded out by the ejector pin (Figure 4.6c). A Topostasin stick is placed in the opening of the bone for haemostasis, the skin is sutured and the wound dressed with a gauze swab. An elastic pressure bandage is placed around the pelvis which remains for 24 hours during which period the patient is advised to stay in bed.

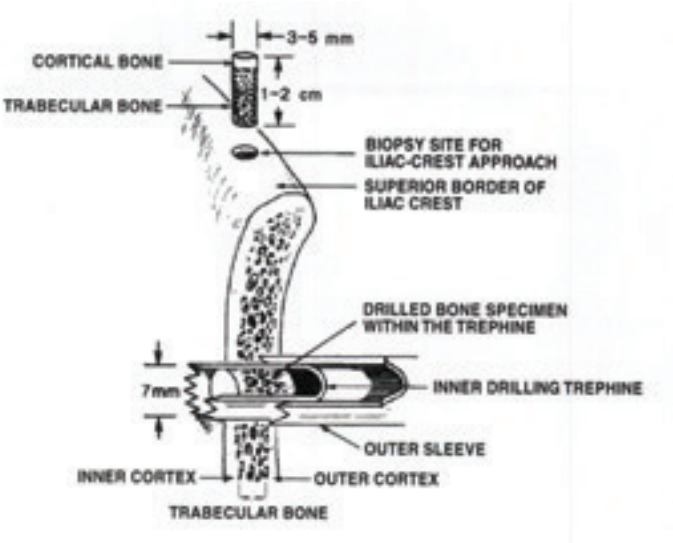


Figure 4.5 Details of two [vertical (superior) and horizontal (transiliac)] types of iliac bone marrow biopsies. (Reproduced from *Bone Histomorphometry: Techniques and Interpretation* by Robert R. Recker (1983), CRC Press, Inc, Boca Raton, Florida.)

Although the preservation of trabecular architecture is usually better with the electric myelotomy drill than with an ordinary trephine needle but this procedure is more invasive, complicated, and requires an assistant. Here, again above all, the technique cannot be repeated on the same site for at least 4-6 months. There are also two other problems in the use of electric drills; first, in the use of electric drills there may be an accumulation of 'bone powder' in the periphery of the spongy bone if pressure is exerted during the drilling, and secondly, heat artefacts of bone cells may appear if the speed of the instrument is too high. Thus, experience, care and skill are necessary on the part of the physician while using the instrument to avoid

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trabecular and cellular damage. Recently introduced OnControl needle described later also falls into this category.

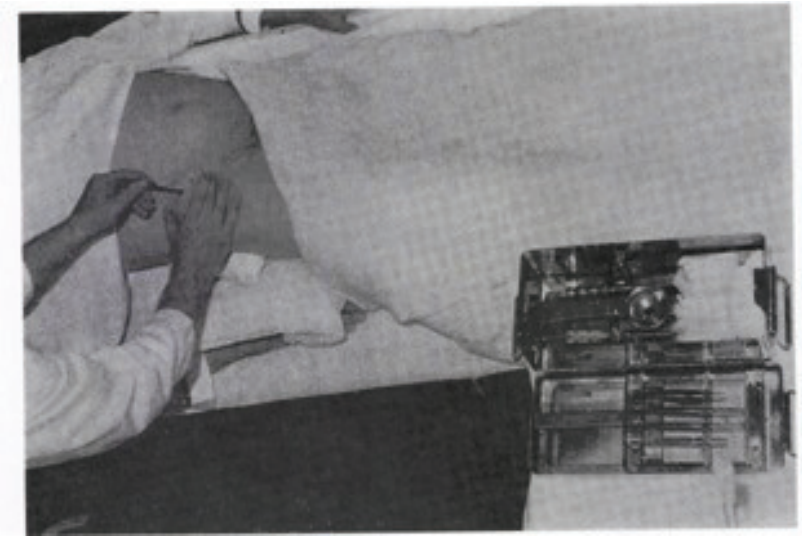


Figure 4.6a The Burkhardts procedure. Shows an incision being made directly over the iliac crest border. (Reproduced from *Bone Marrow and Bone Tissue: Color Atlas of Clinical Histopathology* by Rolf Burkhardt (1971), Springer-Verlag, New York, Heidelberg, Berlin.)

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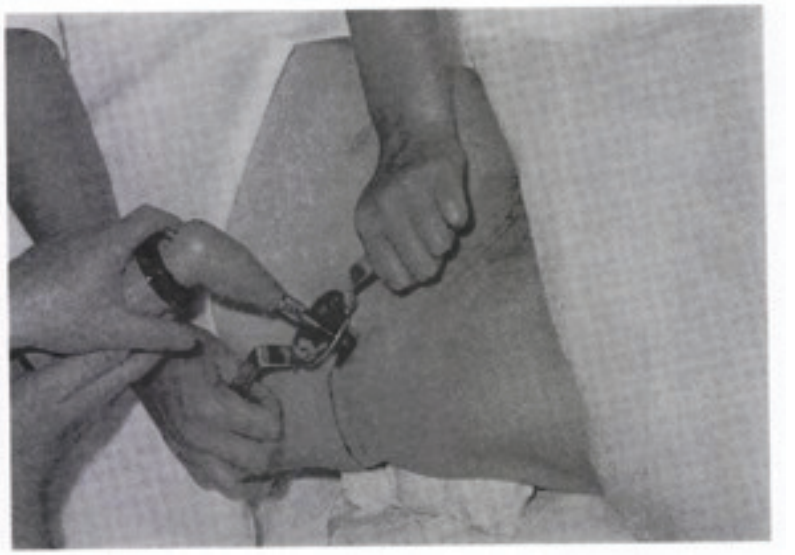


Figure 4.6b Illustrates the holding of the funnel by an assistant and introduction of the motor driven drill along the funnel. (Reproduced from *Bone Marrow and Bone Tissue: Color Atlas of Clinical Histopathology* by Rolf Burkhardt (1971), Springer-Verlag, New York, Heidelberg, Berlin.)

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Figure 4.6c Removal of the biopsy sample by the ejector pin. (Reproduced from *Bone Marrow and Bone Tissue: Color Atlas of Clinical Histopathology* by Rolf Burkhardt (1971), Springer-Verlag, New York, Heidelberg, Berlin.)

Manually operated boring trephines (Figures 4.7 & 4.8)

Trephines such as Notter Labhart (figure 4.7) and Bordier's (figure 4.8) are generally used for transiliac (or horizontal) biopsies (figure 4.9 a&b). This approach is slightly more invasive than one through the iliac crest (vertical approach) and usually takes a little longer time (30 to 60 minutes). During this lateral approach the patient assumes a supine lateral position with semi flexion at both hip and knee. A triangular area which is known as "Bordier's Triangle" is outlined with the anterior superior iliac spine as a guide. Roughly, it is a 5 cm isolateral inverted triangle (figure 4.9a), the base of which is formed by the border of the iliac crest. Following preparation of the skin, and local anesthesia [more local anesthetic (15 to 30 ml) is needed because of the bulk of subcutaneous tissue and muscle in this region] a 2-3 cm long incision is made along the dotted line indicated in Figure 4.9a exposing the glistening fascia lata. The fascia itself is then incised along the direction of its fibers and the dissection is continued until the scalpel touches the subadjacent periosteum and bone. The periosteum is scraped after further local anesthesia which

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helps in minimizing the discomfort. Using the index finger, the surface of the bone is freed of its muscle attachments, and the plane of the body of the ilium is ascertained. The trephine is introduced and the outer sieve is fixed on the bone perpendicular to its plane (figure 4.9b). The procedure is then completed by advancing the inner drilling trephine with clockwise and counterclockwise rotary motion while applying steady but gentle pressure. After the trephine has pierced the inner cortex it is rotated completely 2 or 3 times to achieve separation of the specimen from the inner muscle attachment. The trephine is then gently withdrawn with circular, clockwise motions and the outer sleeve is removed. Incised fascia lata is sutured with interrupted absorbable chromic material to avoid herniation of the underlying muscle. The wound is then closed in two layers using chromic suture for the subcutaneous tissue and nylon or silk for the skin. A pressure dressing is applied with elastic tape and the patient is asked to turn over and lie on the incision site for at least 15 to 20 minutes. The patient is also advised to lie on that side as much as possible for the next 24 hours although this is not an absolute necessity. Minor analgesics are usually needed for 1 or 2 days.

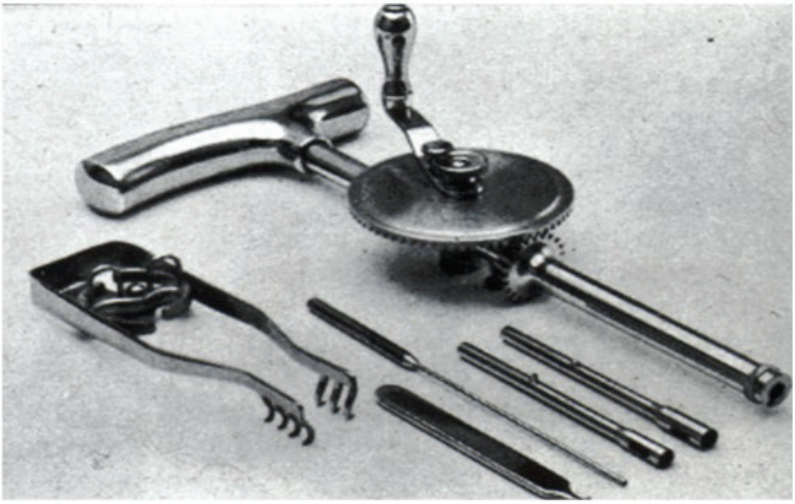


Figure 4.7 Notter Labhart bone marrow trephine biopsy instrument

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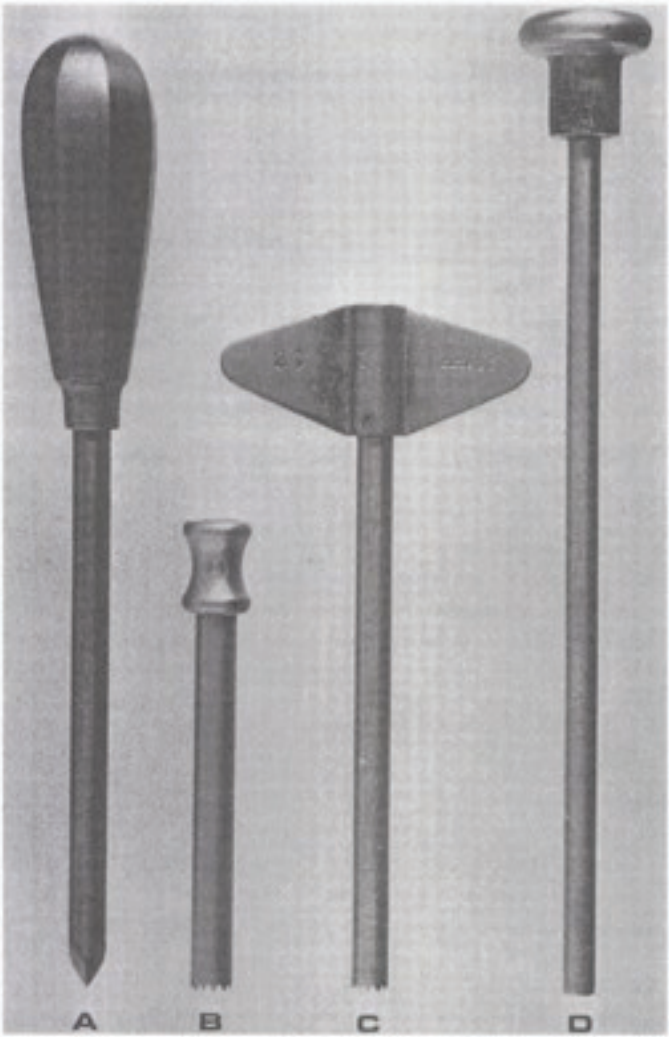


Figure 4.8 Bordier's trephine for iliac crest biopsies. (A) The trochar. (B) External cylinder with serrated edge. (C) The internal cylinder with a serrated edge. (D) The pin used to expel the biopsy from the instrument. (Reproduced from *Bone Histomorphometry: Techniques and Interpretation* by Robert R. Recker (1983), CRC Press, Inc, Boca Raton, Florida.)

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Although transiliac biopsy can safely be performed in 30 to 60 minutes this approach appears to be more elaborate and time consuming. There are a number of complications that are specific to a transiliac biopsy. First, a specimen may dislodge from the trephine during its withdrawal. Second, the cutting end of the trephine may separate from the shaft after penetrating the outer cortex of the ilium. In a few cases the trephine teeth may be bent or distorted as a result of undue pressure applied during the procedure. Third, hematomas are more common with this version than either the vertical or iliac crest approach. Fourth, transient neuropathy due to severance or entrapment of one of the cutaneous branches of the femoral nerve may cause hyperesthesia at the biopsy site. Fifth, pain and discomfort during and after the bone biopsy procedure is slightly more with transiliac than with the iliac crest approach. The transiliac biopsies (7-8 mm width with Bordier trephine) are mainly used by endocrinologists and osteologists for histomorphometric measurements of cortical and trabecular bone.

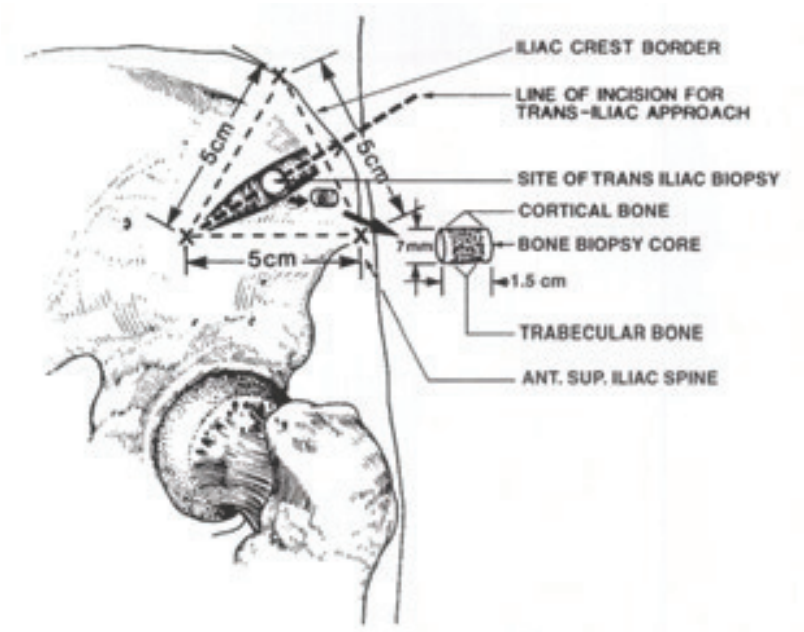


Figure 4.9a Outline of "Bordier's Triangle" and anatomic orientation for transiliac bone biopsy procedure. (Reproduced from *Bone Histomorphometry: Techniques and Interpretation* by Robert R. Recker (1983), CRC Press, Inc, Boca Raton, Florida.)

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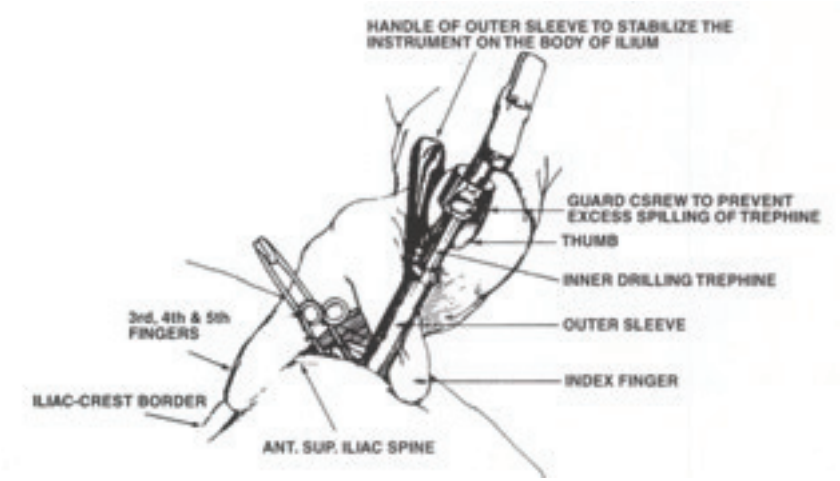


Figure 4.9b Illustrates the positioning and introduction of transiliac trephine and its components. (Reproduced from *Bone Histomorphometry: Techniques and Interpretation* by Robert R. Recker (1983), CRC Press, Inc, Boca Raton, Florida.)

Manually operated Bone marrow biopsy needles

There are several types of needles which are used for obtaining bone marrow trephine biopsy samples from the anterior or posterior iliac crests. Turkel and Bethel described a microtrephine (figure 4.10) (~2 mm bore) which is passed through a hollow introducing needle only slightly larger than a regular marrow aspiration needle. No skin incision is necessary and the instrument was initially designed for sternum. The latter has also been used for anterior iliac crest. However, the cylinders of bone and underlying marrow obtained with these needles are small, and they usually fragment while being prepared for processing and sectioning.

The Westerman-Jensen needle (modified Vim-Silverman needle) (figure 4.11) was designed for obtaining bone marrow biopsy specimens from the posterior iliac crest. With adequate training and experience such needles may provide adequate material but they yield smaller specimens than most other needles and technical failure of securing an adequate sample at any one given attempt remains a serious problem. In addition, the cutting blades are often splayed and occasionally completely destroyed during the procedure even after proper care has been taken. A major disadvantage in addition to delivering a rather small sample and failure to retain the core

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(by the Vim-Silverman and Westerman-Jensen needles) is that not infrequently the specimen is crushed and its architecture is distorted.

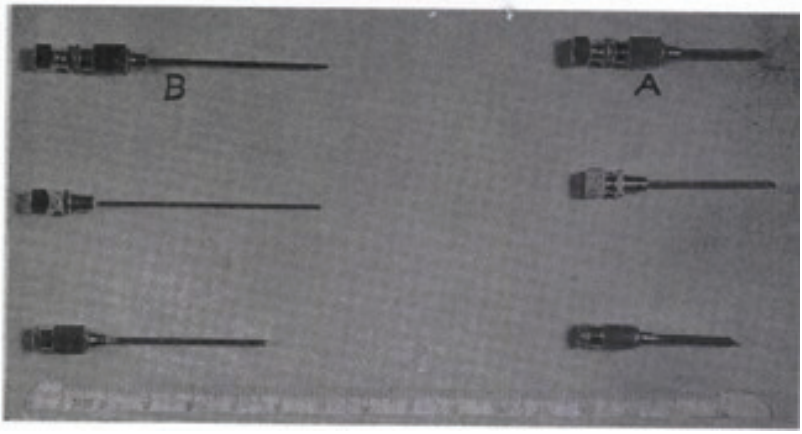


Figure 4.10 Trephine needle for bone marrow biopsy designed by Turkel and Bethel. (Reproduced from *Biopsy of bone marrow performed by a new and simple instrument* by Turkel H and Bethel, F.H.: *J. Lab. Clin. Med.,* 28, 1246-1251, 1943)

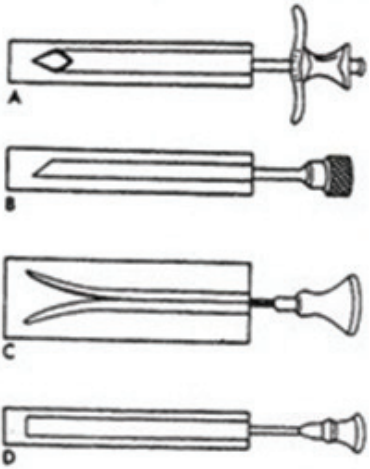


Figure 4.11 Westerman-Jensen bone marrow biopsy needle. (A)10 gauge, 4 1/4 inch long outer cannula. (B) Stylet for outer cannula. (C) Cutting prongs. (D) Stylet for cutting prongs which are used to eject bone marrow specimen. (Reproduced from *Bone Marrow Biopsy* by Perman, V. *et al.* in *Vet. Clin. N. America,* May (4), 293-309, 1974)

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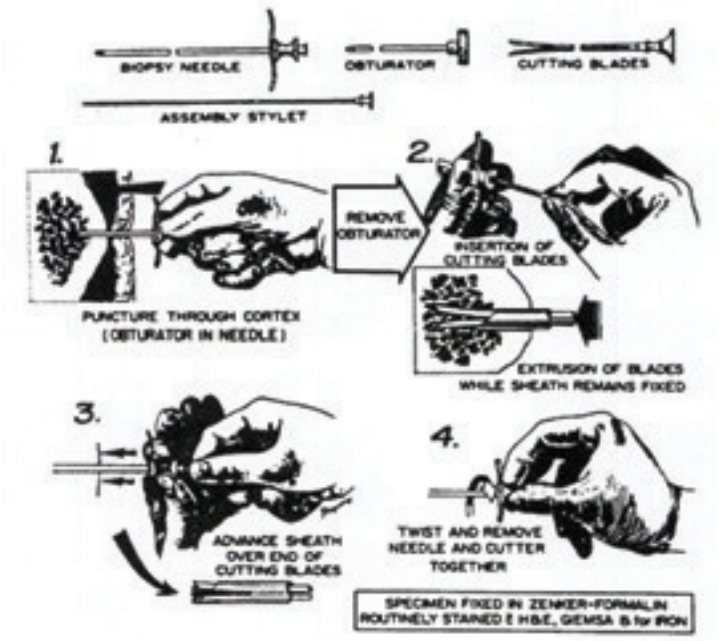


Figure 4.12 Obtaining of bone marrow biopsy from posterior iliac crest with Westerman-Jensen needle. See text for details. (Reproduced from *Needle Biopsy of Bone and Marrow by* Ellis, L.D. *et al., Arch Intern Med.,* 114, 213-221, 1964.)

Maintenance of these instruments is relatively time-consuming and requires that the cutting surface be gently rubbed with the finest possible water paper to ensure a sharp edge after every two or three usages. Any distortion of the delicate blades renders biopsy very difficult and leads to an immediate increase in crush artifact.

The biopsy technique utilizing the discussed needles in which a biopsy specimen is obtained from the posterior iliac crest is similar to that described by McFarland and Dameshek. The procedure, using the Westerman-Jensen needle, is illustrated in Figure 4.12. The needle has finger grips, an assembly stylet, and an obturator which locks in position in addition to being larger and sturdier than the regular Silverman needle. The patient is placed in the right or left lateral recumbent position. The needle with the obturator locked in place is inserted into the previously anaesthetized skin, subcutaneous tissue and periosteum overlying the posterior superior iliac spine. Once the cortex is penetrated and the

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medullary cavity reached, the stylet is unlocked and removed (figure 4.12-1). The cutting blades, with the assembly stylet in place, are then inserted into the outer cannula, the assembly stylet is removed, and the blades advanced into the medullary cavity until the desired depth has been reached (figure 4. 12-2). The outer cannula is then advanced over the cutting blades with entrapment of the tissue (figure 4.12-3), and the entire unit is then removed by a gentle twisting movement (figure 4.12-4).

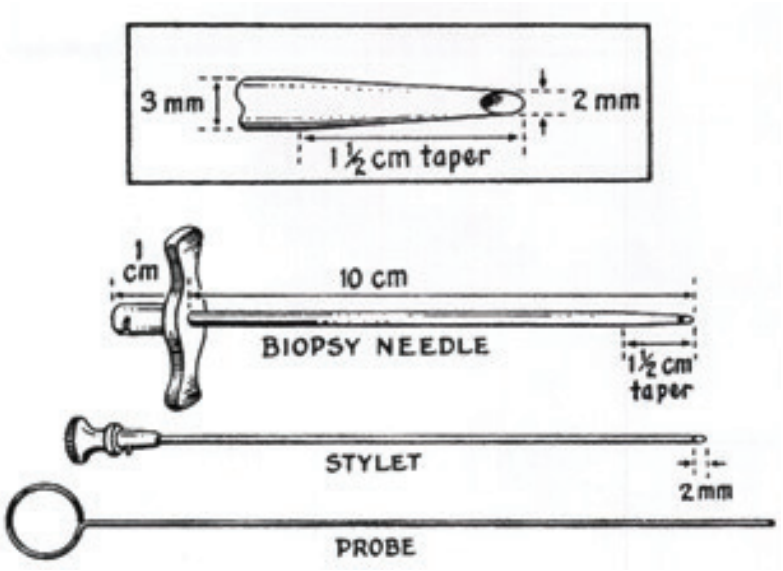


Figure 4.13 Details of the Jamshidi bone marrow biopsy needle. (Reproduced from *A New Biopsy Needle for Bone Marrow by* Jamshidi, K. *et al., Scand. J. Haemal,* 8,69-71, 1971.)

The specimen is removed from the cutting blades by teasing it from the tip before withdrawing the blades through the cannula. Specimens are placed immediately into an appropriate fixative, processed in a routine fashion prior to staining.

The Jamshidi needle (figure 4.13) which has a tapering end appears to overcome most of the problems associated with other bone marrow biopsy needles. Sometimes, however, the sample fractures during its entry into the lumen of the needle and thus only its proximal (outer) segment (7-10 mm) is retrieved leaving the distal (inner) portion within the patient. In other cases the entire biopsy specimen remains firmly attached at its base

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and slips out of the needle (figure 4.14) during retraction thereby requiring a second or third attempt to secure an adequate specimen. Since the Jamshidi technique requires some rocking or sculling movements with the needle to detach the biopsy specimen at its base, the needles as a result, are often bent and damaged.

These disadvantages have been overcome by incorporating a core retention device, as in the Islam bone marrow biopsy needle (figure 4.15 and 4.16 inset). This makes it possible to cut the trabecular connections of bone very cleanly avoiding any crush artefact and also holding the core so that it does not slip out of the needle during the process of extraction (figure 4.17).

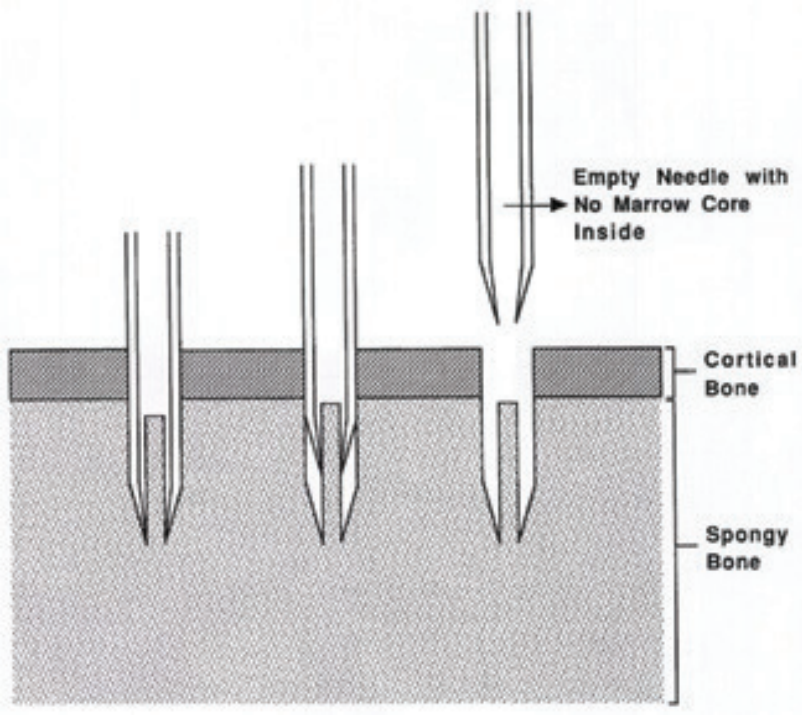


Figure 4.14 Schematic representation of the Jamshidi needle showing absence of any core securing device which may sometimes result in the loss of biopsy specimen during retraction or withdrawal of the needle.

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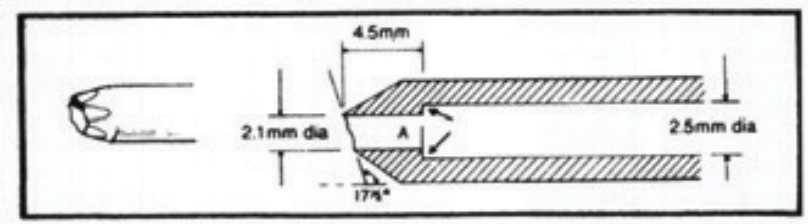


Figure 4.15 Shows details (internal view) of the distal cutting end of Islam bone marrow biopsy needle with core retention device and fluted cutting end.

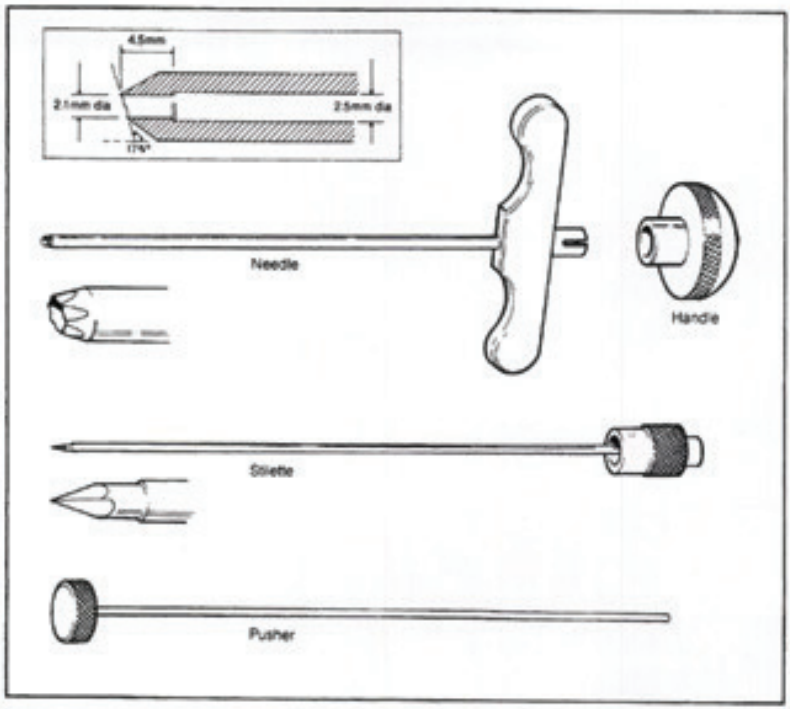


Figure 4.16 Islam bone marrow biopsy needle (see text for details).

Instrumentation

At present, the vast majority of bone marrow biopsies are obtained with either Jamshidi or Islam needles or one of the modified versions of these

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needles. These biopsy needles have proven to be convenient, safe, simple and easy to manipulate and without significant complications. They have now replaced almost all other methods of histologic sampling of bone and bone marrow for hematological and non-hematological diagnosis.

Both Jamshidi and Islam needles are designed to obtain bone marrow biopsies from the posterior iliac crests. In most part they offer an identical procedure except for the Islam technique where no rocking or sculling movements or change in the direction of the tip of the needle are necessary to secure the marrow core before the needle is withdrawn. With the Islam version the needle can be withdrawn with a straight pull (as it has a core retention device) without the fear of losing the core sample.

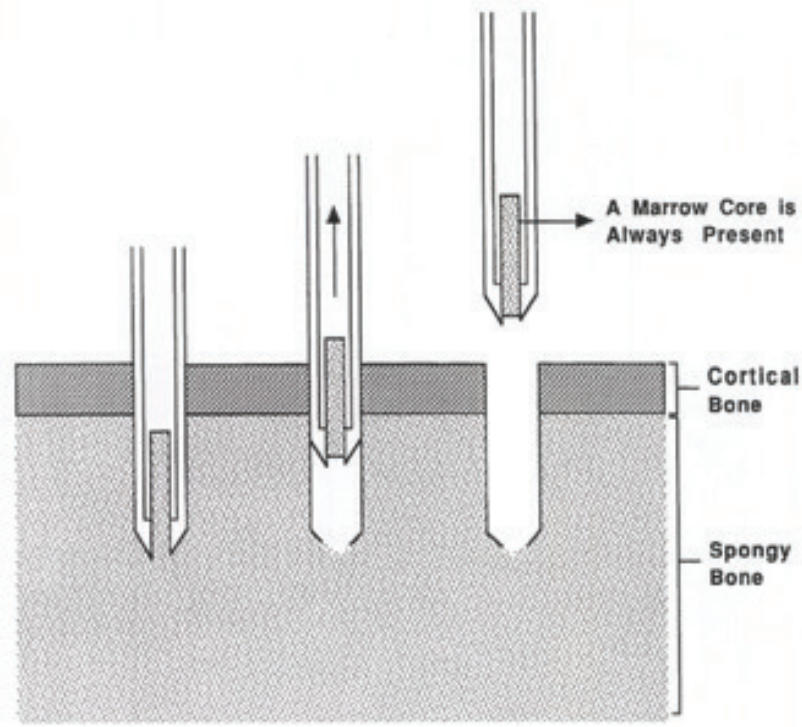


Figure 4.17 Schematic representation of the Islam bone marrow biopsy needle illustrating the core retention device which securely holds the biopsy specimen during withdrawal of the needle.

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The Islam bone marrow biopsy needle

The instrument

The steel instrument[3] (figure 4.16) consists of four parts. *The needle* has an overall length of 122 mm, a uniform external diameter of 3.25 mm, and a constant internal diameter of 2.5 mm except for the 4.5 mm, distal portion where it is beveled, fluted, and has a sharp cutting edge. The internal diameter of this latter segment (2.1mm) is less than the internal diameter of the longer proximal region whose interface with the distal segment ends in a short step of 0.2 mm. This specially designed distal portion cuts the trabecular connections which might keep the biopsy attached at its base and holds on to the biopsy specimen (with a lip like support) so that it does not slip out of the needle during the process of its extraction. The wider internal diameter provides ample free space within the interior of the instrument thus avoiding compression of the tissue and plugging the lumen of the needle; it also allows the specimen to be delivered freely through the proximal end of the needle. The proximal end of the instrument has been fitted with a large metal *T-bar handle* for a firm grip. In addition, it is centrally fitted with a 15 mm high round hollow metal tube to receive the stilette and also to fit the dome handle. *The stilette* is a solid shaft of 2.4 mm in diameter except for the distal portion where its diameter is 2.00 mm to fit the narrower distal cutting end. It terminates with a 3.0 mm long three- faceted sharp-pointed cutting tip which projects beyond the end of the needle in order to protect the cutting edge of the needle and to provide a means of easy penetration of the soft tissue and bony cortex.

The stilette has a round fitting for both the domed segment and the T-bar of handle of the needle as well as a 10 mm outer shaft with serration for grip. The *pusher* (probe) is used for extrusion of the biopsy from within the needle. It is a solid shaft 1.9 mm in diameter and has an overall length of 140 mm. Its distal end is blunt and the proximal end is fitted with a 5 mm thick, flat, round knurled disc 15 mm in diameter. The *domed* segment of the T-bar handle is a semicircular smooth, solid plastic, 30 mm in diameter, 15 mm deep and has a 5 mm lightly milled edge. It rests snugly in the palm of the hand and avoids palmar pain and blister formation during the biopsy procedure. This is particularly noteworthy during the coring of a very hard bone or bone of increased density.

[3] The instrument is available in several different sizes (bore diameter and lengths). Some minor changes have recently been made to this original design.

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Schematic representation of the biopsy procedure using the Islam bone marrow biopsy needle (Figure 4.18)

1. The outer needle (a) with the stilette (b) in place is inserted down to the bone.

2. The cortex of the posterior ilium is then penetrated with a forward thrust and gentle rotary motion of the needle with the stilette in place. Once penetration has been achieved, the stilette is withdrawn.

3. The needle is then advanced with a slow, steady and controlled clockwise and counter-clockwise rotary motion. When an adequate depth (15-20 mm) is reached, the needle is rotated several times along its long axis and then slowly withdrawn with a straight pull. Only gentle alternating rotary motions are necessary to facilitate the withdrawal of the needle. No accessory movements (e.g. rocking or sculling) or change in the direction of the tip of the needle to break the marrow core at its base is necessary.

Schematic representation of the biopsy technique using the Islam bone marrow biopsy needle (Figure 4.19)

The schematic representation of the biopsy technique shows the needle wall (a), the space between the core and the internal wall of the needle (b). The free space between the marrow core and the internal wall of the needle helps prevent compression of the tissue and plugging the lumen of the needle. It also allows easy delivery of the core through the proximal end of the needle. The specially tooled distal cutting end (c) cuts the bony trabecular connections to the core and also assists in the retention of the core during its extraction (so that it does not slip out of the needle during its withdrawal). The base of the marrow core (d) is also shown in the illustration.

Comparison of the Islam and other (conventional) bone marrow biopsy needles

Basically, there are three types of manually operated bone marrow trephine biopsy needles:

Figure 4. 20 shows a representative of a class of needles which are straight hollow tubes with beveled or serrated cutting ends. These do not have a

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core retention device and as a result when the marrow core is firmly attached to its base it may slip out of the tube and remain in the patient when the needle is withdrawn. Another important drawback of such needles is the fact that there is no free space between the specimen and the internal wall of the needle. As a result, a biopsy procedure with this type of needle can produce a considerable amount of crushing. Due to the absence of a free space (between the marrow core and the internal wall of the needle) the biopsy sample may also become impacted within the lumen of the needle. In such circumstances it may be difficult to push the biopsy sample out of the needle. Attempt to force the specimen out can produce a severely distorted, crushed and mangled sample as shown in Figure 4.21.

Figure 4.22 illustrates the bone marrow biopsy technique by Jamshidi needle. In the early 1970's Dr. Khosrow Jamshidi conceived the idea to provide a free space between the internal wall of the needle and the marrow core in order to avoid crushing and promoting easy delivery of the tissue through the proximal end of the needle. For some time the Jamshidi needles appeared to offer the best compromise between the straight hollow needles (Figure 4.20) and the much larger Notter Labhart, Bordier's trephines (Figures 4.7 & 4.8)) and Burkhardt's electric myelotomy drill (Figure 4.4). But in a significant proportion of the cases the Jamshidi specimen becomes fractured (as shown in Figure 4. 23) while it is being extracted and only the smaller proximal (outer) portion (7-10 mm) is retrieved. The Jamshidi needle also does not have any core retention device and as a result sometimes when the needle is withdrawn the biopsied sample slips out of the needle and remains inside the patient thus requiring a second or third attempt to secure a biopsy sample. These repeat biopsy procedures are not without risk and are carried out at the expense of potential pain and suffering to the patient.

One of the most important drawbacks of Jamshidi or similar kind of trephine biopsy needles without any core retention device is the fact that as the biopsy needle is being withdrawn from the patients body the biopsy specimen contained within the lumen of the needle may start to slip out of the needle (as illustrated in figure 4.24 – 4.27) and ultimately a good portion of the biopsy specimen is caught and remains buried in the skin and soft tissue. If and when this happens (see figure 4.26 and figure 4.27) it can be dangerous for the patient as there is definite fear of implanting/disseminating the disease outside the bone marow cavity.

The Islam needle (figure 4.16) was developed to incorporate the advantages of the Jamshidi version of the bone marrow biopsy needle as

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well as to include newly conceived features (core retention device) to negate its shortcomings. Because of the presence of core retention device the biopsied tissue is always retained within the lumen of the needle and cannot slip out of the needle during the process of its extraction.

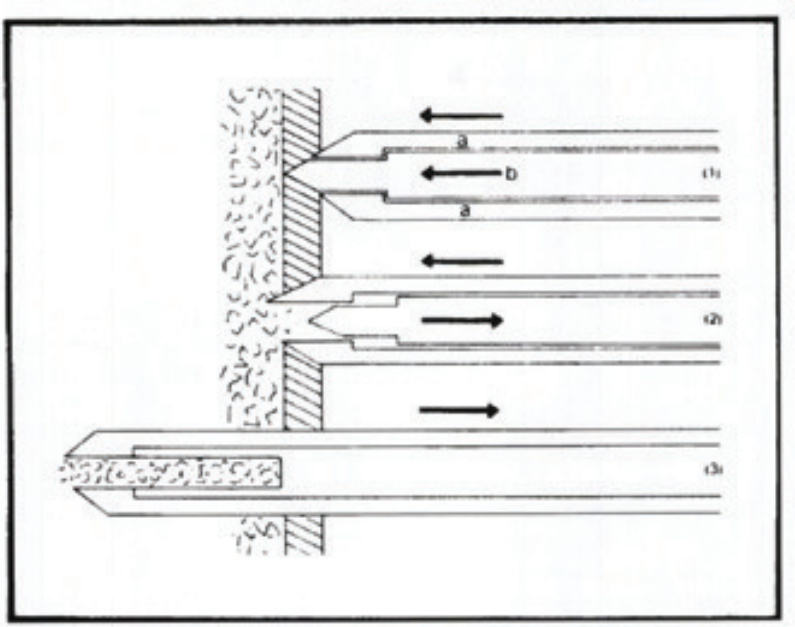


Figure 4.18 Schematic representation of the biopsy procedure. The outer needle (a) with the stilette (b) is inserted down to the bone (1). The cortex over the posterior ilium is then penetrated by gentle rotary motion of the needle with the stilette in place and once this penetration has been achieved, the stilette is withdrawn (2). The needle is then advanced with slow, steady and controlled clockwise-counterclockwise rotary motion. When an adequate depth is reached the needle is rotated several times along its long axis and then slowly withdrawn with a straight pull. No rocking, skulling or gyratory movements are necessary.

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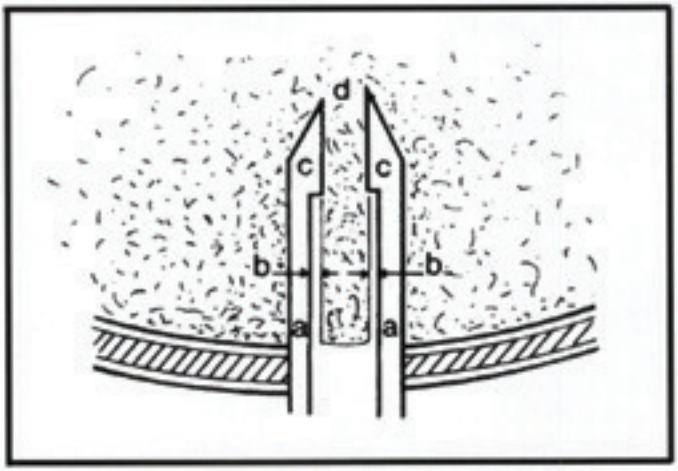


Figure 4.19 Schematic representation of the biopsy technique. (a) the needle wall, (b) space between the core and internal wall of the needle which avoids compression of the tissue and plugging the lumen of the needle. It also allows easy delivery of the core through the proximal end of the needle. (c) Specially tooled distal cutting end which cuts all the trabecular connections of the core with its base and holds the core during its extraction so that it does not slip out of the needle. (d) Base of the marrow core in the spongy bone.

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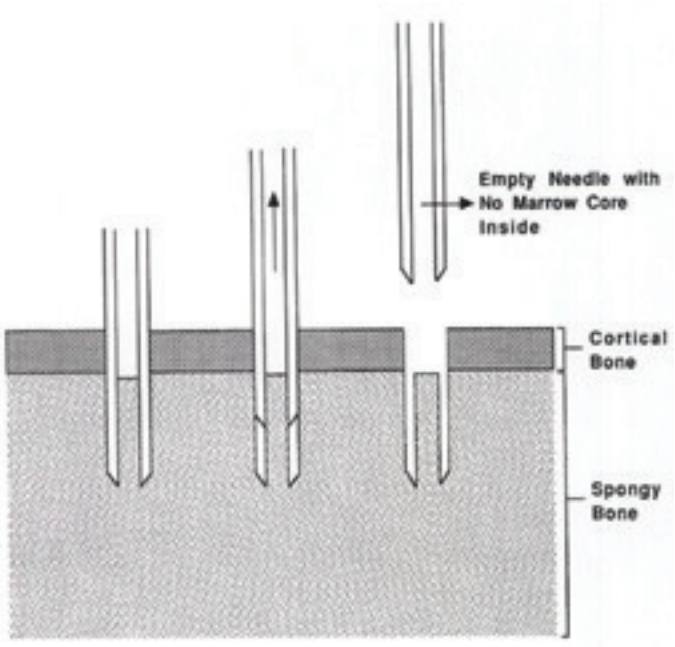


Figure 4.20 Schematic representation of the conventional bone marrow biopsy needle. Note the uniform diameter of the lumen of the needle and the absence of any free space between the marrow core and the internal wall of the needle and no core capturing device.

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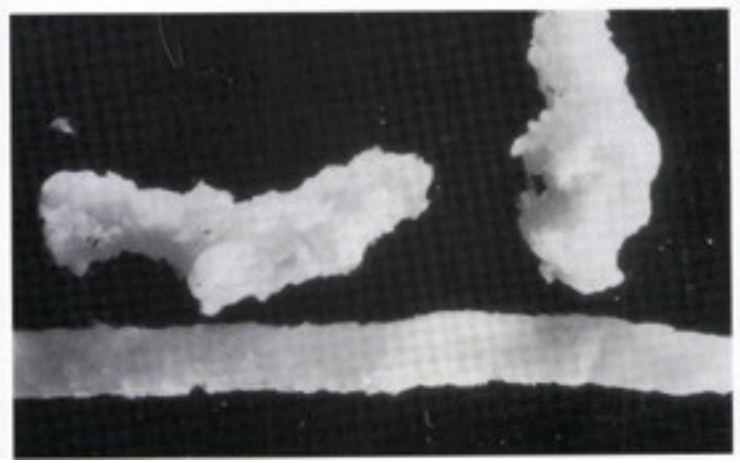


Figure 4.21 Shows two severely crushed bone marrow biopsy samples (upper) which resulted in trying to force the impacted sample out of the needle. Lower: an undamaged biopsy sample.

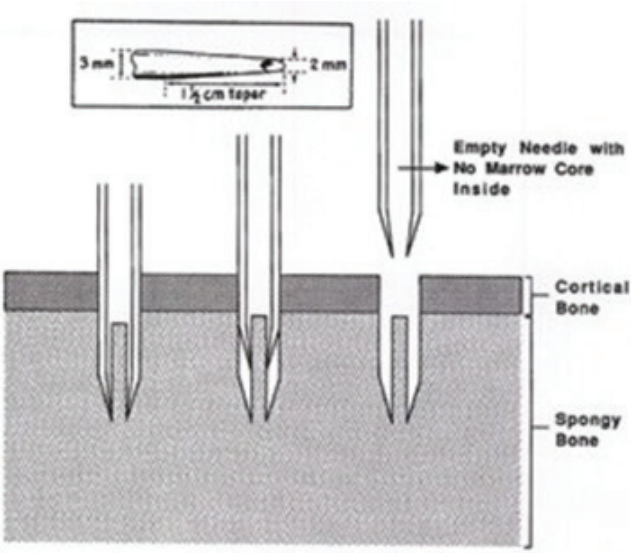


Figure 4.22 Schematic representation of the Jamshidi needle technique. Note the presence of free space between the marrow core and the internal wall of the needle. The inset illustrates the narrower distal end and wider proximal portion of this needle.

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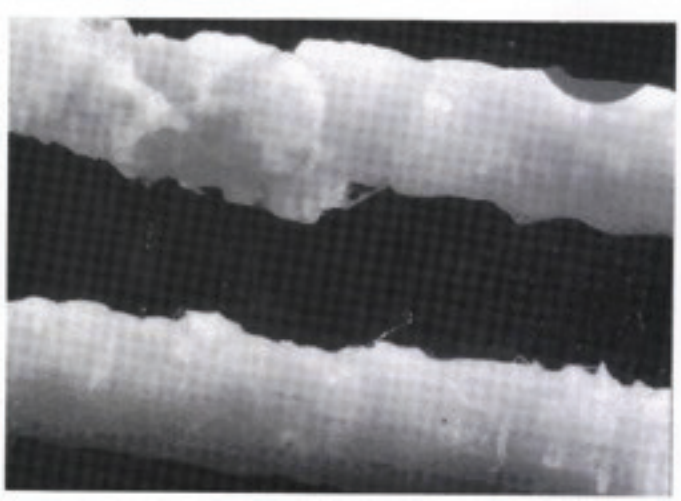


Figure 4.23 Upper: Illustration of fractured Jamshidi derived specimen. Lower: An intact, undamaged biopsy sample.

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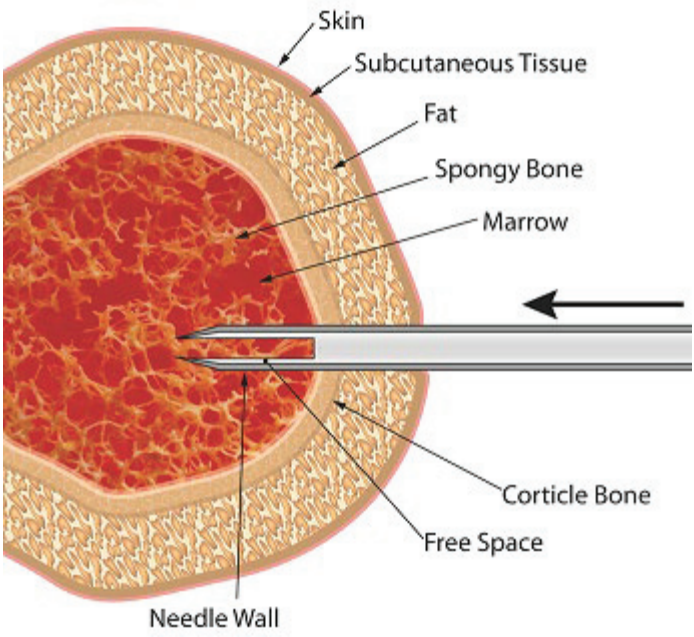


Figure 4.24 This illustration shows a biopsy procedure using a Jamshidi needle ***without*** a core retention device. The needle has been introduced through the skin, soft tissue and cortical bone and into the marrow cavity. It shows the biopsy specimen sitting within the lumen of the biopsy needle.

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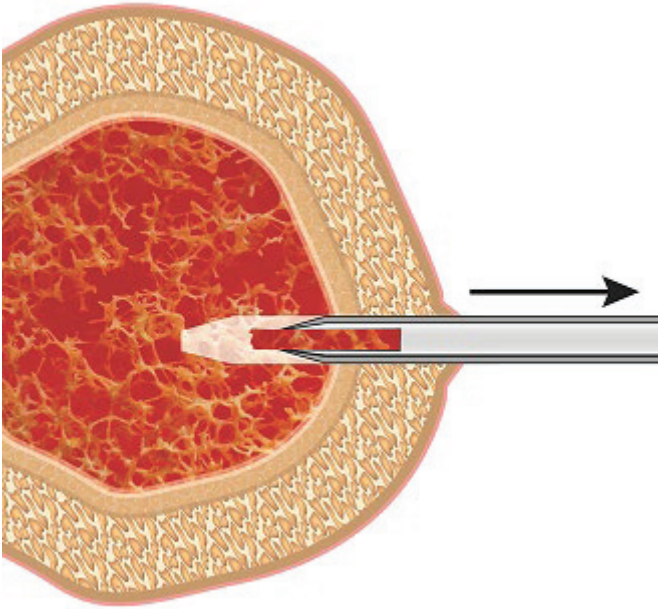


Figure 4.25 This illustration shows the biopsy needle (containing the biopsy specimen) as it is being withdrawn from the patient's body. It demonstrates that due to the lack of a core retention device the biopsy specimen has started to slip out of the needle.

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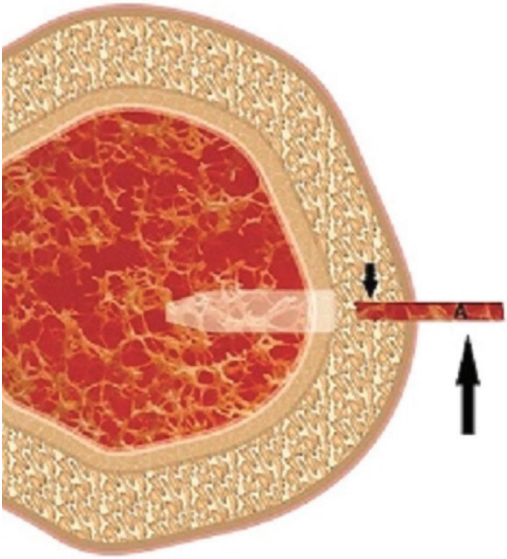


Figure 4.26 This illustration shows a portion of the biopsy specimen that is trapped in the skin and subcutaneous tissue (short arrow) and a portion of the biopsy that remains on the surface of the skin once the needle has been completely withdrawn (long arrow)

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Figure 4.27 This Illustration shows the actual phenomenon that the author has encountered on several occasions with some of his patients. This can be very hazardous as a portion of the biopsy that remains buried/trapped beneath the skin and soft tissue may disseminate the disease outside the bone marrow where the biopsy remains lodged.

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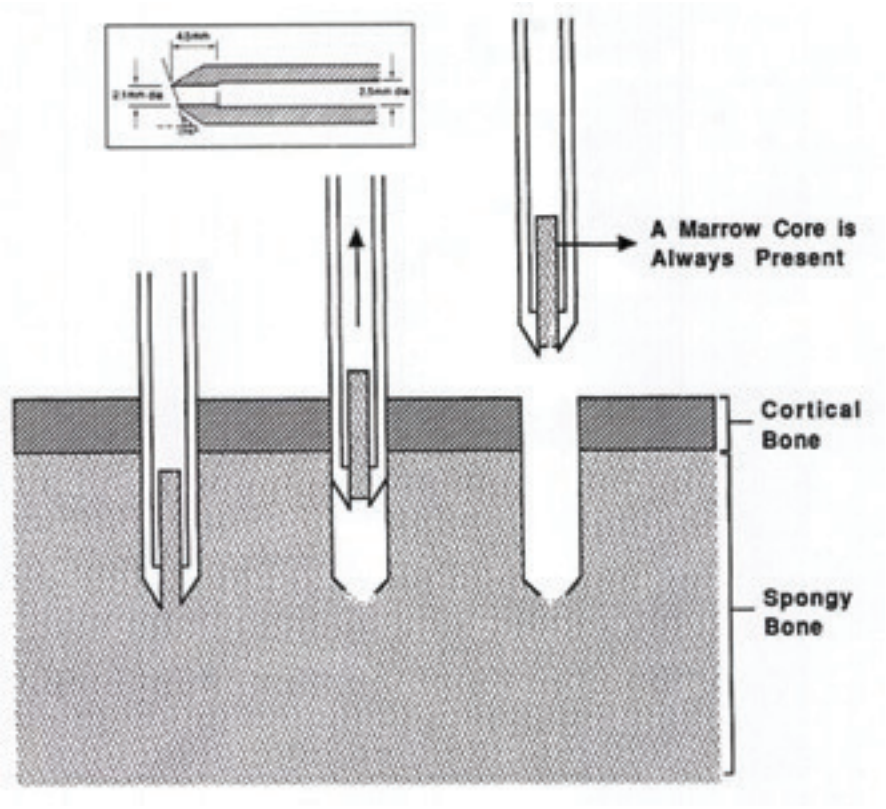


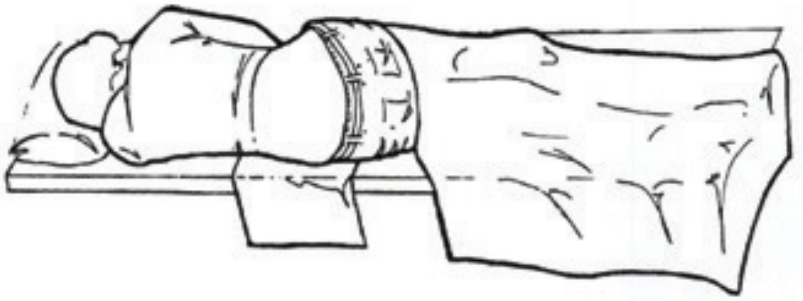
Figure 4.28 Schematic representation of the Islam needle technique. Note the presence of free space between the marrow core and the internal wall of the needle and the core retention device. The inset illustrates the core retention device in greater detail.

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Biopsy Procedure

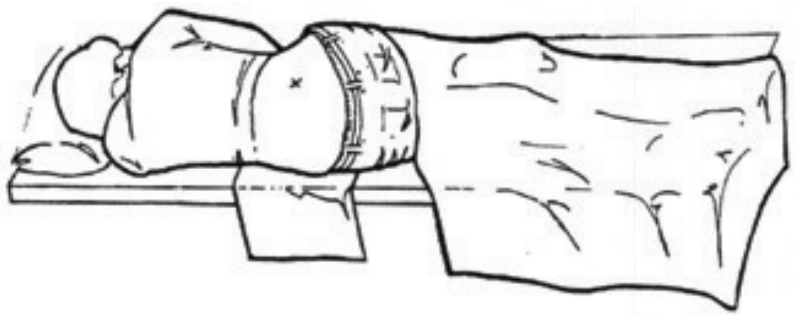


1. Site of the puncture — In adults the bone marrow biopsy is usually performed on the right or left posterior iliac crests. They form the lateral points (arrows) of the rhomboid of Michaelis and can be easily located.

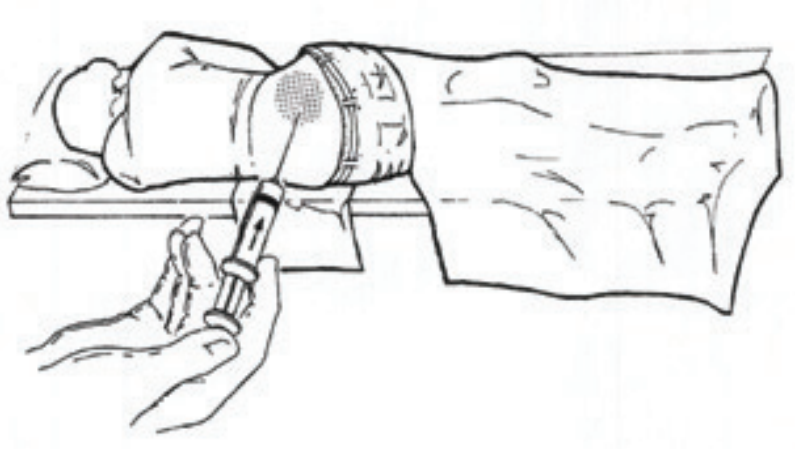


2. Position of the patient — place the patient in a right or left lateral decubitus position with the knee tops drawn up and back comfortably flexed or in a prone position with a pillow beneath the hips.

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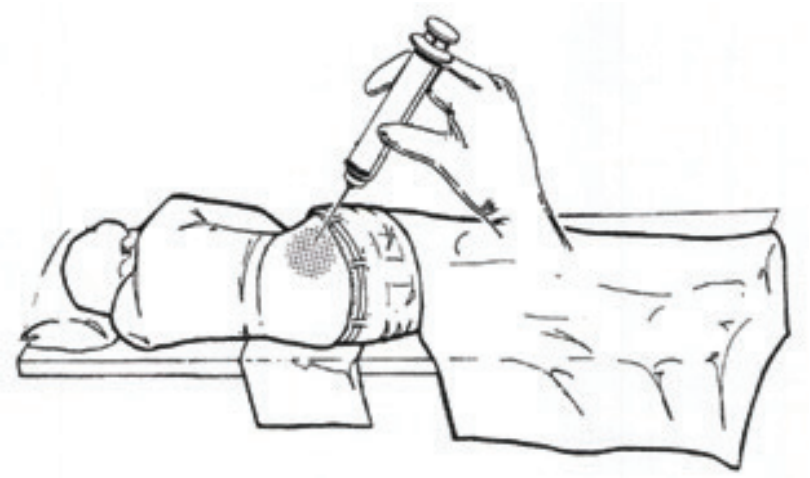


3. Once the area of the posterior iliac crest (the one selected for obtaining a bone marrow biopsy sample) is located by palpation, mark the area with thumbnail pressure and prepare the region with alcohol and iodine, and then drape.

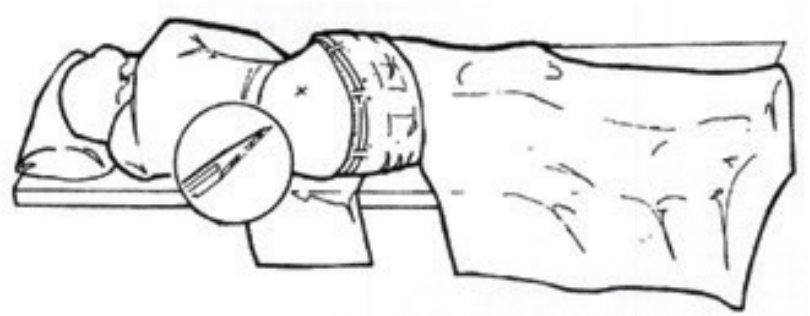


4. Infiltrate the skin, subcutaneous tissue and periosteum with a local anesthetic (using a 25 gauge 5/8 inch needle for skin and 21 gauge 1 1/2 inch needle for soft tissue, muscle and periosteum). Provide ample time for anesthetic to take effect.

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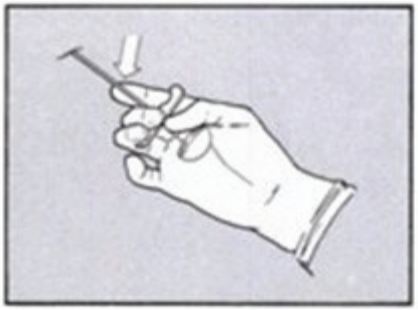


5. It is useful to probe the site with a 21 gauge 11/2 inch needle to see if the area is adequately anaesthetized and roughly to outline the borders of posterior iliac crest. This also gives an indication as to the depth at which the bone will be struck and desired angulation of the needle.



6. Make a small (3 mm) skin incision with a pointed scalpel blade over the marked area.

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7. Holding of the biopsy needle — Hold the needle assembly with its domed handle rested in the palm, middle and third finger over the transverse handle, and the index finger against the shaft of the needle. The application of the index finger over the shaft (arrow) helps stabilize the needle and permits proper control.



8. With the stilette and handle in place — introduce the needle through the incision and slowly advance it pointing towards the anterior superior iliac spine.

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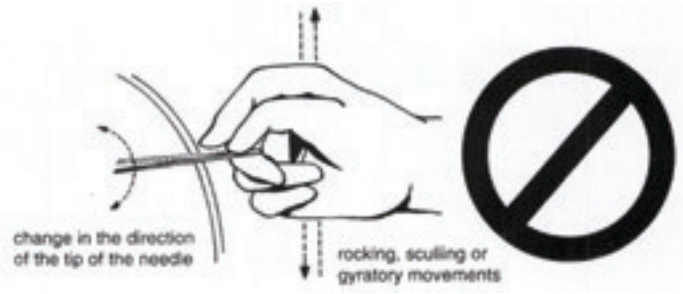


9. It is useful to put one hand over the anterior iliac crest with the middle or index finger on the anterior superior iliac spine as shown in the illustration. This approach not only helps stabilize the pelvis and patient in general but also help in the guidance of the needle towards the anterior superior iliac spine.

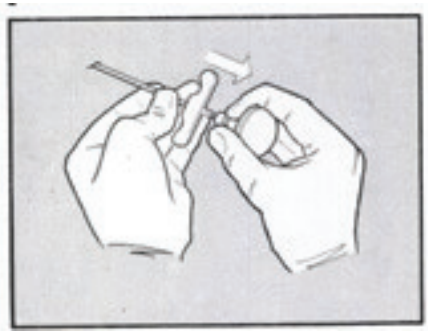


10. When the posterior iliac crest is reached, it is then penetrated by a controlled forward thrust and gentle rotary motions of the needle. Penetration beyond the cortex with the stilette in place should be avoided, as it will reduce the length of the marrow core that will be obtained.

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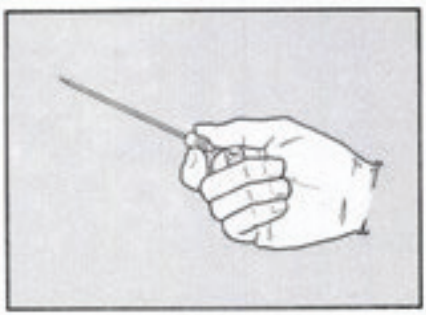


11. While using the Islam bone marrow biopsy needle no lateral force should be applied during the procedure and no gyratory, rocking or sculling movements or change in the direction of the tip of the needle (as shown in the illustration) is necessary to secure the marrow core. This practice (which is essential for the Jamshidi technique) is not only unnecessary (as the Islam needle has an in built core retention device) but may also damage the needle.

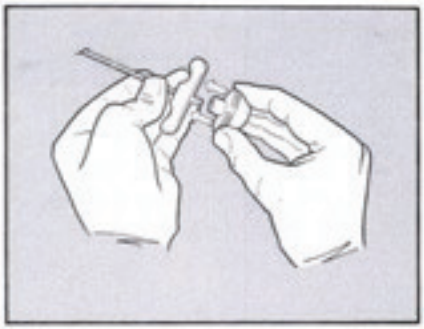


12. Once the cortex is penetrated, the needle becomes locked in the cortical bone. The needle is then held in this position with the left hand (as shown in the illustration) while the right hand is used to withdraw the stilette and domed handle.

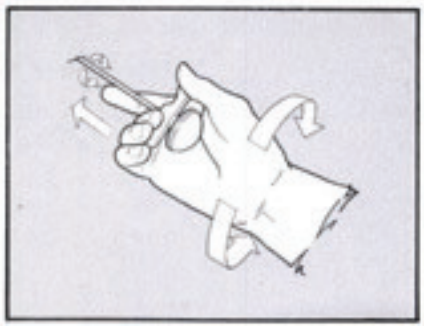
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13. Remove the stilette from the domed handle and place it on the tray.

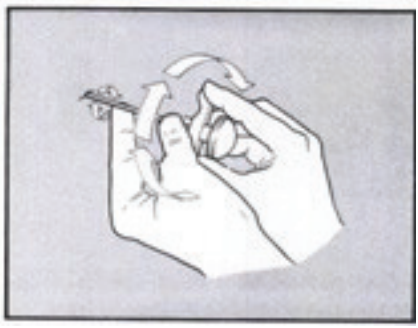


14. Replace the domed handle on the needle mount.



15. Advance the needle gently with slow, steady and controlled clockwise and counter-clockwise rotary motions until an adequate depth is reached. No lateral force should be applied to the needle during this procedure. Failure to observe this could result in damage to the needle or injury to the patient.

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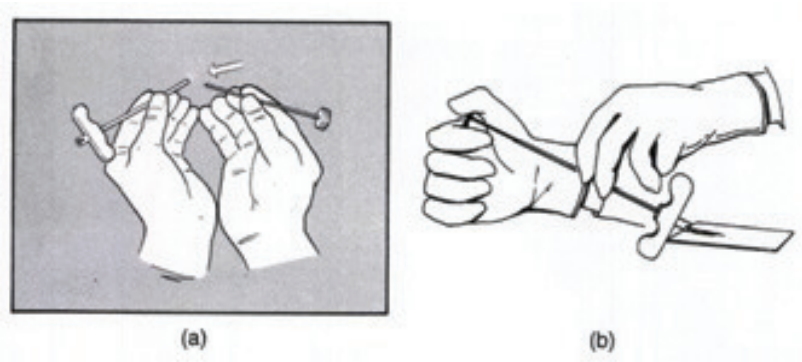


16. Rotate the needle completely (clockwise or counter-clockwise) for several times along its long axis to sever all the trabecular connections at the base of the marrow core.

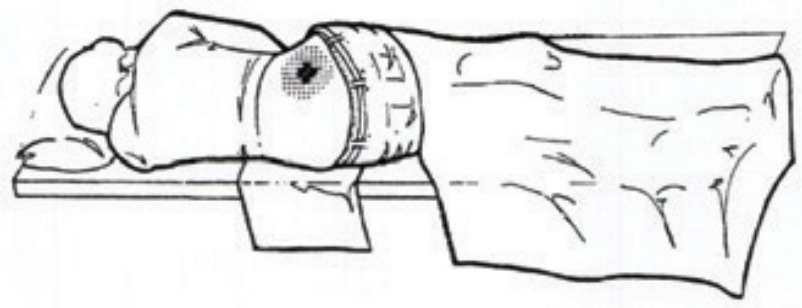


17. Withdraw the needle with a straight pull without the fear of losing the core sample. Because of the core retention device the Islam needle always holds the core captive during withdrawal of the needle. Only gentle alternating rotary motion is necessary to facilitate the withdrawal of the needle. Unlike the Jamshidi and other needle techniques the Islam needle procedure does not require any accessory (rocking, sculling etc.) movements or change in the direction of the tip of the needle to break the marrow core at its base.

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18. Once the needle is withdrawn the biopsy specimen is removed with a blunt probe which must be introduced through the distal cutting end of the needle. During the removal of the specimen, hold the needle and the probe near their tips as illustrated (a). This stabilizes the needle and the probe, prevents damage to the cutting end of the needle and helps easy delivery of the marrow core through the proximal end of the needle (b).



19. After the biopsy procedure, press the edges of the wound together with an adhesive tape. Apply a gauze dressing on the top of the adhesive tape and instruct the patient to lie on his/her back for 10 to 15 minutes, or longer if the patient has a low platelet count.

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CHAPTER 5

SINGLE-USE BONE MARROW BIOPSY NEEDLE

Introduction

The trend towards single-use (disposable) bone marrow biopsy needles instead of re-usable ones has been one of continuous evolution. Where body fluids are involved, especially blood and bone marrow and the concerns of HIV and hepatitis for example, this trend has been far quicker. As the world markets have expressed their reluctance to reprocess re-usable products because of the fear of contamination of both patients and diagnostic specimens, the drive for single-use bone marrow needles has been a constant demand by physicians and surgeons, hematologists and oncologists in particular.

It is now clear in both medical and scientific community that bone marrow biopsy plays an important role in the investigations, diagnosis and management of various haematological as well as non-haematological malignant conditions. Since the development of an improved type of bone marrow biopsy needle by Khosrow Jamshidi and its introduction in a disposable form, there has been a considerable growth in its use. The value of bone marrow biopsy, particularly in different haematological conditions is now well established. However, loss of bone marrow core samples during the process of its extraction, in other words, failure to retain the complete biopsy sample within the lumen of the needle after the needle is withdrawn from the patient's body has been a serious continuing problem. The importance and significance of this particular problem, i.e. the loss of the biopsy sample during the process of its extraction was recognised many years ago and was successfully addressed by the introduction of a re-usable Islam bone marrow biopsy needle with the *core retention device* as described in the previous chapter. But until now, this particular needle had not been available in a disposable form because of the complex nature of its production which made it impossible to produce it in large numbers and the high manufacturing costs which made it difficult for such a product to be commercially viable. In recent years, new technology has

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emerged by which such needles can be manufactured not only in large numbers but also economically. Taking advantage of this new technology, a new single-use bone marrow biopsy needle that retains the original principle of *core retention* device has now been produced. A new feature, external serrations for ease of boring through the dense cortical bone and to facilitate its smooth entry into the spongy haematopoietic bone, has also been added to the design of the needle. In addition, a new and easy technique of removing the biopsy sample from within the lumen of the needle has been introduced. In this technique, the same stilette that occupies the needle during its entry into the marrow cavity, is used as a stilette-pusher in sample removal. Thus the need for an additional pusher which has been the norm till now to remove the biopsy sample from within the lumen of the needle has been eliminated. This is the first time that such a technique has been introduced and it is a significant departure from the conventional method of using an extra/additional part (pusher) to push the biopsy sample out from within the lumen of the needle. A spacer-guide which is placed in between the plastic dome of the needle and the stilette cap to improve the ergonomics of the design and overall handling of the needle has also been an added new feature to this system. This spacer-guide has been specially designed to receive the distal cutting end of the needle on one side and the front end of the stilette on the other side. In this way, the operator can utilize the spacer as a guide to introduce the stilette into the mouth of the needle and help expel the biopsy sample through the proximal end.

Following withdrawal, sometimes redundant and displaced extra bony soft tissue covers the distal opening end of the needle. Because of the presence of such extraneous bony soft tissue around the distal opening end of the needle, it is sometimes difficult to introduce the conventional blunt pushers into the biopsy needle. In such circumstances, this newly designed spacer-guide can be extremely useful in facilitating the introduction of the stilette into the mouth (distal opening end) of the biopsy needle and help easy, atraumatic and effortless delivery of the biopsy sample through the proximal end.

In comparison to blunt pushers the stilette being ‘trocar point’ can find its way into the biopsy needle much more easily even when its mouth is covered/obscured by extra bony and soft tissue.

Instrument

The instrument (figure. 5.1) consists of three parts:

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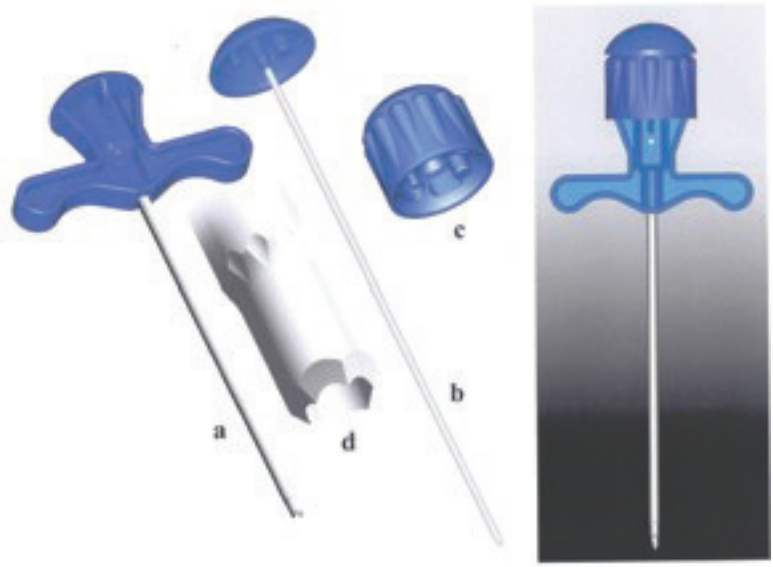


Figure. 5.1 The needle (a), stilette (b), and the spacer-guide (c) .The inset shows a fully assembled needle and (d) shows a magnified profile of the distal cutting end of the needle.

(a) The standard needle (figure 5.1a) has an overall length of 100 mm, an uniform external diameter 3.25 mm, and a constant internal diameter of 2.5 mm except for the 3.5 mm, distal portion where it is narrowed and has multiple outside serrations (figure 5.2 e), and has a sharp cutting edge (figure. 5.2 h). The internal diameter of this portion (2.1 mm) is less than the overall internal diameter and begins with a short slanted step of 0.2 mm. This specially designed distal portion cuts all the trabecular connections at the base of the marrow core which might keep the biopsy specimen firmly anchored to its base and also holds on to the biopsy specimen so that it does not slip out of the needle during the process of its extraction. The larger internal diameter of the needle provides free space within the interior of the instrument, thus avoiding crushing and compression of the tissue as well as plugging the lumen of the needle. It also allows easy delivery of the biopsy sample through the proximal end of the needle. The introduction of the needle through the hard cortical bone may be hampered by the wider proximal portion of the needle, which may act like shoulder. To prevent this obstruction and help easy and smooth entry of the needle into the marrow cavity, multiple outside serrations are

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provided at the junction of the distal narrower portion with its adjoining proximal wider portion. These serrations provide a means of drilling as the needle is being rotated by clockwise and counter-clockwise rotary motions and introduced/advanced through the hard cortical bone. The proximal end of the needle has been fitted with a large plastic T—bar for a firm grip and is dome-shaped to fit the distal end of the spacer-guide.

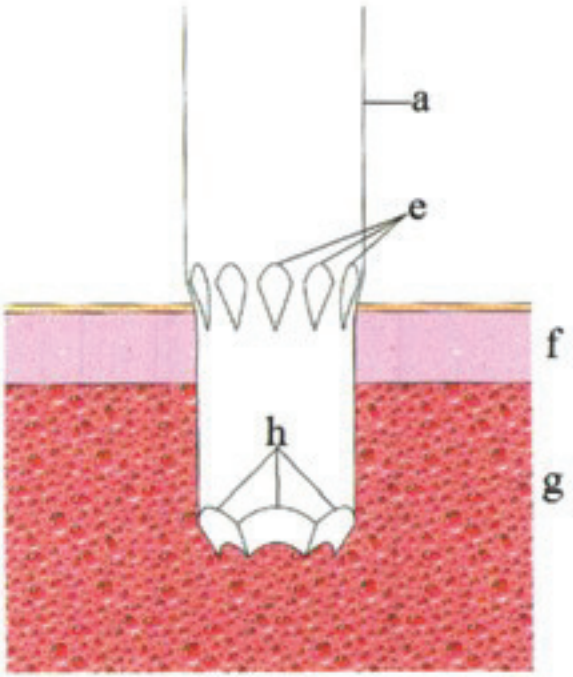


Figure 5.2 Schematic representation of the distal cutting end of the needle showing details of external serration's that facilitate drilling/cutting through the hard cortical bone (f) and helps to provide an easy and smooth entry of the needle into the marrow cavity (g). The sharp cutting facets of the distal end of the needle (h).

(b) The stilette (figure 5.1b) is a solid shaft of 2.1 mm in diameter. It ends with a 3.0 mm long three-faceted, sharply- pointed tip which projects beyond the cutting edge of the needle in order to protect the sharp cutting edge of the needle. The stilette also provides a means of easy penetration of the skin, soft tissue and dense cortical bone. The proximal end of the stilette is fitted with a plastic cap which fits the proximal end of the spacer-guide.

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(c) The spacer-guide (figure 5.1c) is a solid mass of plastic 20 mm long and 30 mm wide in its maximum diameter. Its proximal portion is convex to receive the cap of the stilette and the distal portion is concave to fit on to the plastic dome of the needle. The center of the distal portion of the spacer-guide is funnel shaped to receive and anchor the distal cutting end portion of the needle and the center of the proximal (top) portion of the spacer- guide is also funnel shaped to receive and guide the stilette in place for proper alignment with the needle and for easy dislodgement and extrusion of the biopsy sample through the proximal end of the needle.

Biopsy Procedure (Figures 5.3 & 5.4)

The instrument has been designed to obtain bone marrow biopsy specimens from the right or left posterior iliac crests. The technique is very similar to what has already been described earlier in chapter 4. The patient is placed in a right or left lateral decubitus position with the top knee bent forward and drawn up and back comfortably flexed or in the prone position with a pillow beneath the hips. The site of posterior iliac crest is identified by palpation. The area over the posterior iliac crest is then prepared with betadine, alcohol and draped. Then the skin, subcutaneous tissue, and the periosteum are infiltrated with local anaesthetic. A small 3 mm skin incision is made with a sharp pointed scalpel blade. The biopsy needle with the spacer-guide and stilette in place is advanced slowly through the incision, pointing towards the anterior superior iliac spine and when the posterior iliac crest is reached it is then penetrated by rotary motions of the needle. Once the cortex is penetrated the needle gets locked in the bone. The stilette is then removed with one hand while holding the needle and the spacer-guide in place with the other. The biopsy needle is then advanced with slow, steady and controlled clockwise-counterclockwise rotary motions until an adequate depth is reached. The biopsy needle is then rotated completely several times about its long axis to sever all trabecular connections at its base and break the core sample loose from the surrounding spongy bone and is then slowly withdrawn with a straight pull and gentle alternating rotary motions. No rocking, sculling or change in the direction of the tip of the needle is necessary. Once the needle is withdrawn, the spacer-guide is attached to the distal cutting end of the needle (figure. 5.5). The biopsy specimen is then removed with the stilette that is introduced through the opposite side of the spacer-guide (figure. 5.6). The new mechanism by which the core biopsy specimen is retained within the lumen of the needle is an excellent demonstration of how well the core retention device works. Because of this the biopsy specimen on

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occasion may get tightly lodged in the narrower distal portion of the needle particularly if the cortical bone is trapped here. In such circumstances a simple rotary movement of the stilette while gently pushing it forward (as shown in figure 5.7) will easily release the core sample. A detailed procedure of the attachment of the needle and the introduction of the stilette to spacer-guide to remove the biopsy specimen is illustrated in figure 5.8.

Once the biopsy procedure is complete, the edges of the wound are pressed together with an adhesive tape. A gauze dressing is applied, and the patient is instructed to lie on his/her back for 10-15 minutes or longer if the patient has a low platelet count or other bleeding disorder.

On clinical testing an adequate biopsy sample was obtained with this needle at each attempt. Bony trabeculae were cut cleanly and crushing artefact was almost negligible even at the edges of the biopsy specimens. The quality of the specimen obtained with this needle has been excellent (figure 5.9). Although the length of the specimens obtained at each attempt varied from 15 to over 25 mm, there never was any loss of specimens. Since this needle requires the use of a trocar point stilette rather than a blunt pusher in order to push out the biopsy sample out of the needle, this did not appear to cause significant microscopic trauma to the distal end of the biopsy specimens. The technique is considered to be simple and does not require much manipulation of the biopsy needle within the patient in order to secure a biopsy specimen, as a result, patient tolerance was high.

The spacer-guide is a new addition to this technique and it can be used to facilitate the extrusion of the biopsy specimen. Its distal (bottom) portion is designed to receive the distal narrower portion of the needle and the proximal (top) portion is designed to receive the front (pointed) end of stilette. This guiding system helps proper alignment of the stilette (used as a pusher in this case) with the mouth (distal end opening) of the needle and eases the dislodgement and removal of the biopsy sample through the proximal end of the needle. In many cases, there are adherent and redundant extra bony soft tissue that obscures the mouth (distal end opening) of the needle after its withdrawal from the patient's body. Consequently, because of the presence of this redundant extra bony soft tissue at and near the mouth of the needle, conventional flat/ blunt pushers cannot readily enter this area and often slip off the needle when attempt is made to push the biopsy sample out of the needle (figure 5.10 A). In such circumstances, the trocar pointed stilette of the new needle can easily find its way into the mouth of the needle (figure. 5.10 B). In addition the

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spacer-guide is an excellent means of reducing the risk of sharps injury to the operator whilst manoeuvring the tip of the stilette into the mouth of the biopsy needle. Furthermore, the biopsy technique is simple and does not require any manipulation of the biopsy needle within the patient in order to secure the biopsy sample. This in turn makes this potentially uncomfortable procedure more tolerable for the patient.

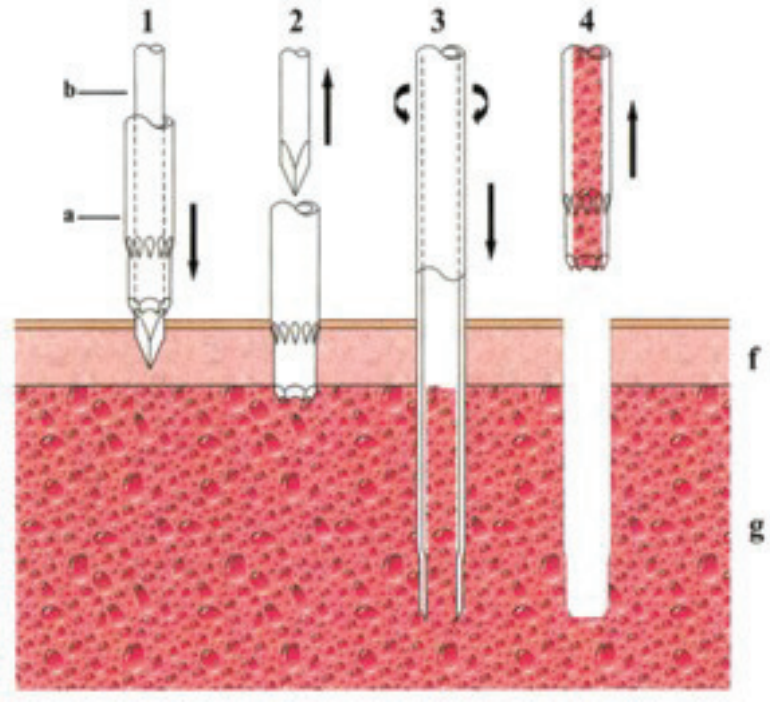


Figure 5.3. Schematic representation of the biopsy procedure.

(1) The needle (a) with the stilette (b) in place is inserted down to the bone. The cortex (f) over the posterior ilium is then penetrated by gentle rotary motion of the needle.

(2) Once this penetration has been achieved, the stilette is withdrawn.

(3) The needle is then advanced with slow, steady and controlled clockwise-counterclockwise rotary motion into the marrow cavity (g).

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(4) When an adequate depth is reached the needle is rotated several times along its long axis and then withdrawn with a straight pull. No rocking or sculling movement or change in the direction of the tip of the needle are necessary. (f) Cortical bone, (g) spongy bone.

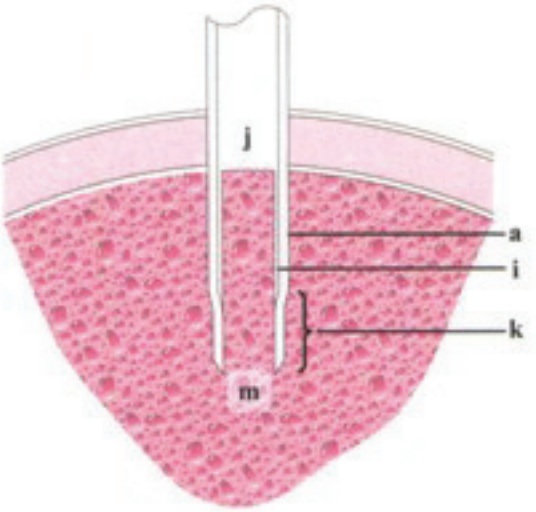


Figure 5.4 Schematic representation of the biopsy technique. (a) the needle wall, (i) free space between the core (j) and the internal wall of the needle. (k) Specially tooled distal cutting end of the needle which cuts all the trabecular connections of the core at its base (m) and holds the biopsy specimen during the process of its extraction so that it does not slip out of the needle.

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Figure 5.5 Photograph showing attachment of spacer-guide to the distal cutting end of the needle.

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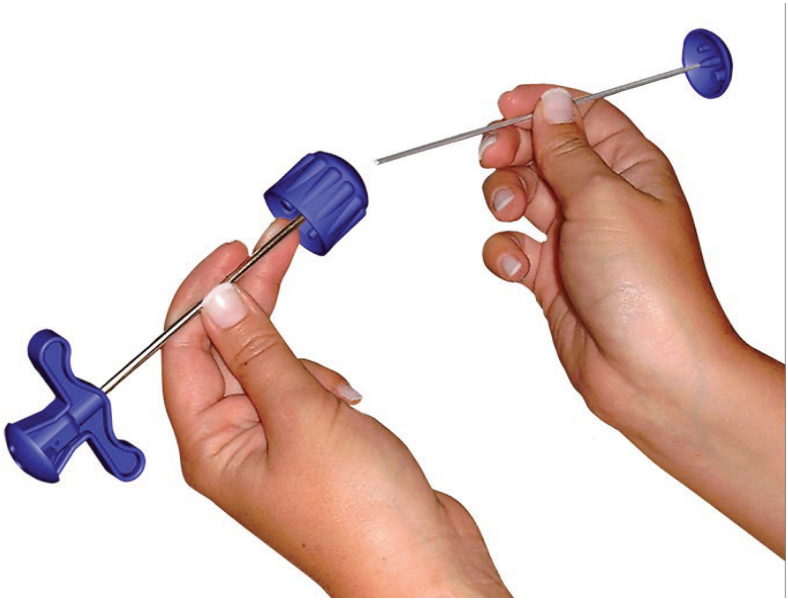


Figure 5.6 Photograph showing introduction of the stilette through the spacer-guide to push the biopsy sample out from within the lumen of the needle.

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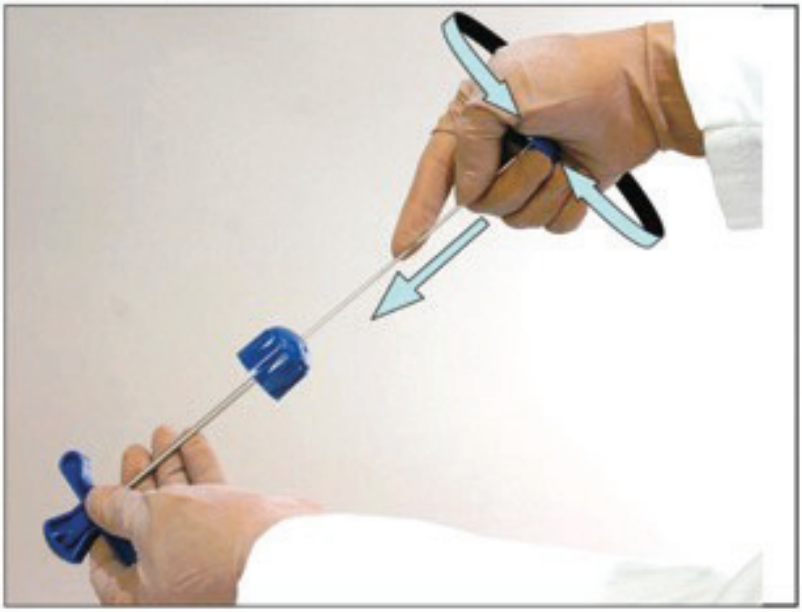


Figure 5.7 Photograph showing an alternative method of introduction of the stilette through the spacer-guide to push the biopsy sample out from within the lumen of the needle (see text for details).

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Figure 5.8. Illustrates a longitudinal section of the spacer-guide (n) and its attachment to the distal cutting end of the needle (a) and its alignment with the stilette (b) which is used as a pusher in this system. Note the funnel shaped design at the top of the spacer which guides and facilitates the introduction of the stilette into the mouth of the needle.

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Figure. 5.9. A sample of bone marrow biopsy specimen obtained with this needle. Note the long and uniform core of marrow tissue obtained by this needle.

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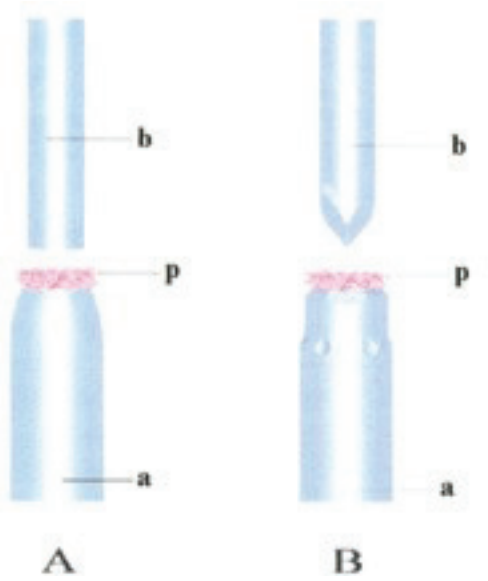


Figure. 5.10 [A] Schematic representation of a conventional biopsy needle to demonstrate the difficulty in introducing the conventional flat/ blunt pusher when its mouth is obscured by redundant, extra bony and soft tissue. (a) needle, (b) pusher and (p) redundant extra bony soft tissue.

Figure. 5.10 [B] Schematic representation of the new single use bone marrow biopsy needle to demonstrate the ease of introducing the trocar-pointed stilette even when its mouth is obscured by redundant extra bony soft tissue. (a) needle, (b) pusher and (p) redundant extra bony soft tissue.

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Figure 5.11 Newer Jamshidi needle with marrow acquisition cradle showing the number of component parts to complete a bone marrow biopsy procedure.



Figure 5.12 The Goldenberg SNARECOIL needle to capture a biopsy specimen.



Figure 5.13 The new Islam single use bone marrow biopsy needle showing the three component parts required to complete a bone marrow biopsy procedure.

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Figure 5.14 Cut section of a Islam single use bone marrow biopsy needle showing the internal core retention device.

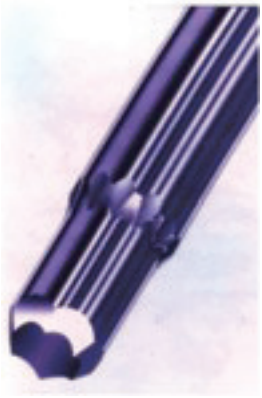


Figure 5.15 Picture of the distal cutting end of an Islam single use bone marrow biopsy needle showing outside serrations that help cut through the hard cortical bone and promote an easy and smooth entry of the needle into the spongy bone. It also shows the sharp cutting facets that help cut the bony trabeculae cleanly.

Comparison of the Islam and other single use bone marrow biopsy needles

BM biopsy, since its introduction by Ghedini in 1909 has achieved significant importance in the field of medicine, and haematology and oncology in particular. It is now routinely used in the investigations, diagnosis and management of various haematological as well as non-haematological malignant conditions. The Jamshidi needle, which popularised the technique

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of bone marrow core biopsy in the 1970's, had one major problem: its inability to consistently retain the biopsy specimens within the lumen of the needle at each and every attempt. Although it is known that core loss rates vary between individual users of the same make of needles, due in part to variations in the level of experience and intrinsic skill of different operators. Nevertheless, it has been a serious problem. The Jamshidi and other brands of needles had this problem because they did not have a core retention device. Because of this the operator had to resort to some extraneous movements with the needle such as rocking, sculling or gyratory movements or change in the direction of the tip of the needle to secure a core sample. Although the 'sample or core losing' problem of the Jamshidi needle was soon recognised and was addressed by the development of a new bone marrow biopsy needle with a core retention device, this particular needle has not been available in a disposable—i.e., in single-use form until the present time.

The problem of core loss by the most popular bone marrow biopsy needle—the Jamshidi needle—and other makes of similar needles is now universally recognised. To overcome this problem several different single-use needles have recently been introduced. Each of these needles features different methods of securing a core sample during withdrawal of the needle from the patient's body. Unfortunately, in the process of doing this, all of these needles significantly complicate the procedure by introducing multiple steps and a nearly unmanageable assortment of extra parts and components. Indeed, in some cases, these needles contain up to six or more additional parts (figure 5.11). Furthermore, these core-capturing devices (figure. 5.12) as they grasp the biopsy specimen may also cause a crush artefact and reduce the amount of marrow tissue available for histological examination.

Accordingly, the advantage of this new needle lies not only in its simplicity to use but also in the reduced number of parts and steps to complete the biopsy procedure. This new needle essentially has only three parts—the needle, the stilette, and the spacer guide (figure 5. 13). In this new system, the same stilette is used as a pusher to extrude the biopsy sample out of the needle. In addition, the distal cutting end of the needle, which bears the biopsy retention device (figure. 5.14), has also been fitted with multiple outside serration's/flutes on the tapering transitional portion, between the main wider portion of the hollow needle and its reduced-diameter front end portion (figure. 5.2 & 5.15). These surface serration's enhance the force of boring through the hard cortical bone and facilitate the entry of the main wider portion of the hollow needle into the marrow cavity.

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The internal diameter of the distal narrower portion is less than the overall internal diameter of the proximal portion. This specially designed distal (3.5 mm) portion of the needle with sharp cutting facets (figure. 5.2, 5.15) not only cuts all the trabecular connections at its base which might keep the biopsy specimen firmly anchored to its base but also holds the core sample with pincer-like action so that it does not slip out of the needle during its extraction. Once the biopsy specimen has passed through the distal narrower portion and enters into the wider proximal segment of the needle, the biopsy sample itself also expands to some extent. Here, the internal step (figure. 5.4) acts as a shoulder which prevents the slightly expanded biopsy sample from slipping out of the needle during its withdrawal. In addition, the larger internal diameter of the needle provides free space within the interior lumen of the needle. This prevents crushing and compression of the tissue as well as plugging the lumen of the needle (figure. 5.4). This also allows easy delivery of the biopsy specimen through the proximal end of the needle. The distal cutting end of the needle—where it joins the main body of the needle—is wider. As a result, the introduction of the needle through the hard cortical bone may be hampered by the wider proximal portion of the needle. To avoid this potential obstruction and to promote an easy and smooth entry of the needle through the hard cortical bone multiple outside serration's are provided at this junction (figure. 5.2 & 5.15).

The spacer-guide is a new addition to this technique and it can be used to facilitate the extrusion of the biopsy specimen. Its distal (bottom) portion is designed to receive the distal narrower portion of the needle and the proximal (top) portion is designed to receive the front (pointed) end of stilette. This guiding system helps proper alignment of the stilette (used as a pusher in this case) with the mouth (distal end opening) of the needle and eases the dislodgement and removal of the biopsy sample through the proximal end of the needle. In many cases, the adherent and redundant extra bony soft tissue obscures the mouth (distal end opening) of the needle after its withdrawal from the patient's body. Consequently, because of the presence of this redundant extra bony soft tissue at and near the mouth of the needle, conventional blunt pushers often slip and cannot readily enter this area (figure. 5.10A) to push the biopsy sample out of the needle. In such circumstances, the trocar pointed stilette of the new needle can easily find its way into the mouth of the needle because of the funnel shaped design of this area (figure. 5.10B). In addition the spacer-guide is an excellent means of reducing the risk of sharps injury to the operator whilst maneuvering the tip of the stilette into the mouth of the biopsy needle. Furthermore, the biopsy technique is simple and does not require

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any manipulation of the biopsy needle within the patient in order to secure the biopsy sample. This in turn makes this potentially uncomfortable procedure more tolerable for the patient.

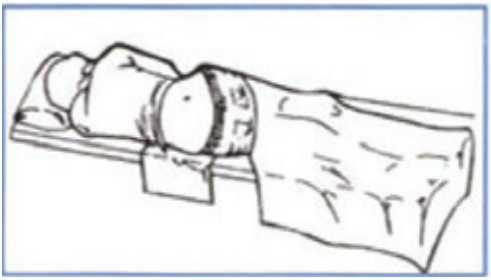
Recently, electric powered disposable bone marrow biopsy needles have been introduced. It has been reported that such powered bone marrow biopsy procedures produce larger core specimens, with less pain and in less time than the standard manual devices. However, this assumption is debatable as the size of the core depends on the size of the needle used. There is also little or no pain if the procedure is performed under a proper local anaesthetic and adequate time is given for the anaesthetic to take affect before the biopsy procedure is done. These instruments are also expensive and difficult to use. They require several component parts and multiple steps to complete the procedure. Most importantly they do not have a core retention device; as a result the core samples can slip out of the needle and remain inside the patient as the needle is withdrawn. These powered devices can also be dangerous if extra care and adequate control is not maintained during the biopsy procedure. This may lead to bodily harm and injury to underlying structures (nerves and blood vessels) particularly if and when the bone marrow biopsy site – the posterior iliac crest—is missed.

Actual Operative Procedure

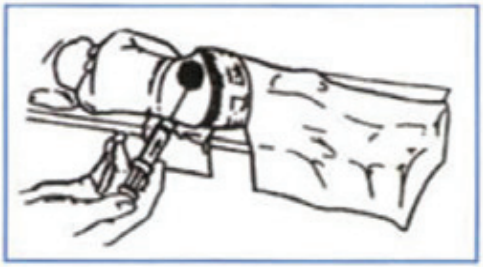


1. Site of the puncture: In adults the bone marrow biopsy is usually performed on the right or left posterior iliac crests. They form the lateral points (arrows) of the rhomboid of Michaelis.

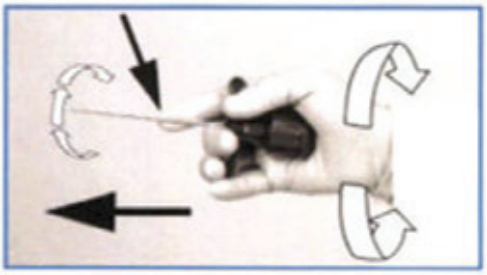
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2. Position of the patient: Place the patient in a right or left lateral decubitus position with the knees drawn up and back comfortably flexed; or, place the patient in a prone position with a pillow beneath the hips.

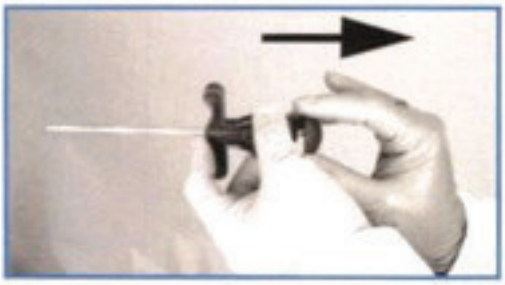


3. Local Anaesthetic and initial skin incision: Infiltrate the skin, subcutaneous tissue and periosteum with a local anaesthetic. Make a small skin incision with a pointed scalpel over the previously marked area.

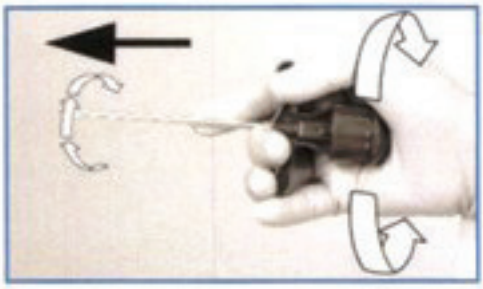


4. Holding and introduction of the needle: Hold the needle assembly with the domed handle resting in the palm, and the index finger supporting the shaft of the needle (top arrow). Introduce the needle through the incision and slowly advance it with clockwise and counter-clockwise rotary motion pointing towards the anterior superior iliac spine.

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5. Withdrawal of the stilette: Once the cortex of the ilium is penetrated, hold the needle assembly in place with the left hand. This can be achieved by firmly holding the spacer/guide with thumb and middle finger and the transverse handle with the index finger of the left hand. Then withdraw the stilette with a straight pull.

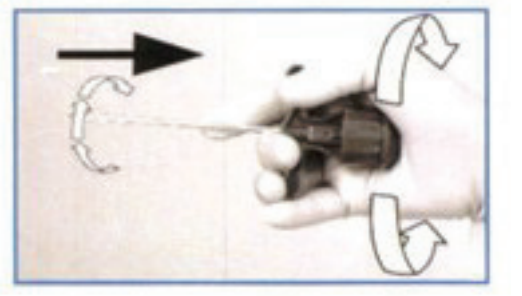


6. Specimen Retrieval: Now advance the needle with slow, steady and controlled clockwise and counter- clockwise rotary motions until the desired depth (about 20 mm) is reached. If preferred the spacer/ guide can be removed to give a different feel in the hand.

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7. Rotate the needle completely (clockwise or counter- clockwise) for several times along its long axis to sever all the trabecular connections at the base of the marrow core.



8. Withdraw the needle (now containing the biopsy specimen) with a straight pull. Gentle alternating rotary motions may be used to facilitate its removal.

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9. Removal of the biopsy specimen from the needle: Once the needle is withdrawn from the patient's body the internal hollowed-out (bottom) side of the spacer/ guide is attached by pushing it forward to the distal cutting end of the needle.



10. The stilette is introduced through the spacer/guide to gently push the biopsy specimen out of the needle through its proximal end.

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CHAPTER 6

SECOND GENERATION ISLAM SINGLE-USE BONE MARROW BIOPSY NEEDLE

The second generation Islam single-use bone marrow biopsy needle retains its unique and original biopsy/core retaining design, is easy to operate, and consistently provides good quality biopsy specimens.

Salient features and profile of the new needle are as follows:

The steel instrument consists[4] of five parts:

(i) the needle (figure 6.1A) which has an overall length of 125 mm, an uniform external diameter 3.25 mm, and a constant internal diameter of 2.5 mm except for the 3.5 mm distal portion where it is narrowed and has multiple surface serrations/flutes (figure 6.2 C). The terminus of the needle has six sharp cutting facets (figure 6.2B). The internal diameter of the needle's distal portion is less than the overall internal diameter of the needle and begins with a short slanted step of 0.2 mm. This specially designed distal portion (figure 6.3 & 6.4E) cuts all the trabecular connections of bone which might keep the biopsy specimen anchored to its base and also holds on to the biopsy sample so that it does not slip out of the needle during the process of its withdrawal. The larger internal diameter of the needle at its proximal segment provides free space (figure 6.4B) within the interior of the instrument thus avoiding crushing and compression of the tissue as well as plugging the lumen of the needle. It also facilitates easy delivery of the biopsy sample through the proximal end of the needle. The introduction of the needle through the cortical bone could potentially be hampered by the wider proximal portion of the needle (figure 6.4G). To prevent this obstruction and assist an easy, smooth entry of the needle into the marrow cavity, multiple surface serrations/flutes (figure 6.2C) are provided at the junction of the distal narrower portion

[4] The needle is available from Cardinal Health. Visit Cardinalhealth.com/Core Retention Bone Marrow Biopsy Needle.

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with its adjoining wider proximal portion. These surface serrations (flutes) provide a means of drilling/cutting as the needle is being advanced through the hard cortical bone while rotating the needle by clockwise and counter-clockwise rotary motions. The proximal end of the needle is fitted with a large plastic T- bar handle (figure 6.1C) for a firm grip.

(ii) The stilette (figure 6.1B) is a solid steel shaft of 2.0 mm in diameter. It ends with a 3.0 mm long three-faceted, sharply-pointed tip (figure 6.2A) which projects beyond the cutting edge of the needle in order to protect the sharp cutting facets of the needle. The stilette also provides a means of easy penetration of the cortical bone. The proximal end of the stilette is fitted with a round knurled plastic knob which fits into the proximal (top) end of the needle.

(iii) The plastic cap (figure 6.1D) fits and covers the top of the plastic T-bar handle (figure 6.1C). It also fits snugly in the palm of the operator's hand and is used to avoid discomfort during the biopsy procedure.

(iv) The insertion aid (figure 6.1E) is a tubular mass of plastic 30 mm long and 5 mm wide except at the end that fits the mouth of the needle where it is flat and 10 mm in diameter. It is centrally hollowed out to receive and passage of the pusher during removal of the biopsy specimen through the proximal end of the needle.

(v) The pusher (figure 6.1F) is a solid steel rod of 2.0 mm in diameter attached to a knurled, flat plastic disk. The Pusher rod is used to remove the biopsy specimen from within the lumen of the biopsy needle with the help of the insertion aid which guides the pusher rod into the mouth needle.

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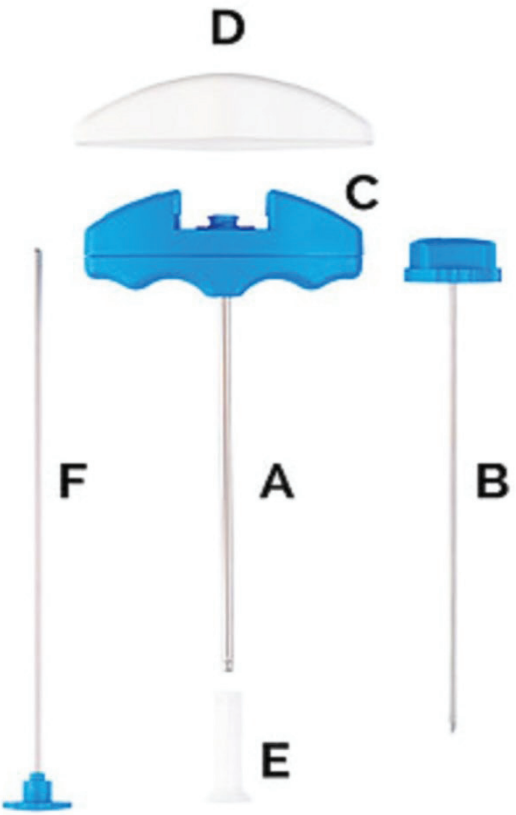


Figure 6.1 Illustrates the complete needle set: the needle (A), trocar (B), T-bar handle (C), plastic cap (D), pusher/core extraction rod (F) and insertion aid (E) that guides the pusher rod into the mouth of the needle and assists in delivery/removal of the marrow core.

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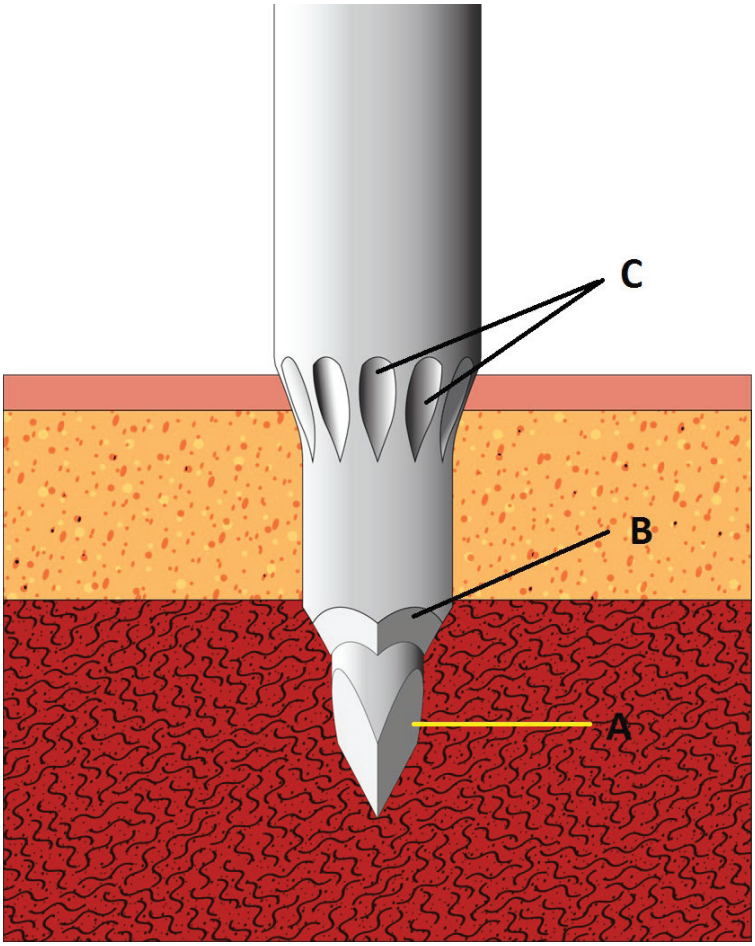


Figure 6.2 demonstrates the long and sharp trocar pointed stillette (A) that helps easy penetration of the skin, soft tissue and the cortical bone, the sharp cutting facets (B) that cleanly cut the bony trabeculae, and the outside serrations/flutes (C) that help cut the dense cortical bone and facilitates the needle entry into the marrow cavity.

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Figure 6.3 Shows an internal view of the distal cutting end of the needle demonstrating the internal self-core retaining device (arrows) that captures and secures the biopsy specimen so that it does not slip out of the needle while the needle is withdrawn.

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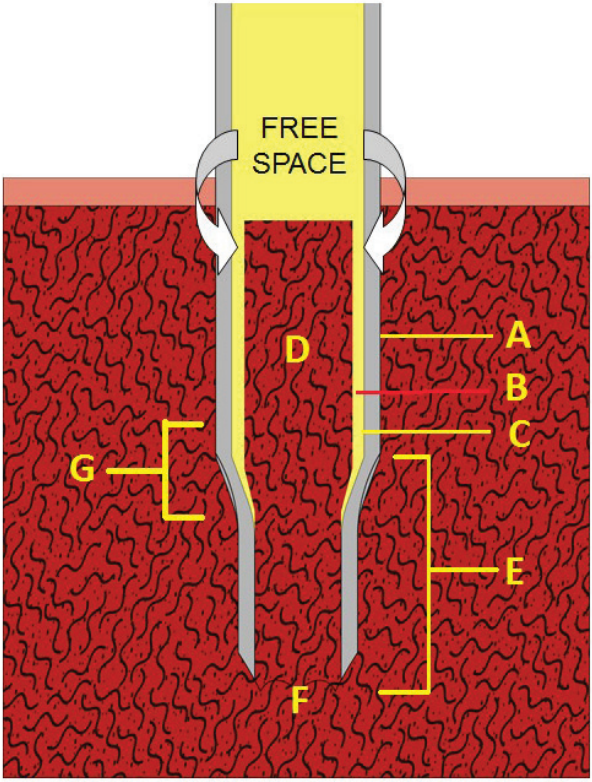


Figure 6.4 Illustrates the free space (B) that lies between the internal wall of the needle (A) and the biopsy specimen (D) which prevents crushing and compression of the tissue and also avoids plugging the lumen of the needle. In addition, this design aids smooth delivery of the marrow core through the proximal end of the needle.

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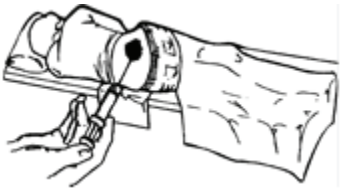
Operating Procedure

1 

1. **Site of the puncture**: In adults the bone marrow biopsy is usually performed at the right or left posterior ilium near the iliac crest. The two iliac crests form the lateral boundaries (arrows) of the rhomboid of Michaelis and can be easily located by palpation or with ultrasound guidance.

2 

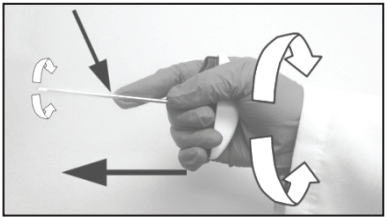
2. **Position of the patient:** Place the patient in a right or left lateral decubitus position with the knees drawn up and back comfortably flexed; or, in a prone position with a pillow beneath the hips. Once the area of the posterior iliac crest is located by palpation or by ultrasound guidance, mark the area with thumbnail pressure or indelible ink and prepare the region for the procedure with alcohol or iodine and then drape the area.

3 

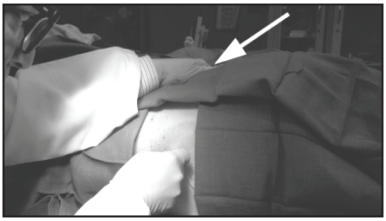
3. **Local anesthetic and initial skin incision:** Infiltrate the skin, subcutaneous tissue and periosteum with a local anesthetic (1% or 2% lidocaine). It is useful to probe the site during infiltration with the local anesthetic with a long (21 gauge 1½ inch) hypodermic needle to ensure that the area is properly anesthetized and to roughly outline the borders of the posterior ilium. This also gives an indication as to the depth at

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which the bone will be met and for proper angulation of the biopsy needle. In obese patients longer needles such as the spinal needles may be necessary to reach the bone. Make a small (3mm) skin incision with a pointed scalpel over the marked area.

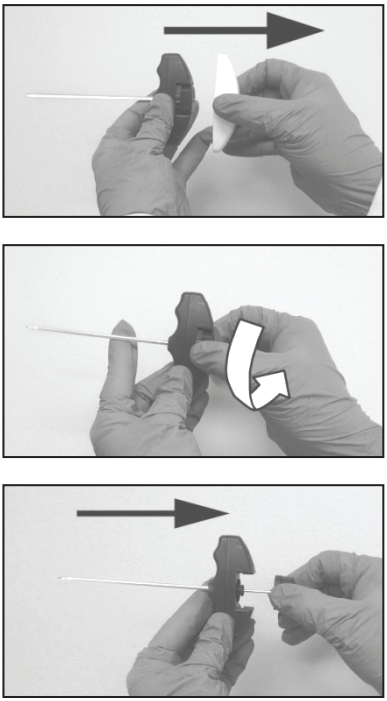


4. **Holding and introduction of the needle:** Hold the needle assembly with the T-bar (transverse) handle with the plastic cap in place resting in the palm, and the thumb, middle and ring fingers gripping the transverse handle and the index finger supporting the shaft of the needle (top arrow). The position of the index finger over the shaft helps stabilize the needle and permits proper control and maneuverability during its introduction. Then advance the needle forward through the incision and slowly push it towards the posterior ilium with clockwise and counter-clockwise rotary motion pointing towards the anterior superior iliac spine.



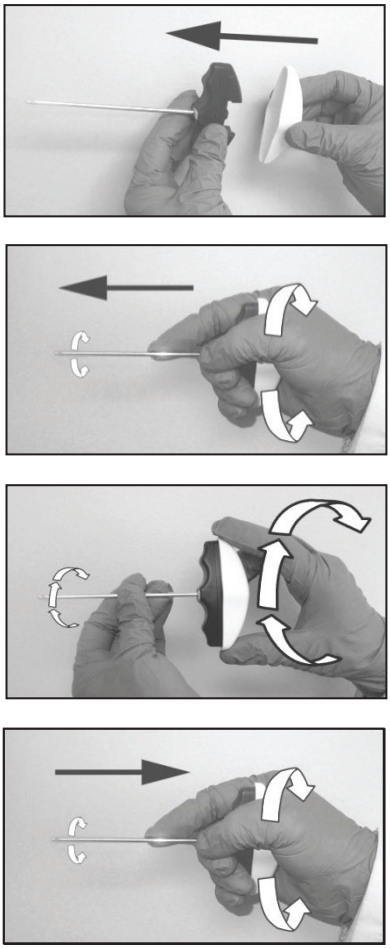
It is useful to put one hand over the anterior iliac crest with the middle or index finger on the anterior superior iliac spine as shown in the photograph above (arrow). This approach not only helps stabilize the patient's pelvis but also helps in the guidance of the needle towards the anterior superior iliac spine.

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5. **Removal of the plastic cap and withdrawal of the trocar/stilette:** When the posterior ilium is reached, it is then penetrated by a controlled forward thrust and gentle rotary motion of the needle. Penetration beyond the cortical bone with the stilette in place should be avoided, as it will reduce the length of the marrow core that will be obtained. Once the cortex of the posterior ilium is penetrated, hold needle assembly in place with the left hand and remove the plastic cap by pulling it off as shown in the top photograph. Next, the stilette is withdrawn by first unlocking it from the T-bar handle by twisting the knurled head of the trocar anti-clockwise as shown in the middle photograph and then withdrawing the stilette with a straight pull as shown in the lower photograph. Following its withdrawal the stilette is then placed on the sterile operating tray in case it is needed again.

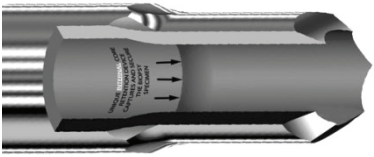
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6. **Replacement of the plastic cap and biopsy retrieval:** After removal of the stilette from the needle reattach the plastic cap to the T-bar handle (top photograph) and advance the needle forward (second photograph from the top) with slow, steady and controlled clockwise and counter-clockwise rotary motion until an adequate depth (about 20-25mm) is reached. *No lateral force should be applied to the needle during this procedure.* Then rotate the needle (third photograph from the top) completely (clockwise or counter-clockwise) several times along its long axis to sever all the bony trabecular connections at the base of the marrow core. Then withdraw the needle (which now

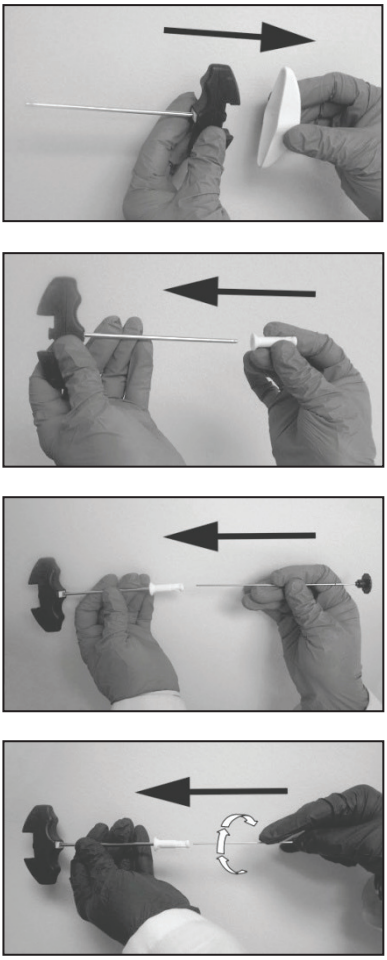
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contains the core biopsy specimen) with a straight pull with gentle alternating rotary motions to facilitate its withdrawal out of the patient's body (fourth photograph from the top). The needle can be withdrawn with a straight pull without fear of losing the core sample. *No rocking, sculling, gyratory movements or additional parts such as sleeves, marrow acquisition cradle (trapping devices) are necessary.*



The design of this needle has incorporated an internal core retention design (above photograph) which holds the core captive during withdrawal of the needle. Only gentle alternating rotary motion is necessary to facilitate its withdrawal.

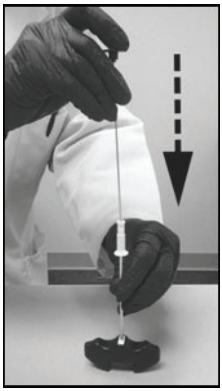
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7. **Removal of the biopsy specimen from the needle:** Once the needle is withdrawn from the patient's body the plastic cap is removed (photograph at the top) and the insertion aid is attached to the distal cutting end of the needle (second photograph from the top). The biopsy specimen contained within the lumen of the needle is then pushed out of the needle by introducing the pusher rod through the insertion aid and gently pushing it forward through the insertion aid and the needle (third photograph from the top). During removal of the biopsy specimen, hold the needle with the insertion aid attached to the distal

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cutting end of the needle with the left hand and the pusher rod with the right hand close to the opposite end of the insertion aid (fourth photograph from the top). This stabilizes the needle and the pusher rod and helps easy delivery of the marrow core through the proximal end of the needle.



Because of the effectiveness of core retention design the biopsy specimen on occasion may get tightly lodged in the narrower distal portion of the needle particularly if the bone is dense. In such circumstances a simple rotary movements of the pusher rod while gently pushing it forward will easily dislodge and release the core sample. Alternatively, the needle with the insertion aid in place can be placed upside-down on a table/sterile tray and held by one hand while gentle tapping the pusher rod with the other hand. Such a maneuver will easily dislodge and release the core sample from the mouth of the needle as shown in the photograph above.

8. **Closure of the wound:** After the biopsy procedure, apply a gauze dressing and put an adhesive tape on the top and apply some pressure to prevent potential bleeding. Instruct the patient to lie flat upon a supplied towel-support on his/her back for 10 to 15 minutes, or longer if the patient has a low platelet count or if the patient is on aspirin or anticoagulants.

Bone marrow aspiration before bone marrow biopsy utilizing the same needle: Bone marrow aspiration prior to bone marrow biopsy utilizing the same bone marrow biopsy needle is generally considered *not* an ideal practice. Some practitioners, nevertheless, do prefer to use the same needle for both purposes. If a bone marrow aspiration is to be

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performed before a bone marrow core biopsy is to be obtained then this two-step procedure can be conveniently and successfully accomplished with this needle without requiring an additional part such as an adaptor.

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CHAPTER 7

BONE MARROW SOLID CORE BIOPSY NEEDLE: UTILITY, BENEFITS AND LIMITATIONS OF THE INSTRUMENTS EMPLOYED IN CURRENT DAY HEMATOLOGY AND ONCOLOGY

The optimal clinical evaluation of the bone marrow requires an examination of air dried, well stained films of the aspirated tissue along with a histopathological evaluation of adequately processed and properly stained core biopsy specimens. A bone marrow evaluation can be essential in establishing a diagnosis, determining the efficacy of treatment of hematological disorders and to monitor hematological status of patients following bone marrow/stem cell transplantation. It is also an essential component of the staging process for newly diagnosed malignancies. Currently available bone marrow aspiration needles are quite satisfactory and if properly used provide good quality specimens for morphological evaluation. However, when a bone marrow core biopsy is desired there are several needles that are currently in use but not all of them provide good quality biopsy specimens for histological evaluation or are user friendly.

The author has made a methodical comparison of his newest bone marrow biopsy needle (i.e, second generation Islam single use core retention biopsy needle) with the Jamshidi needle with marrow acquisition cradle (CareFusion), J-needle with sleeve (Cardinal Health), Snarecoil needle (Ranfac) and OnControl needle (Teleflex/Vidacare). It was concluded that the Islam needle system has definite advantages over the others, and was recommended for routine use.

The technique of bone marrow aspiration was introduced by Arinkin in 1929 and since its introduction, its use has increased exponentially. It plays a vital role in the diagnosis and management of patients with haematological, non-haematological and oncological disorders. In selected cases such as nutritional deficiency and the acute and chronic leukaemias an aspiration biopsy may be all that is necessary for diagnosis. This

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technique also provides a convenient and simple way of obtaining material from the bone marrow for morphological and molecular studies as well as for immunophenotyping and cytogenetic studies that are necessary for accurate laboratory diagnosis and stratification of hematological malignant dosorders.

On the other hand, when the marrow cavity is hypercellular (chapter 18, figure 18.12 A to E) or if there is increased reticulin (chapter18, figure 18.5) or collagenous fibrosis which may result in a dry tap the core biopsy becomes invaluable adjunct to bone marrow examination. In addition, a bone marrow core biopsy is essential to establish the status of the bone marrow when no realistic alternative evaluation procedure exists, such as aplastic anemia (chapter 18, figure 18.2A). Trephine (core) biopsies are also essential to document focal residual disease (chapter 18, figure 18.10B), regeneration following chemotherapy (chapter 18, figures 18.11 A & B) and identification of infiltrating lesions such as malignant lymphoma (chapter 18, figure 18.17 A, D&F), multiple myeloma (chapter 18, figure 18.15 A & B) and metastatic carcinoma (chapter 18, figure 18.18 & 18.19).

The limitations of bone marrow aspiration were soon recognized after this technique was developed and attempts were made to overcome them by performing solid core trephine biopsies. The earlier trephine instruments such as Nottar Labhard, Burkhardt and Gidlunds instruments were large and bulky, contained multiple components, were cumbersome, and required an open surgical procedure. They also required assistance to carry out the procedure and above all they could not be repeated on the same site for at least 4- 6 months. Then in the 1970s the Jamshidi bone marrow biopsy needle was developed and appeared to offer a compromise between the larger Notter Labhardt, Burkhardt and Gidlunds instruments and the other less satisfactory Sacker Nordin bone marrow biopsy needle. However, a major drawback of the Jamshidi needle was that it did not have a core retention device. As a result the biopsy specimens frequently slipped out of the needle during its withdrawal and remained inside the patient requiring a second or third attempt to secure a biopsy sample. One of the unfortunate consequences of the absence of a core retention system (see chapter 4, figure 4.14) is that occasionally as the biopsy needle is withdrawn the biopsy specimen contained in the lumen of the needle starts to slip (see chapter 4, figure 4. 25) out of the needle and is grasped by the surrounding soft tissue. As a result the core fractures and leaves one segment of the biopsy specimen on the surface of the skin (see chapter 4, figure 4.27) and another within the extra-bony subcutaneous soft tissue

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(see chapter 4, figure 4.26). The latter dislocated piece of marrow tissue may serve as a locus of dissemination of potentially malignant or bacterially laden material. Furthermore, the Jamshidi needle technique also required rocking, sculling or gyratory movement or a change in the direction of the tip of the needle to secure the biopsy specimen. As a result the needles were often bent and damaged. The problem of core loss was soon recognized and was overcome by a newly developed bone marrow biopsy needle with a core retention device (see chapter 4). Following the introduction of this latter bone marrow biopsy retentive needle other manufacturers of bone marrow biopsy needles, including the Jamshidi needle recognized that this problem existed and soon developed their own version of needles to capture the biopsy specimen. To accomplish this they have introduced additional components such as a drain spade shovel like marrow acquisition cradle (Jamshidi) or a tweezer like sleeve (Cardinal and other manufacturers) to capture the biopsy specimen.

In order to compare the benefits and effectiveness of these instruments performance testing was conducted on adult human cadavers using the Jamshidi needle (BD/CareFusion), J-needle (Cardinal Health), Snarecoil needle (Ranfac), OnControl needle (Teleflex/Vidacare) and the newly introduced second generation Islam core retention bone marrow biopsy needle. The aim was to compare each needle with regard to general function, penetration characteristics, tissue sample size (length and diameter), number of fragments/segments obtained and visual quality and mechanical durability of the devices.

Tissue collection was performed on vertebral bodies from adult human cadavers as the consistency of vertebral body bone is very similar to the consistency of the bone of the posterior ilium which is normally used for obtaining bone marrow biopsies from patients. In order to derive a significant assessment of the biopsy procedures six punctures were made with each needle. The sites of the biopsies were at the right and left of the anterior midline of thoracic #12 and lumbar # 1-5 vertebrae.

The tissue samples size was examined for length (in mm), diameter (in mm), number of segments obtained and macroscopic visual quality. They were categorized in the following grading:

Excellent (+++) Satisfactory sample (intact biopsy specimen with length 20 mm or over) for histological evaluation.

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Good (++) Satisfactory sample (intact biopsy specimen with length 15-20 mm) for histological evaluation.

Satisfactory (+) Less than ideal length of biopsy sample (intact biopsy specimen with length 8-14 mm or two fragments with total length 8-14 mm) but histological evaluation is possible.

Poor (--) Inadequate biopsy sample (intact biopsy length less than 8 mm or small fragmented samples, each fragment measuring 5 mm or less in length). Not evaluable histologically.

Each of the samples was also subject to histological evaluation. Six samples each were taken with a Islam (11G/4 inch) and with J-Needle (Cardinal Health) (11G/4 inch), Jamshidi needle (11G/4 inch), Snarecoil needle (Ranfac) (11G/4 inch), and OnControl needle (11G/4 inch). The steps of the procedures and penetration depth were essentially identical in order to get comparable results. Needles and particularly the needle tips remained intact throughout all the biopsy manipulations.

Generally speaking Islam, Cardinal, Jamshidi and Snarecoil needle devices are manually operated and used in a similar way. However, they differ in the method of their capturing and retention capacity of the specimen within the lumen of the needle as it is removed from the subject. The J-needle by Cardinal Health (and others that utilizes a tweezer like sleeve) and Jamshidi needles require an additional core capturing device (shovel like marrow acquisition cradle) to capture the biopsy specimen whereas the Islam needle does not require any additional components or parts to do so. With the Islam needle this is accomplished by a patented internal core retention device located near the distal cutting end of the needle (figure 7.1A). OnControl needle system on the other hand has an internally placed thread/sickle near the distal cutting end of the needle that projects into the lumen of the needle (figure 7.1B). In this system the thread/sickle is considered to act as a snare to capture and hold the biopsy specimen during its withdrawal. The Ranfac-Snarecoil system, on the other hand, incorporates multiple coil located near the tip of the needle (figure.7.1C) that winds around and grasps/capture the biopsy specimen as the lever is moved forward to the on positon.

Procedures

Procedure with the second generation Islam core retention BMB needle: The biopsy needle with the stilette in place was inserted into the vertebral

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body. Once the needle was in the marrow cavity, the stilette was removed. In the next step the biopsy needle was pushed forward manually by exerting a rotating and forward thrust in order to drive the biopsy specimen into the lumen of the biopsy needle. Once an adequate depth (about 20 mm) was reached the biopsy needle was then withdrawn (containing the biopsy sample within the lumen of the needle) by slightly rotating the needle with clockwise and counter-clockwise rotary motions. Following withdrawal of the needle from the cadaver the insertion aid (which is used to facilitate the insertion of the pusher rod directly into the mouth of the needle) was then attached to the distal cutting end of the needle. The biopsy specimen was then removed by introducing and pushing the pusher rod forward through the insertion aid and through the needle.

Procedure with the J-needle (Cardinal Health) and the Jamshidi needle (BD/CareFusion): The biopsy needle with the stilette in place was inserted into the vertebral body. Once the needle was in place, the stilette was removed. In the next step the biopsy needle was pushed forward manually by exerting a rotatory motion and forward thrust in order to drive the biopsy specimen into the lumen of the biopsy needle. Once an adequate depth (about 20 mm) was reached the sleeve/tweezers (Cardinal Health), or the shovel like marrow acquisition cradle (BD/CareFusion) was then introduced into the lumen of the needle and gently pushed forward with slight rotatory motion over the biopsy specimen. Once the sleeve/tweezers or the marrow acquisition cradle was locked in place, the needle along with the sleeve/tweezers or marrow acquisition cradle along with the biopsy specimen was withdrawn. The sleeve/tweezers or marrow acquisition cradle containing the biopsy specimen was removed from the needle and the specimen was pushed out by introducing a pusher through the opposite end of the sleeve or marrow acquisition cradle.

Procedure with Ranfac-Snarecoil needle: The biopsy needle with the stilette in place was inserted into the vertebral body. Once the needle was in place, the stilette was removed. In the next step the biopsy needle was pushed forward manually by exerting a rotatory motion and forward thrust in order to drive the biopsy specimen into the lumen of the biopsy needle. Once an adequate depth (about 20 mm) was reached the lever was moved from ‘off’ to the ‘on’ position which helped the coil to move over and grasp/capture the biopsy specimen. The needle was then withdrawn, the lever was pushed back to ‘off’ position and the biopsy specimen was pushed out of the needle by introducing a pusher through the opposite end of the needle.

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Procedure with the OnControl needle: The OnControl bone marrow biopsy system consists of a reusable battery powered driver, a disposable bone marrow biopsy needle with internal core capturing thread/sickle near the distal tip of the needle, a stylet, depth guide, an alignment guide and an ejector rod. The needle with the stylet in place was inserted through the cortex of the bone by activation of the driver. Once the needle was firmly seated in the bone, the driver was separated from the hub of the biopsy needle by retracting the collar on the driver coupler. The stylet was then removed from the needle-hub leaving the biopsy needle seated in the bone. The driver with the attached coupler was then reattached to the biopsy needle and the power driver was activated. The biopsy needle was then advanced to the desired depth (about 20 mm) into the medullary cavity for capturing the bone marrow biopsy sample. The entire needle assembly was then withdrawn using power to facilitate its withdrawal. Following removal of the needle the driver was separated from the biopsy needle, the alignment guide was attached to the distal cutting end of the needle, and the biopsy specimen was pushed out of the needle with the ejector rod.

Summary of Analysis

The needles have been tested on human cadavers in particular with regard to penetration, cutting ability, ergonomics and comfort of holding the biopsy needle assembly during the procedure. The quality, size, and length of the biopsy specimens obtained were also visually analyzed. In addition, the specimens were fixed in 10% formalin, decalcified and processed in paraffin. Histological sections were prepared and were stained with hematoxylin and eosin. Each slide was evaluated for morphology, structure, trabecular distortion and crush artifacts. The results are summarized in tables 1-3.

Second generation Islam core retention BMB Needle: The six sharp faceted cutting tip of the needle (figure 7.1D) stood out as an excellent cutting tool which transected the bony trabeculae cleanly (figure 7.1E). The bodies of the samples were linear, non-wavy (figure 7.1F) and without crush artifact even at the edges of the biopsy sample (figure 7.2A). The outside serrations/flutes near the distal cutting end of the needle (figure 7. 1D) acted like a saw during rotary motion of the needle and fostered an easy penetration of the needle through the dense cortical bone and facilitated its entry into the marrow cavity. The long and sharp trocar-pointed end of the stilette (figure 7.2B) was helpful with the penetration of the needle through the skin, soft tissue and solid cortical bone. An

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adequate sample in respect to size, shape, quality, and length of the biopsy specimen was obtained with each attempt (Table 1-3). The visual quality of the specimens obtained with this needle was good to excellent at each attempt (Table 1). The biopsies were not fragmented and the length of the specimens obtained varied from 15 to greater than 25 mm (Table 3). In addition they were never lost upon withdrawal of the needle. This was made possible by the internal core retention device of this biopsy system (figure 7.1A). Because of the presence of the internal core retention device, this needle did not require any additional components or parts such as 'marrow acquisition cradle' (BD/Carefusion) or some type of 'sleeve/tweezers' as in J needle (Cardinal) or other types of similar needles to help capture the biopsy specimen. The technique with this needle is simple and does not require any manipulation of the biopsy needle in the form of a twist**,** rocking, sculling or gyratory movements in order to secure the biopsy specimen. The needle is ergonomically designed and easy to maneuver during the biopsy procedure. The *absence* of a protruding retainer (external plastic molding) (figure 7.2C) for holding the needle protector sheath designed to cover the needle when it is in non-use/storage, located at the base of the handle (present in the J-needle, Jamshidi and snarecoil needles - figures 7. 2 D, E & F) the holding and manipulation of the Islam needle was free of pain or discomfort to the operators hand during the biopsy procedure.

J – Needle (Cardinal Health): The diamond pointed tip of the stilette (figure 7.3 A) in the J-needle was found to project too far beyond the distal cutting end of the needle and thus reduced the length of the derived biopsy sample. In addition, the penetrability of the cortical bone with this stilette was found to be less than adequate as compared to Islam (figure 7.2B), Jamshidi (figure 7.3B) and Snarecoil (figure 7.3C) needles. The oval shaped cutting tip of the needle (figure 7.3D) was found to be less than ideal in providing clean cut bony trabeculae and may have been responsible for the breakage and fragmentation (figure 7.3E) (Table 2) of the biopsy samples. This particular cutting tip of the needle may also have been responsible for the frequent crush artifact noted at the edges of the biopsy specimens obtained with this needle (figure 7.3F)

Less than ideal samples in respect to size, quality and length of the biopsy specimens were obtained with each attempt (Table 1-3). The length of the specimens varied from 3 to 7 mm. With the trapping device (figure 7.4 A) biopsy specimens were retained and retrieved at each attempt. However they were small, often fragmented and showed considerable crush artifact at the edges of the biopsy specimen (figure 7.4B). This is due to, at least in

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part, to the fact that there is limited free space between the internal wall of the needle and the biopsy sample. As a result when the sleeve (figure 7.4 C) is rotated and pushed forward over the biopsy specimen the edges are crushed and produce artefactual change.

The technique with this needle is complicated as it requires a semi-closed sleeve (trapping device) (figure 7.4A) to be pushed forward over the biopsy specimen to capture and hold it during withdrawal of the needle. Although, the technique with this needle does not require any manipulation of the biopsy needle in the form of rocking**,** or gyratory movements in order to secure the biopsy specimen, the time required to introduce the trapping device and the manipulation during the procedure may be time-consuming and can be painful to the patient. The design of the needle handle was found to be less than satisfactory (not comfortable) particularly due to the presence of a protruding retainer (external plastic molding) at the proximal end of the needle and under the plastic handle (figure 7.2D). The presence of this protuberance (external plastic molding) caused pain and discomfort to the operator's hand during the biopsy procedure.

Jamshidi needle (BD/Carefusion): The trocar pointed tip of the stilette (figure 7.3B) in this system was found to be satisfactory with regard to the penetrability of the hard cortical bone. Unlike the diamond pointed stilette as in the J- needle (figure 7.3A), introduction of the trocar pointed stilette may be associated with less pain and discomfort for the patient. However the trocar pointed tip of the stilette (figure 7.3B) as in the J- and Oncontrol needle was found to project too far beyond the cutting edge of the distal cutting end of the needle and thus reduced the length of the biopsy sample obtained. The tripple crown cannula tip of the needle (figure 7.3B) performed well as a cutting tool of the bony trabeculae and the biopsy specimens were straight and linear but presented crush artifact particularly at the edges of the biopsy sample (figure 7.4D) which may be attributable, in part, to the forced introduction of the marrow acquisition cradle over the biopsy specimen.

The technique with this needle is complicated as it requires a shovel like marrow acquisition cradle (trapping device) (figure 7.4E) to be pushed forward over the biopsy specimen to capture and hold it during withdrawal of the needle. Although, the technique with this needle does not require any additional manipulation of the biopsy needle in order to secure the biopsy specimen, the time required to introduce the trapping device and the manipulation during the process may be time-consuming and can be uncomfortable for the patient. The design of the needle handle was found

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to be less than satisfactory (not comfortable) particularly due to the presence of a protruding retainer (external plastic molding) at the proximal end of the needle under the plastic handle (figure 7.2E). The presence of the latter protuberance caused discomfort to the operator's hand during the biopsy procedure.

Snarecoil (Ranfac) As in the Islam needle system the combination of the trocar-pointed stilette end and the sharp beveled cutting tip of the needle was found to be satisfactory both in respect to penetration of the cortical bone and to providing a linear clean cut sample. An adequate sample in respect to size, shape, macroscopic quality, and length of the biopsy specimen was obtained with each attempt (Table 1-3). But the technique with this needle is somewhat complicated as it requires a internally positioned coil to be moved over (figure 7.1C & 7.2F) (by moving a lever from 'off' to 'on' position) the biopsy specimen to capture and hold the biopsy sample during withdrawal of the needle. Although, the technique with this needle does not require any additional parts such as the sleeve or marrow acquisition cradle or any manipulation such as twisting or gyratory movement or change in the direction such as withdrawing the needle for a few millimeter and then pushing it forward in a different direction of the biopsy needle in order to secure the biopsy specimen, but the length of the specimens obtained varied from 8 to 20 mm. With the snarecoil (capturing device) biopsy specimens were retained and retrieved at each attempt. However, they were often fragmented and showed considerable crush artifact at the edges of the biopsy specimen. This is due in part to the squeezing effect as the coil is moved over the biopsy specimen. Furthermore, the outside diameter (OD) of Islam needle is 3.0 mm, whereas the OD of the snarecoil needle is 3.3 mm. This is most likely to be due to the arrangement for housing of the snarecoil near the distal end of the needle. In addition, the OD of the biopsy specimen obtained with the Islam needle was 2.1 mm while the OD of biopsy specimen obtained with the snarecoil needle was 1.9 mm - in other words a larger diameter needle yielded a smaller diameter biopsy specimen.

The design of the needle handle was also found to be less than satisfactory (not comfortable) particularly due to the presence of a protruding retainer (external plastic molding) at the proximal end of the needle under the plastic handle (figure 7.2F). The presence of the latter protuberance caused pain and discomfort to the operator's hand during the biopsy procedure.

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OnControl Needle (Vidacare): As in Islam needle system the combination of the trocar-pointed stilette end and the six sharp faceted cutting tip of the needle (figure 7.4F) was found to be satisfactory both in respect to penetration of the cortical bone and to providing a linear clean cut sample (figure 7.5A). An adequate sample in respect to size, shape, macroscopic quality, and length of the biopsy specimen was obtained with each attempt (Table 1-3). However, because of the presence of an internal thread/sickle/hook near the tip of the needle which projects into its lumen of the needle (figure 7.1 B) and the high cutting speed of the drill caused considerable damage to the edges of the biopsy specimen (figure 7.5B) thus reducing the total width of the biopsy specimen for histological evaluation. Furthermore, it was difficult to eject the biopsy specimens from within the lumen of the needle as it was tightly anchored by the internal thread/hook near the distal cutting tip of the needle. As a result excessive force was needed to remove the biopsy specimen with the ejector rod. Although the length of the specimens obtained at each attempt varied from 15 to greater than 20 mm (Table 3), there never was any fragmentation or loss of the specimen following withdrawal of the needle (Table 2).

Because of the presence of an internal core capturing thread/sickle near the tip of the needle, this needle did not require any additional components or parts such as marrow acquisition cradle (Jamshidi-Carefusion), or some type of sleeve/tweezers as in J- (Cardinal) and other similar type needles to help capture the biopsy specimen. The technique with this needle is simple and does not require any manipulation (rocking, gyratory etc.) of the needle. The battery operated drill is ergonomically designed (figure 7.5C) and easy to maneuver and is free of pain and discomfort to the operator's hand. The overall procedure appears to be somewhat complicated because of the number of inter-changeable parts that require coupling and uncoupling of the needle with the hand held drill during the procedure. Unlike the manual bone marrow biopsy needles where the operator has full control during the procedure, with the OnControl system, the operator has much less governance with regard to speed, depth of penetration etc. There is also the possibility of needle slipping off the bone during high-speed drilling and injuring surrounding tissue.

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Commentary

Numerous bone marrow biopsies are now performed annually in the USA (over 700,000 US procedures) and throughout the world. The Jamshidi needle, which popularized the technique of bone marrow core biopsy in the 1970s, had one major problem: its inability to consistently retain the biopsy specimen within the lumen of the needle at each and every attempt. In addition, fragmentation of the specimen and occasionally losing a segment of it may also occur. It is recognized that the core loss rates vary among individual users of the same make of needles due in part, to variations in the level of experience and intrinsic skill of different operators. Nevertheless, it has been a serious problem even in the hands of experienced individuals. The Jamshidi and other brands of needles had this problem because they did not have a core-retention device. Because of this, the operator had to resort to some extraneous movements with the needle to secure a biopsy sample. The sample/core-losing problem of the Jamshidi needle was soon recognized and was addressed by the development of a new bone marrow biopsy needle with a core-retention feature. The problem of core loss by the most popular bone marrow biopsy needle—the Jamshidi needle—and other makes of similar needles is now universally recognized. To overcome this problem, several other different single-use needles have recently been introduced as discussed above. Each of these needles features different methods of securing a core sample during withdrawal of the needle from the patient. Unfortunately, in the process of doing this, all of these needles significantly complicate the procedure by introducing multiple steps and an assortment of extra parts and components. Indeed, in some cases, these needles contain up to six or more additional accessories. Furthermore, these core capturing devices such as sleeves (tweezer like component) or ‘drain spade shovel’ like marrow acquisition cradles can induce considerable crush artifact (particularly at the edge of the biopsy specimens) (figure 7.6) and reduce the amount of the marrow tissue that is obtained when they are inserted into the needle and pushed forward over the biopsy specimen in order to grasp/capture and retain it. Accordingly, the advantage of the new Islam single use core retention biopsy needle lay not only in its simplicity but also in the reduced number of parts and steps required to complete the procedure. The important feature of this needle is the internal core retention design (figure 7.1A). In addition, the distal cutting end of the needle, which bears the biopsy retention device, has also been fitted with multiple outside serrations/flutes at the tapering transitional portion between the main wider segment of the hollow needle and its reduced-diameter front-end

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portion (figure 7.1D). These outside surface serrations/flutes enhance the efficiency of boring through the hard cortical bone and facilitate the entry of the main, wider portion of the hollow needle into the marrow cavity. The internal diameter of the distal narrower portion is less than the overall internal diameter of the proximal segment. This specially designed distal (3.5-mm) portion of the needle with sharp cutting facets not only cuts all the trabecular connections at its base, which might keep the biopsy specimen firmly anchored to its base, but also holds the core sample with pincer-like action so that it does not slip out of the needle during its extraction. Once the biopsy specimen has passed through the distal narrower portion and enters into the wider proximal segment of the needle (figure 7.5D), the biopsy sample itself also expands to some extent. Here, the internal step acts as a shoulder, which prevents the slightly expanded biopsy sample from slipping out of the needle during its withdrawal (figure 7.5D). In addition, the larger internal diameter of the needle provides free space within the interior lumen of the needle (figure 7.5D). This free space prevents crushing and compression of the tissue as well as plugging the lumen of the needle. This also allows easy delivery of the biopsy specimen through the proximal end of the needle with the help of the core extraction (pusher) rod. The insertion aid is used to facilitate the entry of the pusher rod into the mouth of the needle and extrusion of the biopsy specimen from within the lumen of the needle. The distal (bottom) portion of this insertion aid is designed to receive the distal, narrower cutting end portion of the needle, and the proximal (top) portion of the insertion aid is designed to receive the front end of the pusher rod. This guiding system helps proper alignment of the pusher rod with the mouth (distal end opening) of the needle and eases the dislodgement and removal of the biopsy sample through the proximal end of the needle. The needle is ergonomically designed and the biopsy technique is simple and does not require any manipulation of the biopsy needle within the patient in order to secure the biopsy sample. This in turn may make a potentially uncomfortable procedure more tolerable for the patient.

Several studies have recently evaluated the use of a battery powered device and found that it decreased the length of time of the procedure, decreased pain and improved core biopsy specimens. Here we present a comparative study of the battery powered rotary device versus the traditional manual devices. As the present investigation was conducted on cadavers it was not possible to determine whether the use of the powered device was less painful. On the other hand, the length of time of the procedure when performed with the OnControl and Islam needles were equivalent but shorter than that of the Jamshidi and J-needles. This is

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because the extra time and additional steps required to introduce/push the shovel like marrow acquisition cradle (Jamshidi) or sleeve/tweezers (Cardinal and others) over the biopsy specimen to capture and hold it during its withdrawal.

The internal core capturing thread/sickle at the distal tip of the needle (figure 7.1B) in the OnControl system was found to be effective in capturing the biopsy specimen and preventing its loss during withdrawal of the needle. However, the presence of this internally projected thread near the distal cutting end of the needle burrowed into the edge of the biopsy specimen and caused considerable damage and crush artifact (figure 7.5B). A similar observation was also made by other investigators in a prospective randomized study of a rotary powered device (OnControl) for bone marrow biopsy. From our study it is difficult to ascertain how much of this crush artifact was generated by the internally projected thread or from thermal damage due to rotation of the needle at a very high speed. But when we tested the OnControl needle on material similar in consistency of the bone (artificial bone) we found that the needle does indeed generate considerable heat when it is introduced into the artificial bone at a high speed. In addition, the thread/sickle firmly anchored the biopsy within the lumen of the needle and hampered its ready removal. This resulted in the frequent necessity of additional force (such as hammering on the ejector rod) in order to extract the biopsy sample. This ‘forcing’ of the biopsy specimen may be contributory to the crush artifact. Although the powered system may allow clinicians to complete the bone marrow sampling procedure quickly, and with less pain, but the damage it causes to the biopsied tissue could outweigh such benefits.

Although it has been reported that the powered device produced larger volume samples, this concept can be subject to interpretation as it depends on the bore of the needle and how deep the needle is introduced. If needles were pushed to a deeper level (more than 20 mm), it would certainly obtain a longer specimen yielding a larger volume of tissue. A wider bore needle will also provide a larger volume samples even when the length of the biopsy specimen is 20 mm or less.

It is believed that the manual devices, particularly the recently introduced Islam single use core retention bone marrow biopsy needle is superior to the Jamshidi (BD/Carefusion), J needle (Cardinal), Snarecoil (Ranfac) needles as well OnControl (Teleflex/Vidacare) needle system. The Islam needle produced biopsy samples that were similar in size, but higher in quality and free of crush artefact than the biopsy specimens obtained via

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the powered method (Oncontrol) or the J-type (Cardinal), Jamshidi (BD/Carefusion), and Snarecoil (Ranfac) needle. Unlike OnControl and other needle systems the technique with this needle is less elaborate, simple and convenient to use.

Table 1 Visual quality of the biopsy specimen

Sample number and quality	**1**	**2**	**3**	**4**	**5**	**6**
Islam Needle (Moeller)	++	++	+++	++	+++	+++
J-Needle (Cardinal)	--	--	--	+	--	--
Jamshidi needle (Carefusison)	++	+	++	++	+	++
OnControl needle (Vidacare)	+++	++	+++	++	++	++
Snarecoil (Ranfac)	++	+++	++	+	++	++

+++ (Excellent)	Satisfactory sample (intact biopsy specimen with length 20 mm or over) for histological evaluation.
++ (Good)	Satisfactory sample (intact biopsy specimen with length 15-20 mm) for histological evaluation.
+ (Satisfactory)	Less than ideal length of biopsy sample (intact biopsy specimen with length 8-14 mm or two fragments with total length 8-14 mm) but histological evaluation is possible.
-- (Poor)	Inadequate biopsy sample (intact biopsy length less than 8 mm or small fragmented samples, each fragment measuring 5 mm or less in length). Not evaluable histologically.

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Table 2 Number of pieces/fragments

Sample number	**1**	**2**	**3**	**4**	**5**	**6**
Islam needle (Moeller)	**1**	**1**	**1**	**1**	**1**	**1**
J-Needle (Cardinal)	**1**	**2**	**1**	**2**	**1**	**1**
Jamshidi needle (Carefusion)	**1**	**1**	**1**	**2**	**1**	**1**
OnControl needle (Vidacare)	**1**	**1**	**1**	**1**	**1**	**1**
Snarecoil (Ranfac)	**1**	**1**	**2**	**1**	**1**	**1**

Table 2 illustrates the number of pieces/fragments obtained with each needle during each attempt.

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Table 3 (Length of the biopsy in millimeter)

Sample number	1	2	3	4	5	6
Islam needle (Moeller)	15	16	26	17	20	22
J-Needle (Cardinal)	6	3 & 5	7	5 & 7	6	5
Jamshidi needle (Carefusion)	16	10	15	8 & 5	9	15
OnControl needle (Vidacare)	22	17	25	12	15	20
Snarecoil (Ranfac)	15	20	10	18	20	15

Table 3 illustrates the length of the biopsy specimens obtained with each needle during each attempt.

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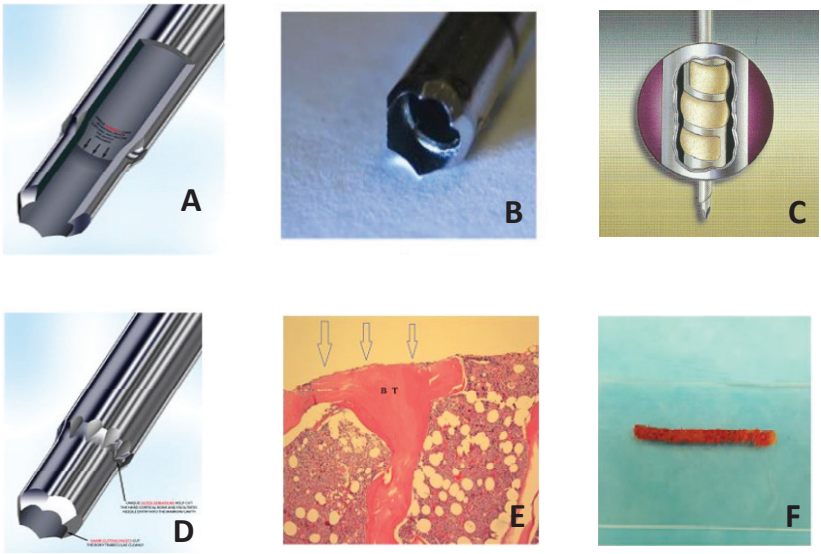


Figure 7.1 A Schematic representation of the internal core retention device (Islam single use core retention biopsy needle). **B.** Photograph of the distal cutting tip of the OnControl biopsy needle (Teleflex/Vidacare) showing the internal thread/sickle. Note the thread/sickle is projecting inwards into the lumen of the needle. **C.** Schematic representation of the core capturing device (Ranfac bone marrow biopsy needle). **D.** Schematic representation of the sharp cutting facets and outside serrations/flutes near the distal cutting end of the needle (Islam single use core retention biopsy needle). **E.** Histological section of a bone marrow biopsy obtained with the Islam core retention biopsy needle. Note cleanly cut bony trabeculae (BT) and little or no crush artifact at the edge of the biopsy specimen. **F.** A macroscopic view of a biopsy specimen obtained with the Islam core retention biopsy needle. Note the uniform and linear cut length of the biopsy specimen.

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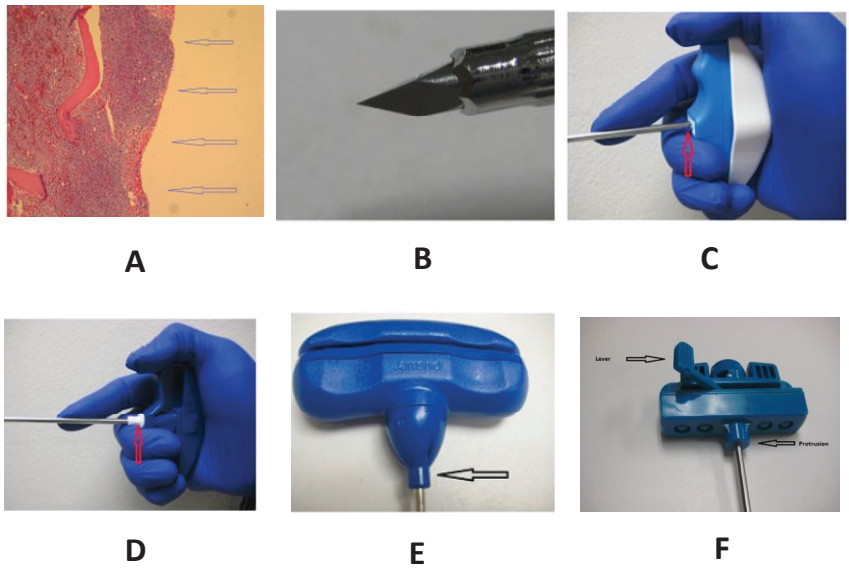


Figure 7.2 A histological section of a bone marrow biopsy obtained with the Islam core retention biopsy needle. Note the cleanly cut biopsy specimen and the absence of any crush artifact at the edge (arrows) of the biopsy specimen. **B.** The trocar pointed stillette of the Islam core retention biopsy needle. **C.** Photograph illustrating the bottom of the handle of Islam core retention biopsy needle demonstrating the *absence* (arrow) of a protuberance (external plastic molding) used as a retainer to hold the needle protector sheath in place as present in the J needle (Cardinal) and Jamshidi needle (Carefusion) and OnControl (vidacare) needle. **D.** Photograph illustrating the bottom of the handle of the J needle (Cardinal) demonstrating the presence (arrow) of a protuberance (external plastic molding) used as a retainer to hold the needle protector sheath in place. **E.** Photograph illustrating the bottom of the handle of the Jamshidi needle (Carefusion) demonstrating the presence (arrow) of a protuberance (external plastic molding) used as a retainer to hold the needle protector sheath in place. **F.** Photograph illustrating the bottom of the handle of the snarecoil needle (Ranfac) demonstrating the presence (arrow) of a protuberance (external plastic molding) used as a retainer to hold the needle protector sheath in place.

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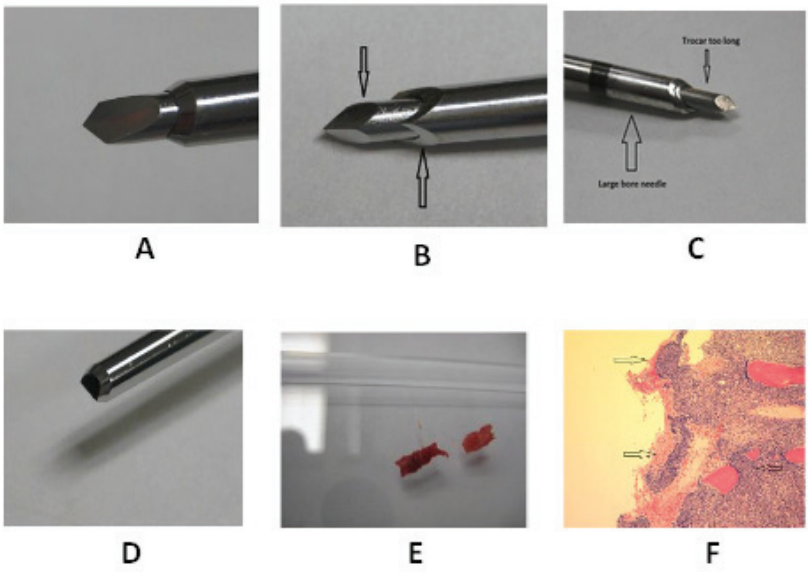


Figure 7.3 A The diamond shaped penetrating end of the stilette of the J needle (Cardinal). **B.** The trocar-pointed tip of the stilette (upper arrow) and the crown-shaped cutting tip (bottom arrow) of the Jamshidi needle (Carefusion). **C.** The trocar-pointed tip of the stilette (upper arrow) of the Snarecoil needle (Ranfac). **D.** The oval shaped cutting end of the J needle (Cardinal). **E.** An Illustration of fragmented biopsy specimen obtained with the J needle (Cardinal). **F.** histological section of a bone marrow biopsy obtained with the Jamshidi needle (Carefusion). Note crush artifact (arrows) at the edge of the biopsy specimen.

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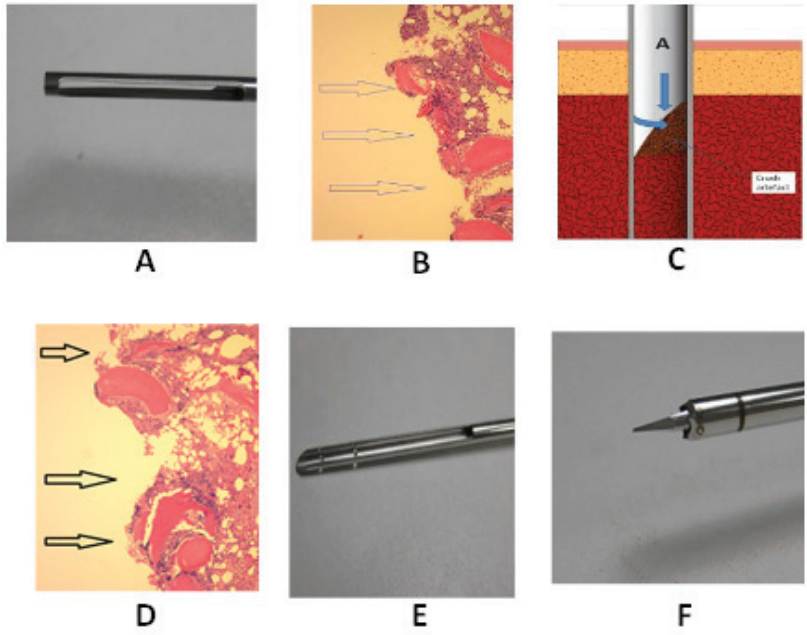


Figure 7.4 A photograph of the sleeve that is used to capture the biopsy specimen for the J needle (Cardinal). **B.** histological section of a bone marrow biopsy obtained with a J needle. Note unevenly cut bony trabeculae and considerable crush artifact (arrows) at the edge of the biopsy specimen. **C.** Schematic representation of the core capturing device by the sleeve (Cardinal), marrow acquisition cradle (Carefusion). Note when the core capturing device (A) is rotated and pushed forward and over the biopsy specimen it produces considerable crush artifact at the edges of the biopsy specimen. **D.** A histological section of a bone marrow biopsy obtained with the Jamshidi needle (Carefusion). Note crush artifact (arrows) at the edge of the biopsy specimen. **E.** A photograph of the marrow acquisition cradle that is used to capture the biopsy specimen for the Jamshidi needle (Carefusion). **F.** Photograph of the trocar pointed stilette and the distal cutting end of the Oncontrol needle (Vidacare).

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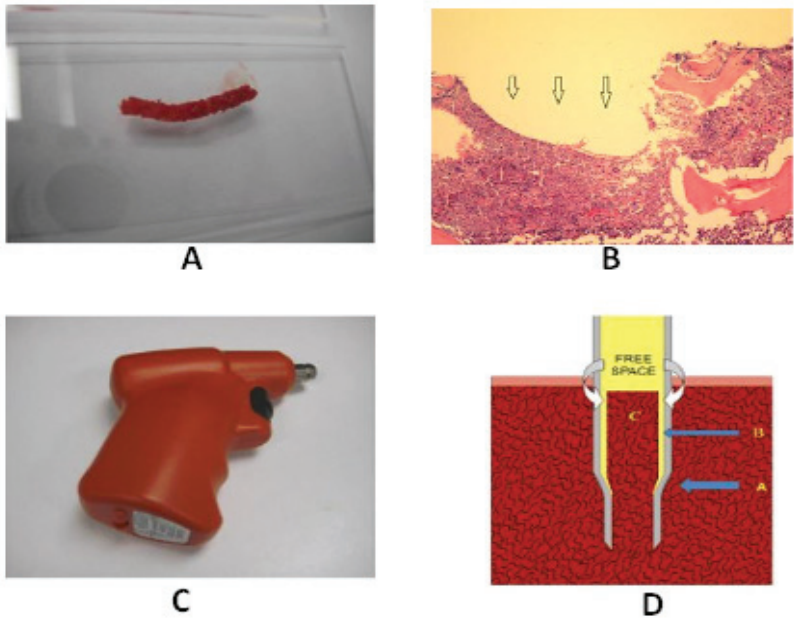


Figure 7.5 A macroscopic view of a biopsy specimen obtained with the OnControl biopsy needle (Vidacare). Note a uniform length of the biopsy specimen. **B.** A histological section of a bone marrow biopsy specimen obtained with OnControl needle (Vidacare). Note the punched out areas (groove-arrows) produced by the internal thread. **C.** Photograph of the OnControl needle hand held power driver (Vidacare). **D.** Schematic representation of the biopsy specimen as obtained with the Islam core retention biopsy needle. Note the internal step (A) that acts as a shoulder which prevents the biopsy specimen from slipping out of the needle as the needle is withdrawn from the patient. Note the free space between the internal wall of the needle (B) and the marrow core (C). This free space allows expansion of the tissue, prevents crushing and avoids plugging of the lumen of the needle. It also allows easy delivery of the core through the proximal end of the needle.

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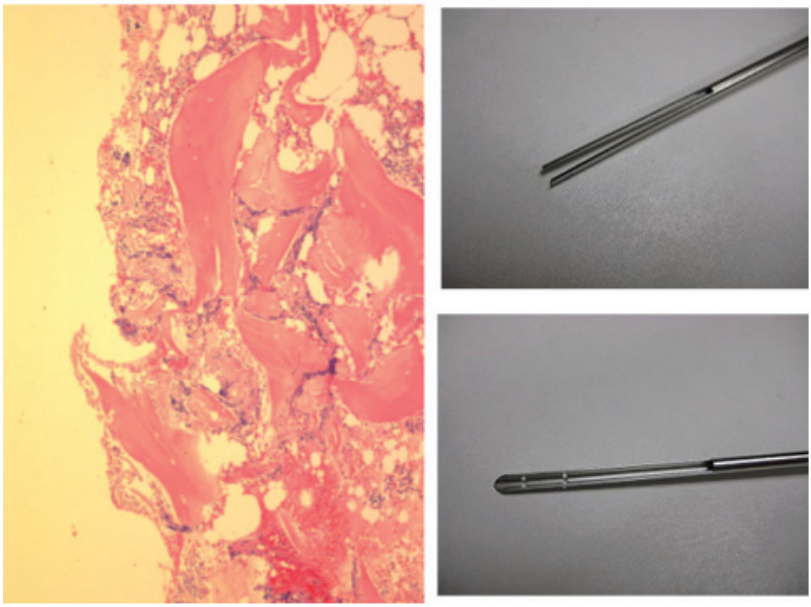


Figure 7.6 (Upper right) A sleeve, which is a tweezer -like component that is used with the needles manufactured by Argon Medical and many other needle manufacturers and (lower right) the marrow acquisition cradle, which is a 'drain spade'- like component that is used with needles produced by BD/ CareFusion. The sleeve acts as a tweezer to grasp the biopsy specimen and the marrow acquisition cradle semi-envelopes the biopsy specimen. Both of these components can cause fragmentation of the biopsy specimen as well as considerable crush artifact particularly at the edge of the biopsy specimen as they are pushed over the biopsy specimen to entrap them. The photomicrograph on the left presents an illustration demonstrating the edge of a traumatized biopsy specimen which was the result of the use of such instruments.

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CHAPTER 8

BONE MARROW ASPIRATION PRIOR TO BONE MARROW CORE BIOPSY USING THE SAME BONE MARROW BIOPSY NEEDLE: A GOOD OR BAD PRACTICE

As stated earlier that bone marrow aspiration and bone marrow core biopsy play an important role in the investigation and diagnosis of haematological as well as non-haematological malignancies and various other diseases. They also play an important role in the management of these conditions particularly in the follow-up evaluation of patients undergoing chemotherapy, bone marrow transplantation, and other forms of medical therapy. The procedure usually involves aspiration of a fluid suspension of bone marrow from the sternum, or from the posterior iliac crests using a sternal puncture or similar needles or with longer needles specially designed to obtain plasma-suspended (liquid) marrow from the posterior iliac crest. The bone marrow core biopsies are usually obtained from the posterior iliac crest with a Jamshidi, Islam or other similar needles. Since the aspirate and core biopsy provide complimentary and useful information, both specimens are routinely obtained at the same time and usually from the same site in a large majority of cases. Posterior iliac crest is most commonly the site of choice. However, because of the extra time required and the inconvenience of using two needles—one for aspiration and one for core biopsy, and the additional cost involved in using the two needles, some investigators use a single bone marrow biopsy needle for both purposes. The technique of aspiration and obtaining a core biopsy at the same time using the same needle and at the same site has inherent technical problems and other disadvantages. In a recent investigation the two techniques, (a) aspiration prior to core biopsy using the same bone marrow biopsy needle (*One needle technique*), and (b) aspiration prior to core biopsy using an aspirate needle for aspiration and then using a separate bone marrow biopsy needle for obtaining the solid core sample (*two needle technique*) was compared. Although the study was purely

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observational and the aim was to identify technical difficulties and gross observational changes that occur in these two techniques of aspiration and biopsy procedures. The actual findings indicated that the two needle technique has definite advantages. It is technically neater and less messy. It also avoids spilling of blood and keeps the surgical area uncontaminated while yielding optimal aspiration and distortion-free core biopsy specimen. It also avoids compromising the technical quality and morphological integrity of the biopsy specimens.

Bone marrow aspiration prior to obtaining a bone marrow core biopsy using the same bone marrow core biopsy needle is called *one-needle technique*. There are two ways by which a bone marrow aspirate sample can be obtained prior to obtaining a bone marrow core biopsy using the same biopsy needle. In one method (figure 8.1), the bone marrow biopsy needle with its stilette in place is first introduced to a few millimetres beyond the cortical bone and into the marrow cavity. Once the mouth of the needle is securely placed inside the marrow cavity, the stilette is withdrawn and aspiration performed with a syringe. Alternatively (figure 8.2), the BM biopsy needle with its stilette in place is introduced just beyond the cortical bone. The stilette is then withdrawn and the needle advanced slowly by clockwise and counter-clockwise rotary motion deep into the marrow cavity until an adequate depth (20-25 mm) is reached. A syringe is then attached at the proximal end of the needle and the aspiration is performed while the core biopsy remains within the lumen of the biopsy needle. After the aspiration, the needle is rotated several times to break loose the core biopsy specimen and the needle containing the core biopsy specimen is then withdrawn.

Bone marrow aspiration prior to obtaining a bone marrow core biopsy using two separate needles, one for aspiration and one for core biopsy is called *two needle technique*. In this technique a bone marrow aspirate sample is obtained first from the posterior iliac using a bone marrow aspiration needle, following which a bone marrow core biopsy is obtained from the same site but from slightly different area of the posterior iliac crest from where prior bone marrow aspiration was performed using a separate bone marrow biopsy needle.

Although in *one needle technique* there was no problem with aspiration of marrow as it flowed very readily and without a tendency to clot. However, the subsequent biopsy process in these cases was bloodier and technically cumbersome due to the spilling of blood through the proximal end of the needle. In addition, after the aspiration process had been completed these

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wide bore biopsy needles usually still contained a considerable amount of blood which often clotted and as a result there was always an elongated thread of clotted blood that preceded the biopsy specimen when it was pushed out of the needle through its proximal end (figure 8. 3). This on occasion also obscured the identification of clot versus core sample when ejected from the needle.

Another important problem that was observed in *one needle technique* that some areas of the sections were depleted or even denuded of marrow cells from the intertrabecular marrow spaces. This observation was easily visualized even under low power (figure 8.4). Such artefactual change and tissue distortion also interfered with proper histological evaluation and interpretation of the core biopsy specimens. The tissue damage was more pronounced in the core biopsy specimens in cases (method 2, figure 8.5) where the biopsy specimen was sitting inside the lumen of the needle when the aspiration was performed. This occurred presumably because the outward flow of the aspirated marrow had to traverse through the core specimen sitting within the lumen of the needle and caused the latter to lose more of its marrow cells in the aspiration process. Tissue distortion however, was minimal and gross artefactual change was not noted (figure 8.6) where aspiration was performed first using a bone marrow aspiration needle followed by a bone marrow core biopsy using a separate bone marrow biopsy needle (*two needle technique*). Although it is recognised that a modest degree of artefactual change can be induced by laboratory processing even under normal conditions the extent of the structural alterations seen in patient's where aspiration was performed prior to biopsy using the same biopsy needle were of such magnitude that they could have occurred only because of the prior aspirational dislodgement of marrow.

Bone marrow may be examined either by an aspiration biopsy or by a trephine biopsy; the latter is also known as a core biopsy. Bone Marrow core biopsy, since its introduction by Ghedini in 1909, and BM aspiration biopsy, since its introduction by Arinkin in 1929 have achieved significant importance in medicine, and haematology and oncology in particular. They are now routinely used in the investigation, diagnosis and management of various haematological and non-haematological malignant conditions as well as in other diseases. They also play important role in monitoring the course of medical therapy. Useful and much needed diagnostic, prognostic and scientific information can be obtained from adequately processed and properly stained specimens of bone marrow aspirate and core biopsy specimens.

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The aspiration biopsy as stated earlier usually involves suction of plasma-suspended liquid bone marrow from the sternum with a sternal puncture needle or from the posterior iliac crest using sternal puncture needles or with needles especially designed to obtain marrow from the posterior iliac crest. Bone marrow aspiration using the sternal puncture (or similar) needles can also be obtained from the anterior iliac crests, ribs, spinous processes of lumbar vertebrae or from any other superficial and easily accessible bones which show radiological or other evidence of osseous lesions. Bone marrow core biopsies are usually obtained from the posterior iliac crest with a Jamshidi, Islam or other similar needles. They may also be obtained from anterior iliac crests or other accessible bony sites such as ribs or vertebral bodies if radiological or other evidence of osseous lesions are present. The advantages of unadulterated bone marrow aspirates and distortion free, cleanly severed bone marrow core biopsy specimens cannot be over emphasized. In order to obtain ideal specimens some investigators have consequently elected to biopsy two independent sites (one for aspiration and one for core biopsy) with two separate needles. The sternal puncture has its rare but serious disadvantages. Considerable morbidity and even death have been reported following sternal puncture due to pericardial tamponade as a result of through and through passage of the needle. The sternum also contains a small amount of marrow and in older patients it contains more fat than marrow. It is also considered to be a less desirable site for aspiration as it causes the most pain and patient apprehension. Now a day's marrow aspiration from the sternum is usually performed only when the posterior and anterior iliac crests are diseased or inaccessible because of massive obesity. Because of the aforementioned disadvantages associated with the sternal puncture, in a large majority of cases both aspiration and core biopsy procedures are performed at the posterior iliac crests. Although the percentages of patients undergoing a trephine biopsy in addition to an aspiration biopsy vary considerably (from 8% to virtually 100%), the trend towards performing both at the same time in order to avoid a repeat procedure later is increasing. In addition, since the aspirate and biopsy provide complimentary and useful information, some investigators now routinely obtain both specimens at the same time. However, because of the inconvenience of using two needles—one for aspiration and one for core biopsy and the additional cost involved in using the two needles at the same time, some investigators use a single bone marrow biopsy needle for both purposes. The need for quality aspirates and biopsies cannot be overemphasized. The complementary nature of the two procedures is also important and performing both in most patients is desirable. Shortcuts, particularly to save the cost of a needle can

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compromise the quality of such specimens and should be avoided if at all possible. It is suggested that aspiration prior to core biopsy using the same bone marrow core biopsy needle should be avoided and if aspiration and core biopsies are to be performed on the same site (posterior iliac crests) and at the same time then two needle approach should be used.

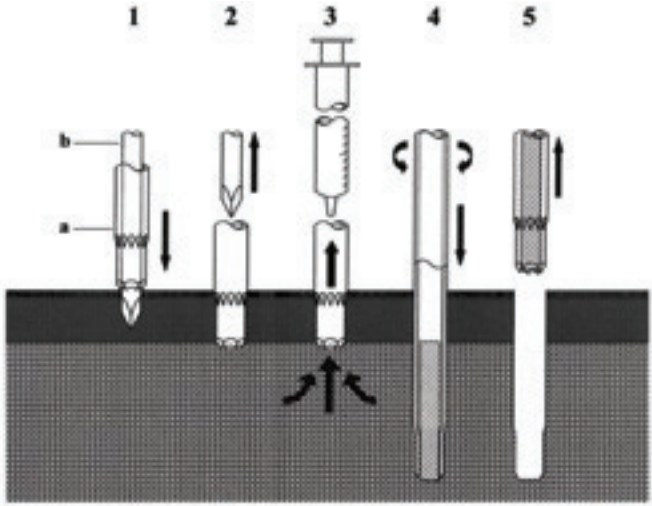


Figure 8.1 Schematic representation of bone marrow aspiration prior to core biopsy, *method one*. (1) The needle (a) with the stilette (b) in place is inserted down to the bone. (2) The cortex over the posterior ileum is then penetrated by gentle rotary motion of the needle. Once this penetration has been achieved and the mouth of the needle has entered into the marrow cavity (spongy bone), the stilette is withdrawn. (3) A syringe is attached at the proximal end of the needle and a bone marrow aspiration is performed. (4) Following the aspiration the needle is then advanced slowly with clockwise-counter-clockwise rotary motion. (5) When an adequate depth is reached, the needle is rotated several times along its long axis to break loose the core biopsy specimen, and the needle containing the biopsy specimen is then withdrawn.

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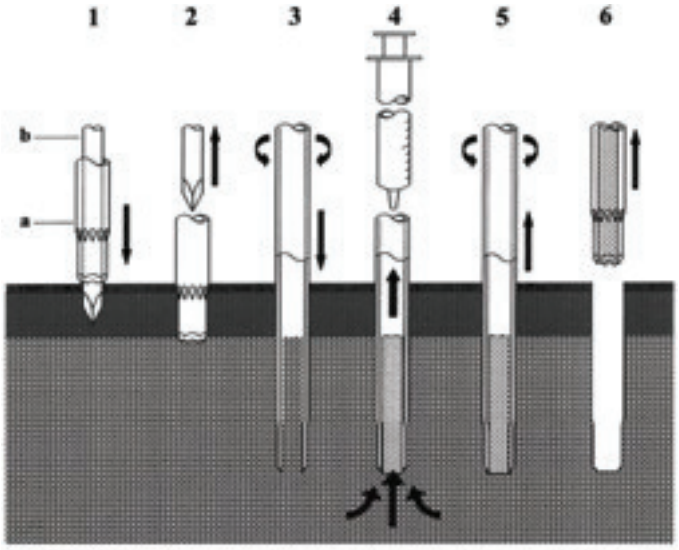


Figure 8.2 Schematic representation of BM aspiration prior to core biopsy, *method two*. (1) The needle (a) with the stilette (b) in place is inserted down to the bone. (2) The cortex over the posterior ileum is then penetrated by gentle rotary motion of the needle. Once this penetration has been achieved, the stilette is withdrawn. (3) Following withdrawal of the stilette the needle is then advanced with slow, steady and controlled clockwise- counter-clockwise rotary motion until an adequate depth (20-25 mm) is reached. (4) A syringe is then attached at the proximal end of the needle and a bone marrow aspiration is performed. (5) Following bone marrow aspiration the needle is rotated several times along its long axis to cut all the trabecular connections at the base of the core. (6) The needle containing the core biopsy specimen is then withdrawn.

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Figure 8.3 Photograph of an elongated blood clot that preceded the expulsion of the core biopsy specimen (arrow) during its removal. In this case bone marrow aspiration was performed prior to bone marrow core biopsy using the method two as demonstrated in figure 8.2.

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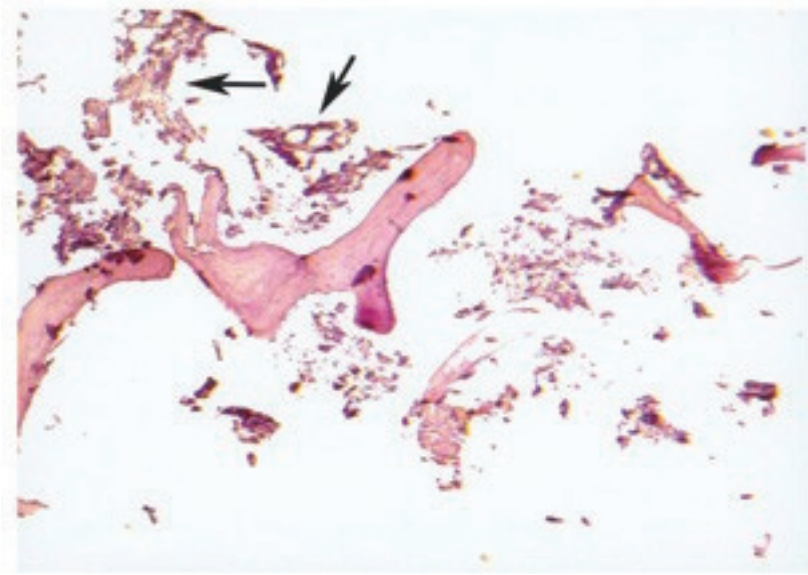


Figure 8.4 Histological section of a bone marrow core biopsy specimen obtained from a patient (method 1, figure 8.1) showing denuded areas from where the marrow tissue was removed during aspiration prior to core biopsy. Note the preservation of some marrow tissue (arrow).

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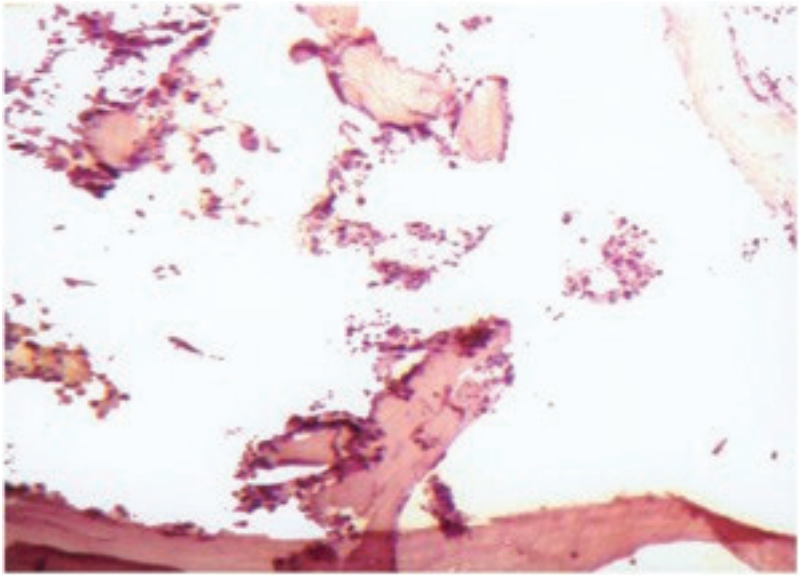


Figure 8.5 Histological section of a bone marrow core biopsy specimen obtained from a patient (method 2, figure 8.2) showing denuded areas from where the marrow tissue was forcefully removed during aspiration prior to core biopsy. Note absence of any preserved marrow tissue.

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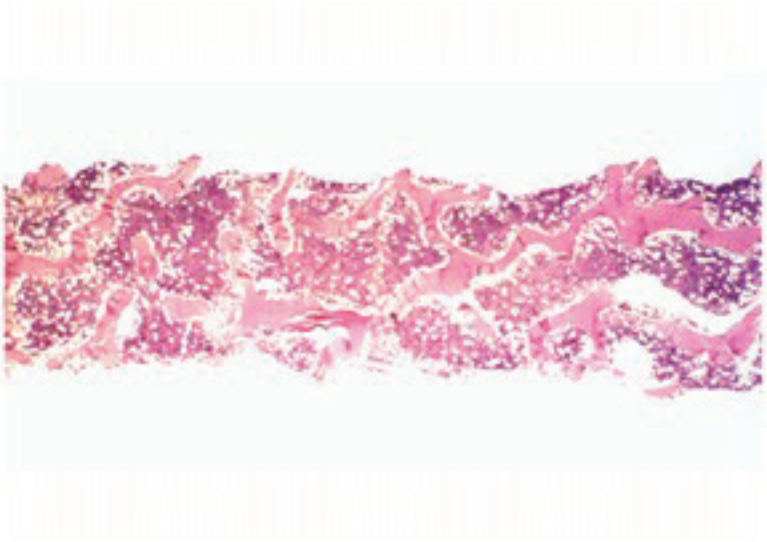


Figure 8.6 Histological section of a distortion-free bone marrow core biopsy specimen showing intact marrow for histological evaluation. In this case a separate bone marrow core biopsy needle was used to obtain the core biopsy specimen. Aspiration prior to coring was performed with a separate aspiration needle on the same site but from a slightly different area of the posterior iliac crest from where the core biopsy was obtained.

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CHAPTER 9

TIPS FOR A SUCCESSFUL BONE ARROW ASPIRATION AND BIOPSY PROCEDURE BY PALPATION METHOD (BLIND ASPIRATION AND BIOPSY)

The technique of obtaining a bone marrow aspiration and biopsy from posterior ilium is simple and straightforward, and in experienced hands its performance poses no difficulty. Even experienced clinicians, however, may sometimes find it difficult, particularly in obese patients, to locate and make contact with the posterior iliac crest in an appropriate area. The following tips may be helpful in identifying and making contact with the ilium specifically at the center of the broadened, enlarged tuberosity-like, medial (paraspinal) region of the posterior iliac crest.

1. The patient is placed in the right or left lateral decubitus position with the knee tops drawn up and back comfortably flexed or in a prone position with a pillow beneath the hips

2. The area of and surrounding the biopsy site is sterilized and adequately draped.

3. The tip of the middle finger of the right hand is placed on the end of the coccyx, and the thumb extended as much as possible over the underlying spinous processes of the lumbar vertebrae (photograph 1a). A close up view of another draped patient (photograph 1b) illustrates the position of the thumb and middle finger. The dotted line indicates the lumbar spinous processes.

4. The thumb is kept in place while the hand is rotated anti-clockwise until the tip of the index finger lies vertically in the same plane and superior to the thumb (demonstrated by dotted line) (photograph 2a and 2b). The “X” indicates the site of entry of the needle midway between the thumb and tip of the index finger.

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5. The small area of the patient's lower back located in the center of the space between the thumb and index finger, is marked, (photograph 2a and 2b). This marked area lies superficial and dorsal to the target area of the posterior iliac crest. A needle introduced through the skin and into the subcutaneous tissue at this point (photograph 3) in a horizontal plane and directed towards the anterior, superior iliac spine (identified by the tip of the middle finger of the left hand, photograph 3) will hit the desired region of the medial segment of the posterior iliac crest. The aspiration biopsy and coring procedure is conducted at this locus.

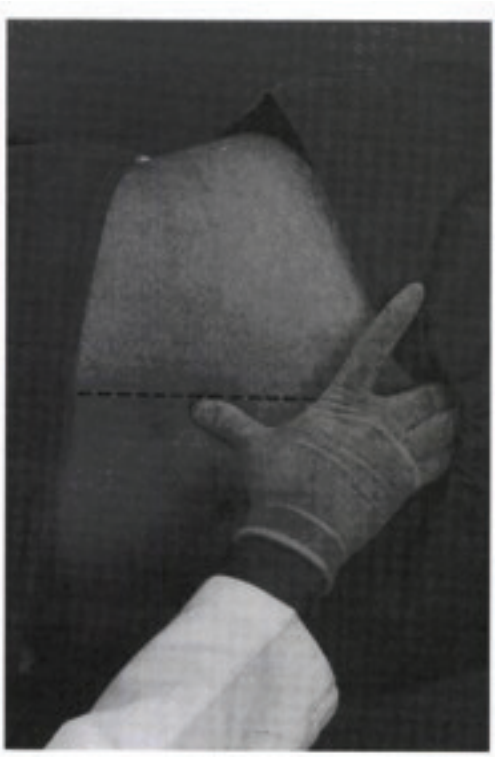
6. While performing the biopsy an attempt should be made to hold the tissue mass surrounding the anterior ilium with the left hand to stabilize the patient (photograph 4) and to retain the correct orientation of the needle. The middle finger of the left hand should rest on the anterior superior iliac spine to serve as a fixed reference point and an indicator of the desired direction of the biopsy needle (see photographs 13 and 4).

The above suggestions are given to provide a guideline to help obtain adequate bone marrow biopsy samples from the posterior iliac crest. Optimally, the technique should be practiced on cadavers to perfect the procedure and to become acquainted with various adjustments that are required to accommodate factors such as the stature of the patient and size of the operator's hand.



Photograph 1a

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Photograph 1b

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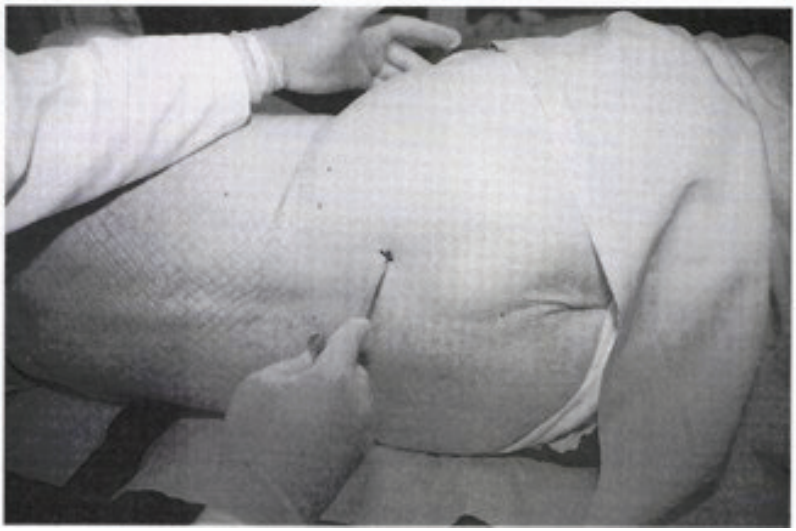
Photograph 2a

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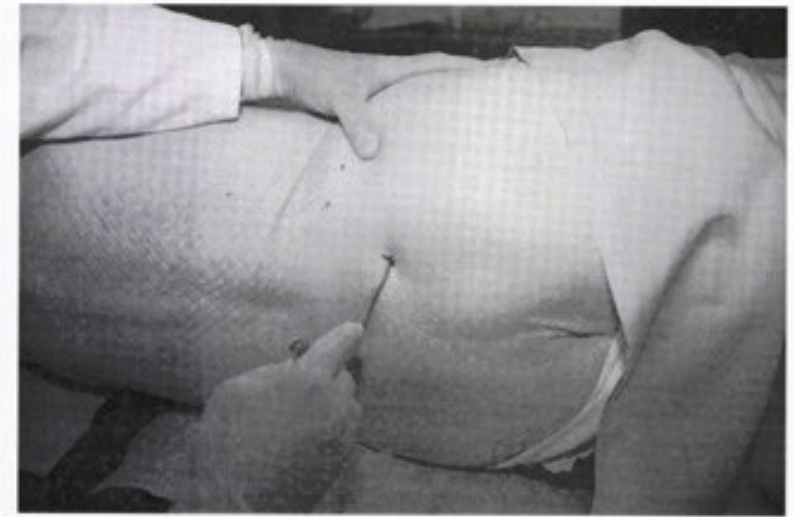


Photograph 2b

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Photograph 3



Photograph 4

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CHAPTER 10

ULTRASOUND GUIDED BONE MARROW ASPIRATION AND TREPHINE (CORE) BIOPSY

As stated earlier bone marrow trephine biopsy plays an important role in the investigations, diagnosis and management of patients with various hematological and non-hematological malignant conditions. It is now routinely used in tandem with bone marrow aspiration because of the advantage it offers over the bone marrow aspiration only. However, the value of bone marrow trephine biopsy depends on the quality of the specimens obtained. It is known that the quality of the bone marrow trephine biopsy depends not only on the type of instruments used but it also depends to a great extent on the knowledge and proficiency of the operator. However, even in skilled and experienced hands and even with appropriate needles the target site such as the posterior iliac crest can be missed or hit off center if it is based on external landmarks (blind aspiration and biopsy). This may result in less than desirable biopsy specimen. In order to precisely locate the posterior iliac crest and to obtain an adequate (long core) bone marrow trephine biopsy, we used ultrasound to accurately define the posterior iliac crest prior to obtaining a bone marrow aspiration and trephine biopsy specimen.

Although ultrasound imaging has evolved as a very useful diagnostic tool in medical science, the technique of ultrasound guided bone marrow aspiration and trephine biopsy has not been routinely used by hematologists and oncologists to help locate the posterior iliac crest during the bone marrow aspiration and trephine biopsy procedure. In this technique, sound waves are projected on the body parts, which bounce back and are collected by computer to generate images of the internal organs. Sound waves cannot penetrate bones and thick tissues; hence these structures can be clearly seen in an ultrasound image. Thus this technique can be very useful in precisely locating the hip bone (posterior iliac crests) and can be very helpful while performing bone marrow aspiration and trephine biopsy particularly when dealing with obese patients whose iliac crest is buried under a carpet of adipose tissue. Recently, we have used the

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technique of ultrasound guided bone marrow aspiration and trephine biopsy in patients diagnosed with various hematological (leukemia, multiple myeloma, myelodysplastic syndrome, thrombocytopenia, non-Hodgkin's lymphoma) and non-hematological malignant (carcinoma of the prostate with bone metastasis) conditions. We found the technique simple and useful in accurately locating the posterior iliac crest. As a result it facilitates the extraction of a satisfactory core sample or aspiration biopsy and is more surgically precise than when access to the target bone is based relying only on external landmarks (blind aspiration and biopsy).

The technique is simple. Generally the patient is placed in a right or left lateral decubitus position, with the knees drawn up and back comfortably flexed or in the prone position with pillow beneath the hips. An ultrasound transmission gel is applied over the right or left lower back covering the lateral points of rhomboid of Michaelis, which overlies the posterior iliac crest. The hip bone (posterior iliac crest) is then located by using a transducer (figure 10.1 a). With the transducer positioned over the bone, an ink dot/line is placed on the skin at the midpoint of each side of the transducer. The dots/lines are connected to form a "+". The accuracy of the marking is checked by placing the transducer at the "+" in both transverse and longitudinal orientations.

Care must be taken to ensure that the marking is directly over the center of the bone where the needle will be introduced. Once the bone is adequately demonstrated on the computer screen (figure 10 .1 b) the area is marked with an indelible marker. Alternatively the central area of the bone can be marked with thumbnail pressure followed by marking with indelible ink by wiping off the gel. After marking the area the site is prepared with the use of sterile technique and the patient is draped. The aspiration and trephine (core) biopsy (figure 10. 1 c and d) are performed under adequate local anesthesia using a bone marrow aspiration and bone marrow biopsy needle.

As illustrated in figures 10.1 c & d that the cortical bone and periosteum are not collected in the biopsies. This is because the method of bone marrow aspiration and trephine biopsy as advocated by Islam is utilized i.e., the cortical bone is not harvested in the biopsy sample. The cortical bone is not relevant to the cytologic assessment of hemopoietic activity. In addition, if the operator removes the trocar when the instrument hits the cortical bone and immediately initiates the rotatory coring through the hard cortical bone to obtain the sample this action damages the sharp cutting edges of the needle and can lead to obtaining an irregularly cut,

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less than optimal biopsy. Thus the trocar is not removed until the cortical bone is fully penetrated and the medullary space is reached. At this time the trocar is removed and the biopsy needle is pushed forward with a rotatory motion into the softer spongy bone to obtain a satisfactory bone marrow trephine biopsy specimen.

Traditionally, bone marrow aspiration and trephine biopsy specimens are obtained relying only on external anatomical landmarks (blind aspiration and biopsy) by palpation. We illustrate the technique of bone marrow aspiration and biopsy from the posterior iliac crest with sonographic guidance. Sonographic evaluation and guidance for bone marrow aspiration and biopsy offer several advantages over the traditional approach. The posterior ilium can be easily located, and the needle can be directed at a correct angle toward the posterior iliac crest following ultrasound guidance.

As stated earlier that the success rate of acquiring a satisfactory bone marrow trephine biopsy sample rests not only on the type of biopsy needle used and the skill and knowledge of the operator, but it also depends to a great extent to precisely locate the site, the posterior iliac crest (figure 10.2 a), which is now the preferred site for both bone marrow aspiration and trephine biopsy. Under typical circumstances hematologists, oncologists (and nurse practitioners) use only external anatomical landmarks (blind aspiration and biopsy) by palpation to locate the posterior iliac crest to perform this important diagnostic procedure. As a result the center of the bone where the needle should hit (figure 10. 2b) to be able to obtain a nice long core biopsy containing trabecular bone and marrow tissue may be missed resulting in an inadequate and unsatisfactory bone marrow trephine biopsy specimen. If the needle does not hit the bone at a correct angle then this may result in a tangential biopsy containing mostly bone and very little marrow tissue (figure 10.3. Furthermore if the needle veers too much to the right (figure 10. 4a) or to the left, (figure 10. 4b) or in any other direction, or misses posterior iliac crest completely, that can cause serious complications, including damage to the sciatic nerve or a massive buttock and thigh extravasation of blood or hematoma (figure 10.5). These complications, although rare, but have been reported. Ultrasound guidance allows safe passage of the needle into the desired marrow-rich intramedullary site while avoiding damage to important surrounding structures.

It is known that a higher rate of inadequate or unsatisfactory biopsy specimens are obtained by less-well- trained hematologists and oncologists; however, the fault also lies in the fact that, particularly in

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obese patients, it is rather difficult to locate the posterior iliac crest by blind aspiration and biopsy. While doing an adequate bone marrow trephine biopsy, the skill of the individual operator and the type of needles used cannot be over-emphasized. Many operators, particularly less-well-trained hematologists and oncologists, fail to obtain an adequate bone marrow trephine biopsy because of the reasons mentioned above. This technique of ultrasound-guided bone marrow trephine biopsy improves our ability to precisely locate the posterior iliac crest and thus may help even a less-familiar hematologist/oncologist to obtain an adequate bone marrow trephine biopsy specimen. We found the technique simple and very useful in precisely locating the posterior iliac crest which helped in obtaining an adequate bone marrow trephine biopsy specimen at each attempt. The patients also tolerated the procedure well and without complaints. Ultrasound guided bone marrow biopsy is also preferable to fluoroscopy guided bone marrow biopsy as it avoids exposure to ionizing radiation, even though it can be very minimal and it is also cost-effective when compared to fluoroscopy guided bone marrow biopsy. A linear transducer of at least 7.5 MHz or higher frequency is recommended depending on the patient's body habitus.

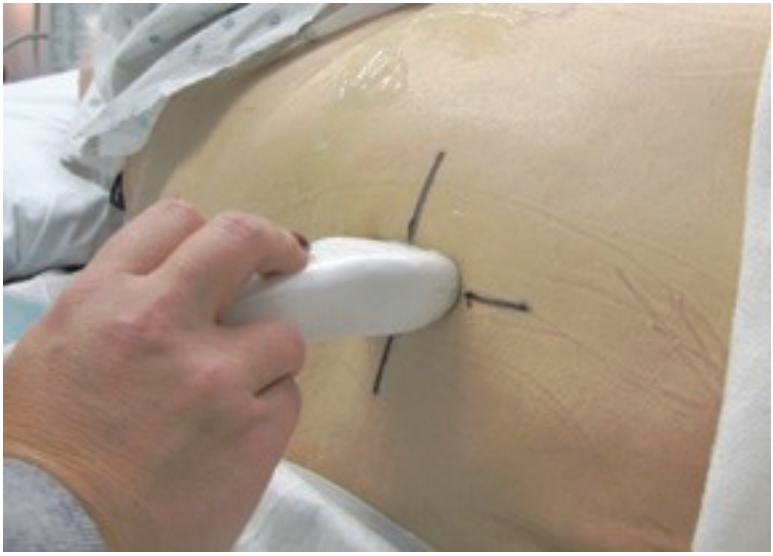


Figure 10.1 [a] Shows the transducer positioning for sonography of posterior ilium. The center of the '+' (covered by the transducer) lies directly over the center of the posterior iliac crest through which the needle will be introduced to obtain bone marrow aspiration and trephine biopsy.

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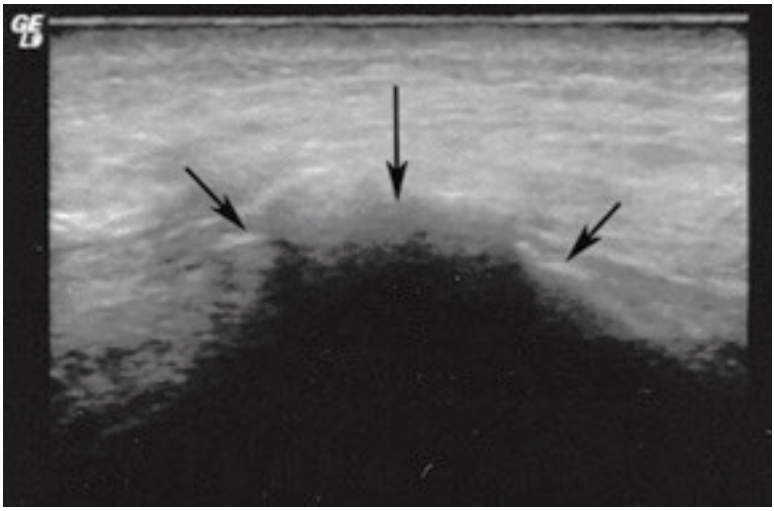


Figure 10.1 [b] Shows the reflective hyperechoic bone cortex (arrows) of the posterior ilium.



Figure 10. 1 [c] Shows a fresh (before the biopsy was placed in a fixative) long (over 20 mm in length) core bone marrow biopsy specimen obtained from a patient using a Islam single use bone marrow biopsy needle under ultrasound guidance.

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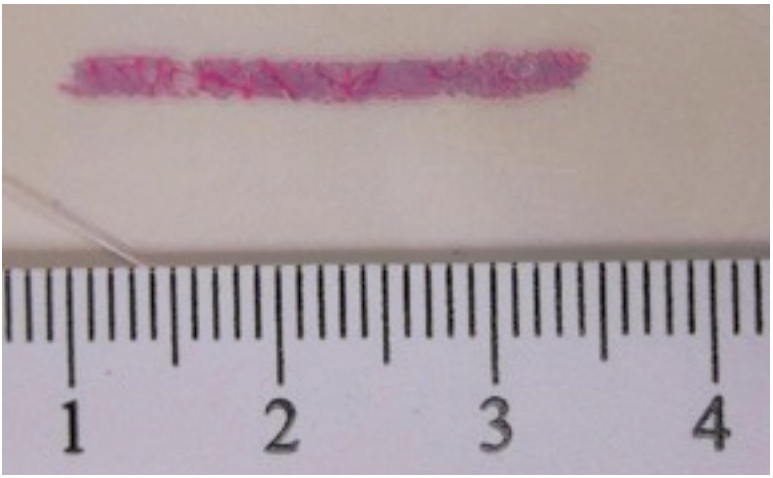


Figure 10.1 [d] Shows a fixed and sectioned long core biopsy specimen obtained from a patient using a Islam single use bone marrow biopsy needle under ultrasound guidance. Here the biopsy was fixed in 10% Zenker's formalin, decalcified, and processed in paraffin. The section was stained with hematoxylin and eosin. Note here the long and undistorted biopsy specimen.

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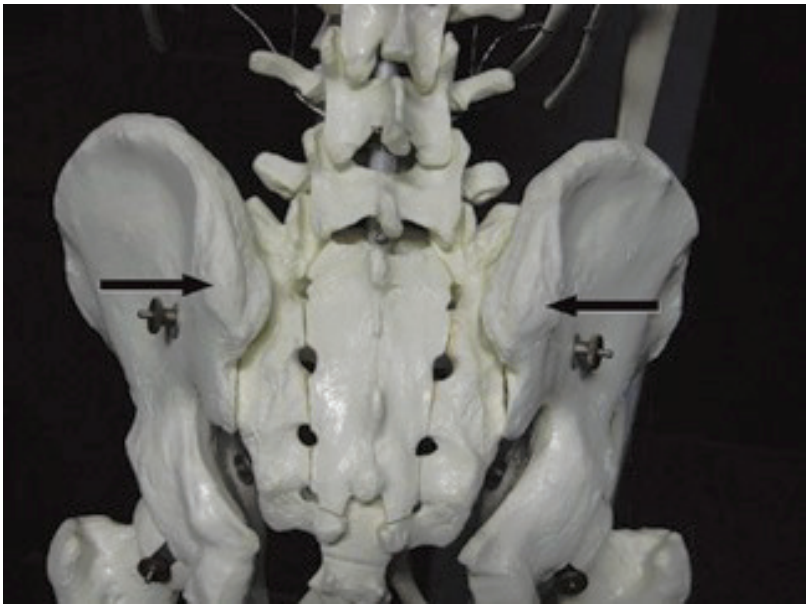


Figure 10.2 [a] demonstrates a human pelvis showing the right and left posterior iliac crests (arrows).

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Figure 10.2 [b] demonstrates a human pelvis showing the right posterior iliac crest the center of which is being hit by the biopsy needle.

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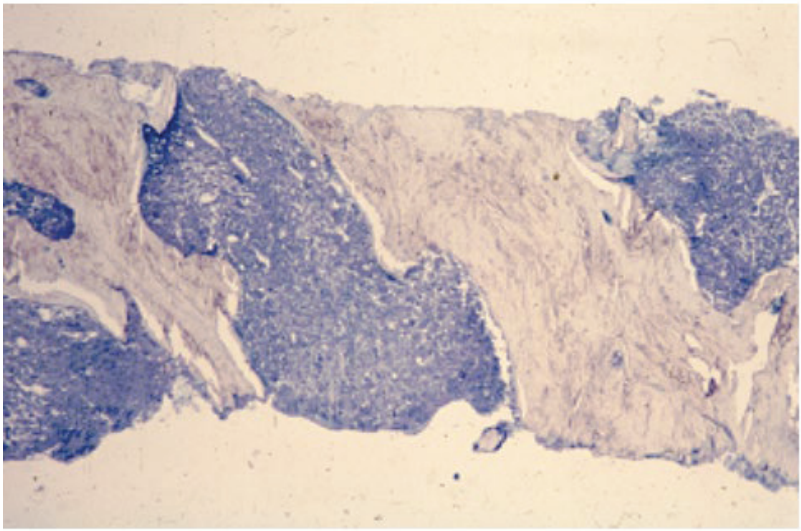


Figure 10.3 A tangential biopsy specimen obtained from a patient with a myeloproliferative disorder. Note mostly bone and some marrow tissue.

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Figure 10.4 [a] demonstrates a human pelvis showing the right posterior iliac crest the center of which has been missed and the biopsy needle has deviated to the right side.

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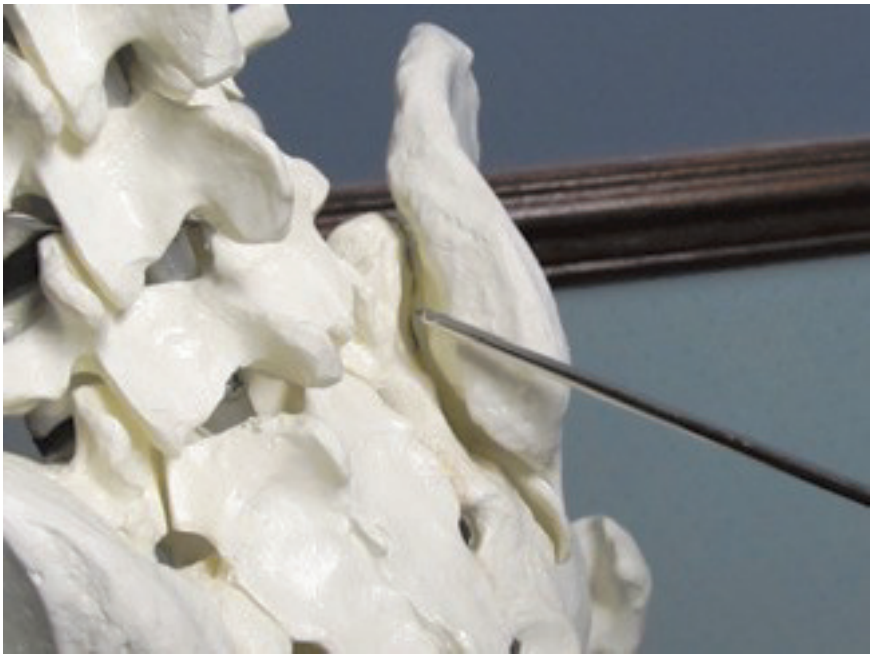


Figure 10.4 [b] demonstrates part of a human pelvis showing the right posterior iliac crest the center of which has been missed and the biopsy needle has deviated to the left side.

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Figure 10.5 the above photograph shows massive extravasation and a hematoma at the site following a bone marrow aspiration and a biopsy procedure in an elderly patient whose platelet count was normal and the patient was not on any anti-platelet agent or anticoagulation. Extensive extravasation was also noted in his thigh and perineal region following the procedure.

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CHAPTER 11

COMPUTED TOMOGRAPHY (CT) GUIDED BONE MARROW ASPIRATION AND TREPHINE (CORE) BIOPSY

Computed tomography (CT) with or without fluoroscopy has evolved as a very useful tool in medical science and is used as an instrument for sampling a solid organ tissue (biopsy), body fluid, or a tumor mass suspected of malignancy. In this system the aspiration and biopsy needle can be visualized by the physician on a CT scanner and assist the practitioner in the accurate localization of the target tissue. Because of the problems associated with accurately locating the posterior iliac crest with surface anatomic landmarks and conventional palpation method (considered a 'blind approach'), CT-guided bone marrow aspiration and bone marrow trephine (core) biopsy in patients diagnosed with various hematological and non-hematological malignancies have increasingly being used. The technique is found to be extremely useful in accurately locating the posterior iliac crest particularly in obese patients. This procedure facilitates an adequate aspiration of bone marrow and extraction of an excellent core biopsy specimens at each encounter and is more surgically precise than when access to the target bone (iliac crest) is based only on palpation of external landmarks ('blind approach').

Bone marrow aspiration and trephine (solid core) biopsy is a crucial tool in the investigation, diagnosis and management of patients with many types of hematological and non-hematological malignant conditions. Both bone marrow sampling procedures are currently used in tandem because each one offers specific and important diagnostic information. However, even in the hands of a skilled professional using the appropriate type of needle, the site (in most cases, the posterior iliac crest) can be missed or not hit at the center of the posterior iliac crest resulting in an inadequate, poor or unsatisfactory bone marrow aspiration and trephine (solid core) biopsy specimen. In order to efficiently and precisely locate the posterior iliac crest and to obtain sufficient aspirate sample and an adequate length of a core biopsy specimen, CT guidance has been used to accurately define and

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locate the posterior iliac crest prior to obtaining a bone marrow sample with good results.

Procedure

After obtaining informed consent a CT guided bone marrow aspiration and trephine (solid core) biopsies are obtained from patients diagnosed with various hematological and non-hematological disorders. In most cases the patients are placed in a right or left lateral decubitus position, with the knees drawn up and back comfortably flexed (figure 11.1), or in the prone position in the CT scanner (figure 11.2). A grid is placed over the posterior iliac region (figures 11.1 and 11.2) and the desired entry point of the needle is identified on the grid under CT visualization. The patient is then partly pulled back out of the CT scanner, the grid is removed and the desired entry point of the needle is marked on the patient's body with an indelible marker. The operative site is prepared with the use of sterile technique and the patient is surgically draped. Following local anesthesia (skin, subcutaneous tissue and periosteum) a 15 gauge bone marrow aspiration needle is introduced through the skin at the earlier marked location and advanced slowly pointing toward the anterior superior iliac spine. Once the needle is stabilized (locked) in the bone the patient is moved back into the scanner to visualize whether the tip of the needle is in the correct position. Although such verification is not always necessary it is a good practice to utilize this procedure as a precautionary measure. Once the accurate positioning of the needle is affirmed the patient is again moved out of the scanner and a routine bone marrow aspiration is performed using a bone marrow aspiration needle. Following the bone marrow aspiration a small incision is made over the marked area with a surgical scalpel to allow for the passage of the 11 gauge bone marrow core biopsy needle. The biopsy needle with the stilette in place is then advanced slowly through the incision, pointing towards the anterior superior iliac spine and when the posterior iliac crest is reached it is then penetrated by gentle rotary motions of the needle. Once the cortex is penetrated the stilette is removed with one hand while holding the needle in place with the other. The biopsy needle is then advanced with slow, steady and controlled clockwise-counter clockwise rotary motions until an adequate depth (about 20-25 mm) is reached. The biopsy needle is then rotated completely several times around its long axis to sever all trabecular connections at its base and break the core sample loose from the surrounding spongy bone and is then slowly withdrawn with a straight pull. Gentle alternating rotary motions may facilitate the needle withdrawal.

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However, no rocking, sculling or change in the direction of the tip of the needle is necessary if the Islam core retention bone marrow biopsy needles are used (see chapters 4, 5 and 6). Once the needle was withdrawn, one end of the insertion aid is attached to the distal cutting end of the needle. The biopsy specimen is then pushed out of the needle with the pusher that is introduced through the other end of the insertion aid. In most patients the procedure is performed under local anesthesia (1 or 2% lidocaine). However, some patients may need conscious sedation with midazolam or a combination of midazolam and fentanyl. It is preferable to perform a bone marrow aspiration with a 15 gauge needle first prior to obtaining a bone marrow trephine (core) biopsy with a separate larger 11 gauge biopsy needle. As discussed in chapter 8 this *two needle technique* offers much better, intact, and undistorted bone marrow biopsy (core) samples than when both bone marrow aspiration and core biopsies are performed with the same core biopsy needle (*one needle technique*).



Figure 11.1 A patient placed in a left lateral decubitus position with the knees drawn up and back comfortably flexed. The grid which helps in selecting the entry site and marking the point of entry of the needle is in place.

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Figure 11.2 A patient placed in a prone position on the CT scanner. The grid which helps in selecting the entry site and marking the point of entry of the needle is in place.

Once the biopsy procedure is complete, the edges of the wound are pressed together with an adhesive tape. A gauze dressing is applied, and the patient is instructed to lie flat on his/her back for 10-15 minutes or longer if the patient has a low platelet count, is on anticoagulation or taking aspirin.

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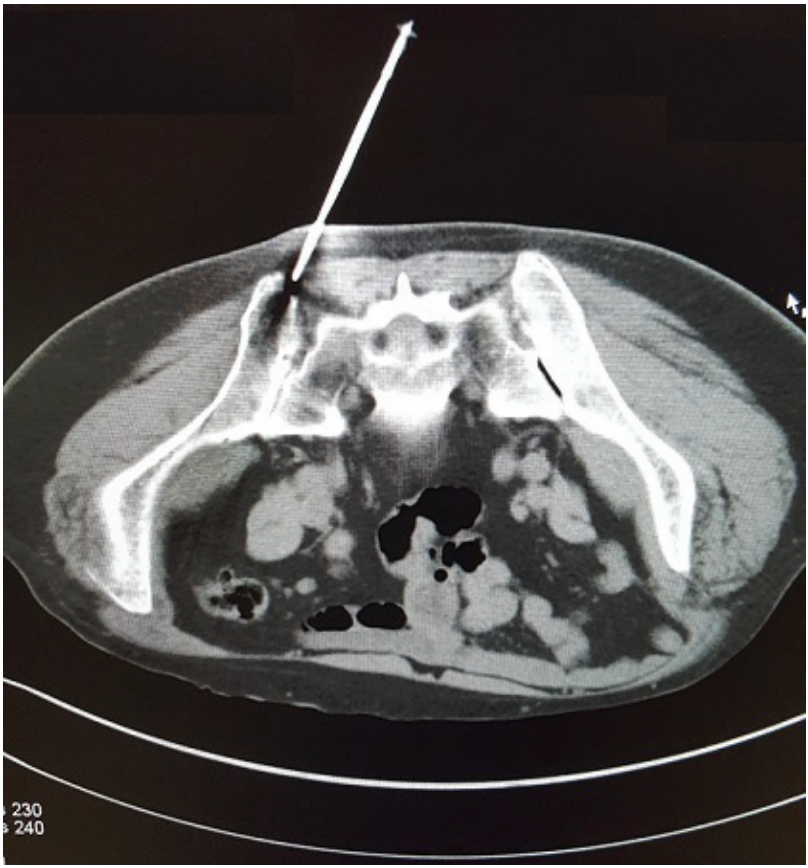


Figure 11.3 A CT image shows the tip of an 11 gauge Islam bone marrow biopsy needle accurately placed over the posterior ilium near the posterior iliac crest before being advanced into the marrow cavity.

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Figure 11.4 A fresh long core biopsy (over 20 mm in length) obtained from a patient using a CT guidance.

Comment

Conventionally, hematologists and oncologists rely on external anatomical landmarks and palpation to identify and locate the posterior iliac crest to obtain bone marrow aspirate and trephine biopsy specimens. This is known as the "blind approach" and quite often it proves to be unsatisfactory as the posterior iliac crest is not contacted (missed). The technique of bone marrow aspiration and trephine biopsy from the posterior iliac crest can be vastly improved when it is performed under CT guidance. CT guidance offers multiple advantages over the conventional approach. The posterior iliac crest can be easily located, and the needle can be directed at a correct angle towards the posterior iliac crest, and most importantly the needle can be visualized entering the bone (figure 11.3).

The success rate of acquiring a satisfactory bone marrow trephine (solid core) biopsy sample is believed to be contingent upon both the selection of biopsy needle as well as the skill and knowledge of the professional using it. Much also depends on precisely locating the target site the posterior iliac crest. While performing a bone marrow aspiration and core biopsy it

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is crucial to be routinely able to locate the posterior iliac crest as this region is currently the preferred site for both bone marrow aspiration as well as trephine samplings. In most situations, hematologists, oncologists and nurse practitioners rely on external anatomical landmarks ("blind approach") to locate the posterior iliac crest in order to perform this important diagnostic procedure. Unfortunately, the blind approach is very unreliable and often misses the center of the bone where the needle should make contact. If the needle misses the center of the bone, it is less likely to obtain a satisfactory core biopsy containing trabecular bone. Also, in such cases, marrow tissue may not be accessed, resulting in an inadequate or unsatisfactory trephine biopsy specimen. Moreover, if the needle does not hit the bone at the correct angle this may result in a tangential biopsy which contains mostly bone and very little of the marrow tissue which is required to make a proper diagnosis. Furthermore, if the needle veers too much to the right, left, or any other direction, or misses posterior iliac crest completely, that can cause serious complications, including damage to the sciatic nerve or a massive extravasation and hematoma at the site and over thigh and buttock (chapter 10, figure 10.4. These complications, although rare, but have been reported. CT guidance greatly reduces the chance of user error and enables the safe passage of the needle into the desired marrow-rich intramedullary site for ample bone marrow aspiration. Most importantly this technique also allows a decent length of a core biopsy specimen (figure 11.4) to be obtained while simultaneously avoiding damage to important surrounding structures.

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CHAPTER 12

THE USE OF THE SMARTPHONE AS A TOOL FOR PRECISELY LOCATING THE POSTERIOR ILIAC CREST TO OBTAIN SAMPLES OF FLUID MARROW (BONE MARROW ASPIRATION) AND TREPHINE (SOLID CORE) BIOPSIES

Ultrasound imaging has evolved as a very important clinical tool in current day medical science. It is frequently used for gaining vascular access, arterial cannulation, and regional nerve block. In addition to its varied uses it can also be used to help accurately locate the posterior iliac crest during a bone marrow aspiration (BMA) and bone marrow trephine (core) biopsy (BMTB). Ultrasound machines are large and bulky (figure 12.1) and generally not suitable for bedside use. Computed tomography (CT) is preferred by interventional radiologists to obtain BMA and BMTB because of the advantage it offers over the ultrasound guidance. However CT guided BMA and BMTB needs to be done in a CT scanner (figure 12.2) and the procedure can be elaborate and expensive. Recently Philips Inc. has developed an app (Lumify) for Android smartphones which can be used as a mechanism for ultrasound detection and visualization of the precise location of the posterior iliac crest. As a result this technique using the smartphone for image guidance can facilitate the extraction of bone marrow specimens from a site (e.g., posterior ilium) that is otherwise imprecisely identified by palpation of external landmarks and blind needle exploration.

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Figure 12.1 Photograph of a conventional ultrasound machine

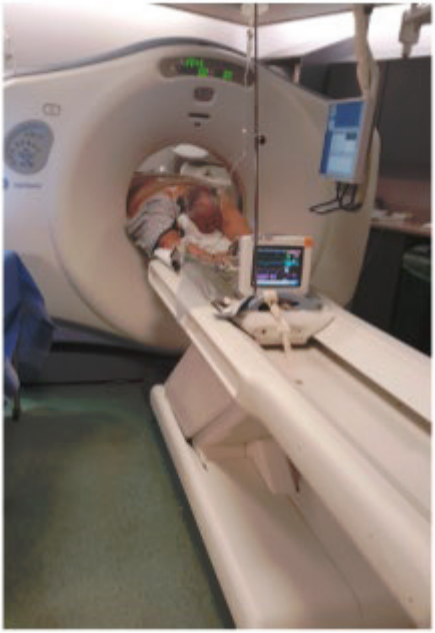


Figure 12.2 Photograph of a CT scanner

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As has been emphasized earlier bone marrow aspiration and trephine (core) biopsy plays an important role in the investigation, diagnosis and management of patients with various hematological and non-hematological, malignant and non-malignant conditions. However, for decades the standard methods of performing BMA and BMTB in patients with these disorders have remained unchanged despite the fact that manual palpation and blind exploration of locating the sites for performing these procedures have significant limitations. Most importantly, the latter approach lacks the precision to accurately locate and penetrate the posterior iliac crest at its center. Patient safety as well as real-time visualization of the tip of the needle during insertion is important aspects of the bone marrow aspiration and biopsy procedure. BMTB is now routinely used in tandem with bone marrow aspiration because of the advantage it offers over sole marrow aspiration. The value of BMTB depends on the quality of the specimens that are obtained. It is known that the clinical usefulness of the BMTB depends not only on the type of instruments used but it also depends to a great extent on the knowledge and proficiency of the operator. However, even in skilled and experienced hands and with appropriate needles the target site (usually the posterior iliac crest) can be missed or hit off center resulting in a less than desirable biopsy specimen. Consequently, a smartphone (or a tablet) using Philips Lumify app for Android has been employed to achieve the described ideal results.

In this technique, sound waves are projected on the body parts, which bounce back and are collected by software installed in the smartphone/tablet to generate images of the internal organs. Sound waves cannot penetrate bone; hence these structures can be clearly seen in an ultrasound image on the smartphone. Thus this technique can be very useful in precisely locating the posterior iliac crest at a bedside. This methodology can be particularly useful for patients in whom it is difficult to reach the biopsy targets such as obese patients whose posterior iliac crests are buried under a carpet of adipose tissue and almost impossible to locate by conventional (blind) method of palpation. Fortunately, investigational engineers of the Philips Corporation have converted smartphone into an ultrasound device by coupling USB-based ultrasound probe technology with the smartphone, enabling a compact, computational platform and a medical imaging device that fits in the palm of a hand. Standard ultrasound scans take about 30-45 minutes using the conventional machines whereas with the Philips-developed app, the duration of procedure time can be cut down to only few minutes. Introduction of such simple technology into the mainstream of hematology/oncology medicine is a new technique. Such imaging modality to access bone marrow at the bedside may eliminate the necessity

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for ultrasound guidance using large and bulky machines or elaborate and expensive CT guided bone marrow examination.

Procedure

Generally the patients are placed in a right or left lateral decubitus position, with the knees drawn up and back comfortably flexed, or in the prone position with a pillow beneath the hips. An ultrasound transmission gel is applied over the right or left lower back covering the lateral points of rhomboid of Michaelis, which overlies the posterior iliac crest. The posterior iliac crest is then located by using a transducer connected with the smartphone/tablet. With the transducer positioned over the posterior iliac crest, an ink line is made on the skin at the midpoint of each of the four sides of the transducer (figure 12.3). The lines are then connected to form a "+". The accuracy of the marking is verified by placing the transducer at the "+" in both transverse and longitudinal orientations. Care should be taken to ensure that the marking (center of the '+') is directly over the center of the posterior iliac crest where the needle is to be introduced. Once the bone is accurately demonstrated on the smartphone screen (figure 12.4) or a tablet (figure 12.5) the central point is marked on the patient's skin with an indelible marker. After marking the site is prepared with the use of sterile technique and the patient is draped. The aspiration and trephine biopsy are performed under local anesthesia sequentially using bone marrow aspiration and core retention bone marrow biopsy needles.

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Figure 12.3 Illustrates the positioning of a transducer over the posterior ilial region for sonographic localization of the posterior iliac crest while the smartphone is being held by an assistant. The center of the discussed '+' (covered by the transducer) lies directly over the center of the posterior iliac crest through which the needle will be introduced into the bone to obtain the bone marrow aspiration and core biopsies.

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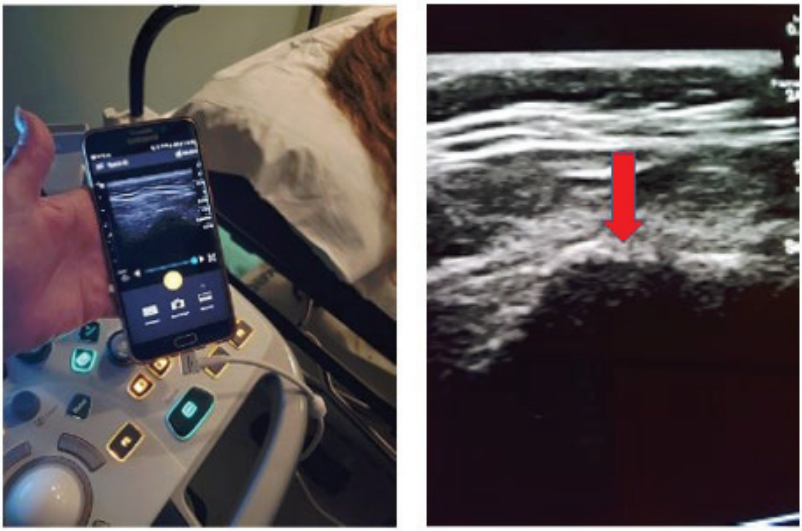


Figure 12.4 [A] A photograph of the smartphone that presents the sonographic on-screen image of the posterior iliac crest. The image which appears as dark black area is identifiable but is limited in definition at the current photographic magnification. **[B]** A photograph of the reflective hyperechoic bone cortex (arrow) of the posterior iliac crest as seen on the screen of the smartphone but at higher magnification.

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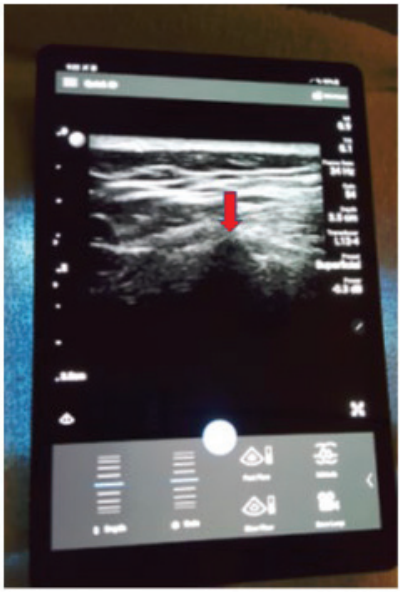


Figure 12.5 A photograph of a tablet that shows the sonographic image of the posterior iliac crest on its screen. The image appears as dark black mass with a central elevation.

The author has carried out ultrasound guided BMA and BMTB using an Android smartphone in adult patients with various hematological and non-hematological conditions. An adequate and satisfactory BMA and BMTB (over 15 mm or longer) specimen (figure 12.6) was obtained from each patient. There were no tangential biopsy specimens (i.e. specimens containing mostly bone, subcortical fat, and little or no marrow tissue) indicating that the needle placement was correct and tip of the needle hit the center of posterior iliac crest. There were also no inadequate or unsatisfactory (i.e., small, less than 5 mm in length or crushed biopsy specimens. The technique was found to be simple and very useful in precisely locating the posterior iliac crest and placement of the tip of the needle into the center of the posterior iliac crest. This assisted in obtaining an excellent BMTB specimen at each attempt. The patients also tolerated the procedure well.

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Figure 12.6 Demonstrates a cylindrical core biopsy specimen that was obtained from a patient from the right posterior iliac crest employing ultrasound localization technique with a smartphone using the Philips Lumify app.

Comment

Traditionally, hematologists and oncologists perform bone marrow aspiration and trephine biopsies relying heavily on external anatomical landmarks and palpation (see chapter 9). This technique has an inherent problem as the site (posterior iliac crest) may be missed resulting in an inadequate or unsatisfactory specimen. If the needle does not penetrate the bone at the correct angle, this may result in a tangential biopsy containing mostly bone and very little marrow tissue (figure 10.3, chapter 10). Furthermore, if the needle veers too much to the right or to the left, or in any other direction, or misses the posterior ilium completely, this can cause serious complications, including damage to the sciatic nerve or a massive thigh and buttock hematoma (figure 10.5, chapter 10). These complications, although rare, have been reported. This new technology of using smartphone as a tool for ultrasound (image) guidance allows the safe passage of the needle into the desired marrow-rich intramedullary site while avoiding damage to important surrounding structures. However if the patient is too

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obese it is preferable to perform the bone marrow aspiration and biopsy under CT guidance.

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CHAPTER 13

BONE MARROW ASPIRATION AND TREPHINE (CORE) BIOPSY BY INTERVENTIONAL RADIOLOGISTS

Bone marrow aspiration and marrow core biopsy are specialized procedures. One has to be cognizant of why they are performed, how they should be accomplished and what results are expected. These procedures also require a defined body of knowledge coupled with practiced surgical skill. Until the recent past these procedures were the exclusive realm of hematologists and oncologists. In recent times interventional radiologists have entered into the field of hematopoietic bone marrow acquisition. This trend has occurred for multiple reasons, particularly because the conventional "blind approach" bears the burden of uncertainty of making contact with the target posterior iliac crest at its center and at a correct angle to consistently derive an excellent clinical sample. There is also the fear of inadvertently injuring the surrounding tissue. Additional factors that support the replacement of conventional bone marrow aspiration and biopsy techniques by hematologist and oncologist include modest reimbursement by third-party payers, the interruption of the biopsy procedures into an otherwise busy schedule, and the problem of doing the procedure without technical assistance.

Unfortunately, the interventional radiologists are not specifically trained to obtain samples of hematopoietic marrow. They excel at performing one step punch biopsies from the liver, kidney, abdominal lymph nodes, lung etc. However, the latter techniques do not require the making of bedside preparation of samples. Bone marrow examination requires a two-step procedure - one for bone marrow aspiration that is to obtain a fluid cellular suspension of marrow from the marrow cavity with a bone marrow aspiration needle which is followed by obtaining a solid core biopsy with a trephine (core) biopsy needle. It also requires bedside preparation of fresh marrow smears from the obtained bone marrow aspirate samples.

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This chapter is designed to assist interventional radiologists from a hematologist's perspective to insure that marrow acquisition is done effectively and appropriate samples are taken and allocated in a proper manner into appropriate containers for (1) morphology, (2) flow cytometry, (3), cytogenetics and (4) molecular studies. These steps are now almost routinely carried out for each patient undergoing bone marrow examination.

When the bone marrow samples are obtained from a patient and sent for analysis, the pathologist's evaluation is derived from the specimen irrespective of the quality of the sample - good or bad. As a result if the sampling is not executed properly, bone marrow smears are not made immediately and best available instruments are not used, one may not formulate the most useful and accurate diagnosis and as a result the patient may be ill-served. One common poor choice made by the interventional radiologists is that they often sequentially use the same bone marrow biopsy needle for both aspiration and core biopsy. This is not a good practice as discussed in Chapter 8. Furthermore, interventional radiologists do not personally make the smears as soon as the bone marrow is withdrawn from the patient. As a result, by the time the samples reach the laboratory (it may be several hours/days in some cases) anticoagulant effect had already begun and smears made from such samples are not pristine and show considerable morphological changes. Bone marrow aspirate smears should be made immediately from the *first pull* (about 0.5 ml of marrow) (figure 13.1). Following the first pull of marrow which is obtained with a three or five ml syringe additional marrow required for other tests can be withdrawn with a 10 ml syringe and dispensed into appropriate tubes. Interventional radiologists on the other hand are likely to withdraw 10 ml or more marrow in one pull with a core biopsy needle. As a result the marrow is markedly diluted with blood and smears prepared from such specimens are inadequate for proper evaluation of the marrow particularly with regard to morphology of cells and bone marrow cellularity (figure 13.4B). Such drastic sequential aspiration of large amounts of marrow from the same site from where the trephine (core) biopsy is then obtained using the same biopsy needle also affects the quality of the core biopsy specimen (see figure 13.2).

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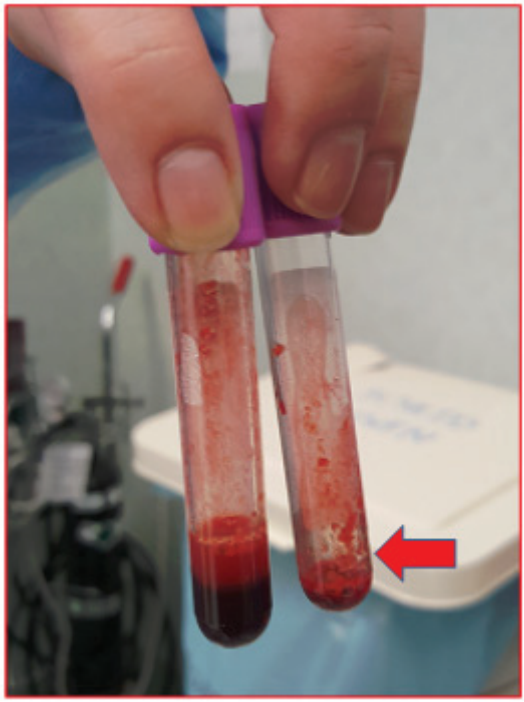


Figure 13.1 An illustration of first pull marrow (tube on the right with arrow) demonstrating most marrow and little blood. Tube on the left shows 2nd pull containing marrow admixed with blood (diluted marrow).

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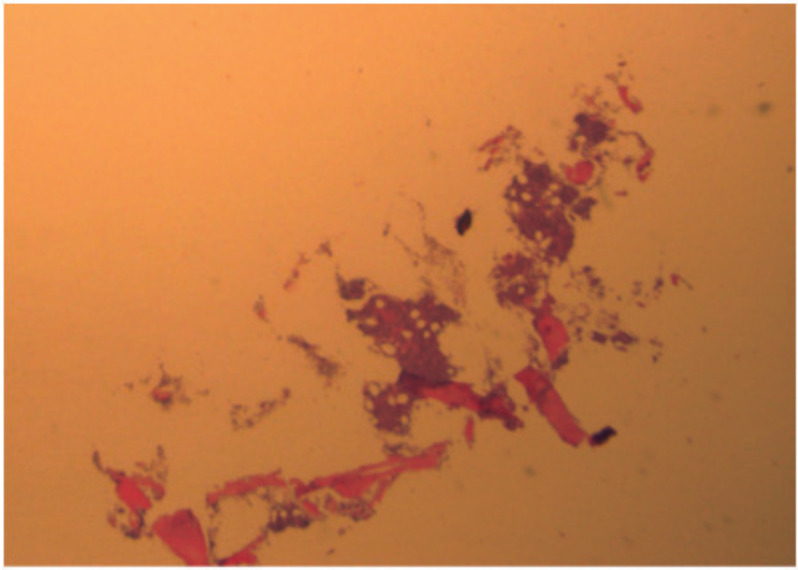


Figure 13.2 A demonstration of a biopsy specimen where evaluation of the marrow was limited due to severe loss of marrow tissue because bone marrow aspiration was performed before the bone marrow core biopsy using the same bone marrow biopsy needle.

Obtaining Marrow Samples and Preparation of Smears

Before beginning the biopsy procedures two instrument tables should be set up as shown in the photographs below. Instrument table 1 should be sterile and contain syringes, needles, local anaesthetic, iodine, drapes, gauze and an indelible marker.

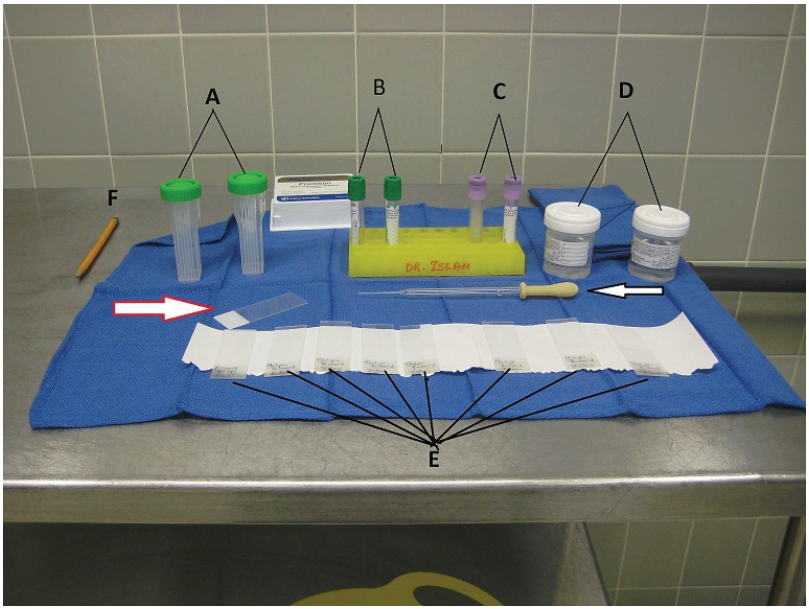
Instrument table 2 is non-sterile and is used for holding the test tubes and containers with fixatives and labelled slides for the preparation of fresh bone marrow smears. (A) Slide containers for transport, (B) heparinized test tubes, (C) test tubes containing EDTA, (D) Containers containing fixative (10% formalin), (E) labelled glass slides, (F) pencil for labelling the glass slides. A glass Pasteur pipette with attached rubber bulb is shown by a black arrow on the right side and a spreader for making the smears is indicated with a red arrow on the left side.

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Instrument Table 1

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Instrument Table 2

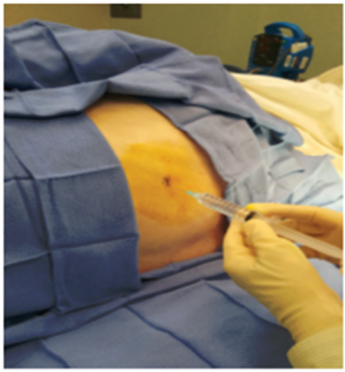


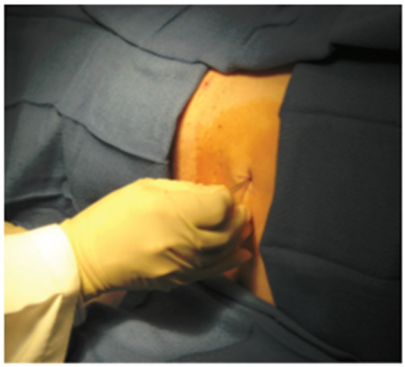


Site of the puncture: Right or left posterior iliac crest. The patient is placed on a right or left lateral decubitus position (picture on the left) with knees drawn up and back slightly flexed or in a supine position (picture on the right) and the operating area (as per grid is best seen in the left photo) that is used to mark the entry point of the needle under CT guidance.

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The patient can be lightly sedated with midazolam (versed) or a combination of midazolam and fentanyl.





Local anesthetic and skin incision: Infiltrate the skin, subcutaneous tissue and periosteum with a local anesthetic (1% or 2% lidocaine) (see picture on the left). In obese patients longer needles such as the spinal needles may be necessary to reach the bone. Make a small (3 mm) skin incision with a pointed scalpel blade over the marked area at the entry of the needle (see picture on the right).

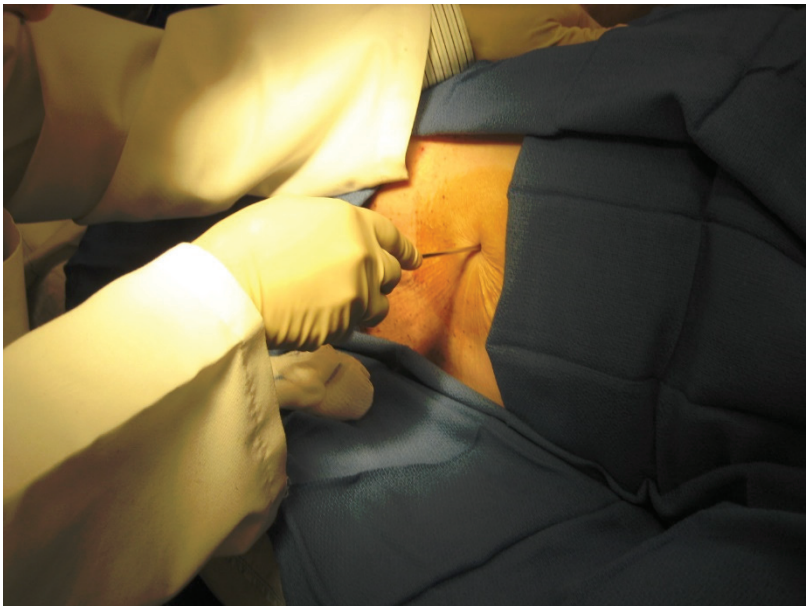




Bone marrow aspiration: Bone marrow aspiration should be attempted first, and it should be carried out with a bone marrow aspiration needle. Bone marrow aspiration prior to bone marrow biopsy, using the same bone marrow biopsy needle should be avoided (see chapter 8). Once the bone marrow aspiration needle is placed into the marrow cavity a small amount (0.5ml) of marrow is aspirated with a 3 or 5 ml syringe (see picture on the

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left) and placed in an EDTA (lavender top) tube which is later (but before the specimens are sent to pathology) used for the preparation of the bone marrow smears. Once the marrow is placed in the tube it should be shaken gently by tapping to prevent clotting. This is called the *first pull* and contains most marrow in its undiluted form. Following the first pull a 10 ml syringe is attached (see picture on the right) and larger amount of marrow is obtained to perform all the specific tests mentioned previously.



Bone marrow trephine (core) biopsy: Following the aspiration, a solid core (trephine) bone marrow biopsy should be attempted (as shown in the above photograph) with a preferred bone marrow biopsy needle using the same entry site but at a slight different angle. Detailed procedures as to how to obtain an adequate bone marrow solid core biopsy specimen has been described in details in chapters 4, 5 and 6.

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Preparation of bone marrow smears: once the entire procedure is completed an attempt should be made to prepare the aspirate smears using the marrow from the *first pull* which had been placed in an EDTA tube as demonstrated in the following pictures (figure 13.3). In this way a rush to prepare the smears immediately following the withdrawal of the marrow is avoided .Once the smears are dry they are placed in a slide container and sent to pathology, along with all the other specimens, including the bone marrow core biopsy specimen in a fixative and the remainder of the second pull which is placed into fixative to form a marrow clot sectioning.

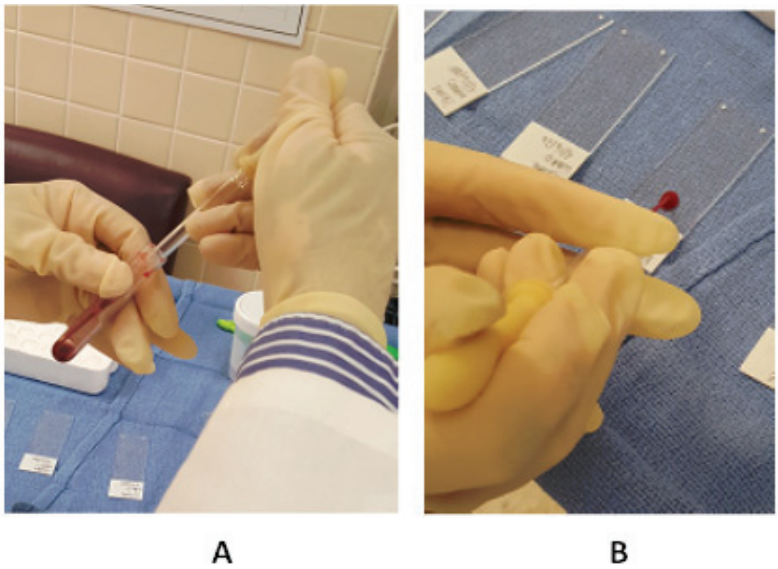


Figure 13.3 [A] Photograph of withdrawal of marrow with a glass pipette (which is preferable to a plastic pipette) from the EDTA tube containing the *first pull* marrow. **[B]** Putting a drop of marrow onto a slide.

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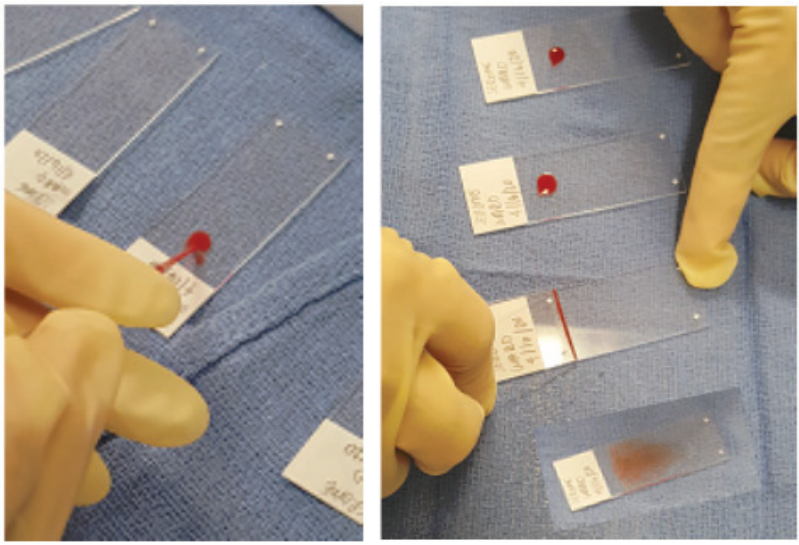


Figure 13.3 [C] An illustration of suctioning of extra blood from the drop of marrow with a pipette. **[D]** Preparation of smear from the drop of marrow. Note the spreader is pulled back over the drop of marrow until the marrow goes to edges before the spreader slide is gently advanced in smooth motion to prepare the marrow smear (bottom right).

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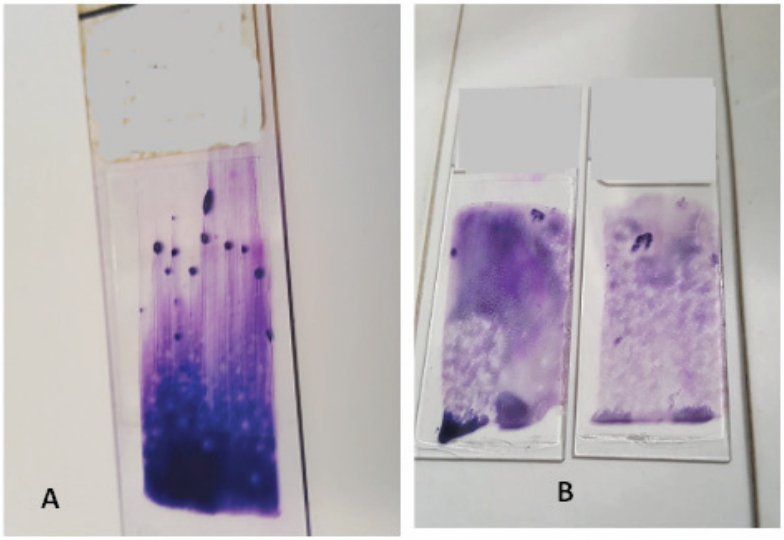


Figure 13.4 [A] Demonstrates a freshly made bone marrow aspirate smear from a first pull marrow. Note the large number of spicules (marrow fragments) present in this slide. **[B]** Demonstrates bone marrow aspirate smears prepared in the lab from a tube containing 10 ml of aspirated marrow which was drawn in one single pull. Note absence of marrow spicules (fragments).

Some interventional radiologists prefer the motorized drill (see chapter 7) to perform the bone marrow aspiration and core biopsy procedure rather than using manual devices. The use of the manual device and the drill are described in chapters 4-6. Both approaches are very similar.

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CHAPTER 14

INTRAVENOUS CONSCIOUS SEDATION WITH LOCAL ANESTHESIA OR LOCAL ANESTHESIA ALONE IN PERFORMING A BONE MARROW ASPIRATION AND A TREPHINE (CORE) BIOPSY

As stated previously the performance of a bone marrow aspiration and a trephine biopsy play an important role in the diagnosis and management of patients with various hematological and non-hematological disorders. They are usually performed under local anesthesia with the patient placed in a prone position with a pillow beneath the hips, or right or left lateral decubitus position with the knees drawn up and the back comfortably flexed. These procedures are typically simple, safe and take only a few minutes in an operating room, an outpatient/ambulatory setting or at the bedside of a patient. But the sampling is not completely free of pain and frequently the patient presents with anxiety, fear and apprehension. Because of this, conscious sedation with intravenous administration of midazolam (versed) or a combination of midazolam and fentanyl in addition to a local anesthetic has gained popularity in recent years. The acquisition of a bone marrow aspirate and trephine biopsy with conscious sedation has become routine for interventional radiologists who also undertake this medical procedure. Accordingly some patients do prefer and select an interventional radiologist for this procedure. However, hematologists and oncologists tend to prefer the sole local anesthesia route because it is well established and quick, inexpensive and has advantages over conscious sedation.

For conscious sedation benzodiazepines are the most commonly used agents, and of these, midazolam is one of the most widely used because of its rapid onset and relatively short duration of action. For conscious sedation midazolam is first administered intravenously and the patients have their vital signs and oxygen saturation monitored continuously by a staff member other than the operator. Reversal of sedation should be available at the bedside in the event that benzodiazepine reversal is needed during the procedure.

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Local sedation is usually carried out with 1 or 2% lidocaine. First, the skin is infiltrated with a local anesthetic using a 25gauge 5/8 inch needle. Once the area is numbed, the subcutaneous tissue, fat and periosteum are anesthetized by injecting the local anesthetic with a 21gauge one and a half inch needle or a 21 gauge lumbar puncture needle if the patient is obese. Patients undergoing bone marrow aspiration and a trephine (core) biopsy procedure with a local anesthetic do not need to have their vital signs and oxygen saturation monitored continuously.

It has been stated that patients who have received conscious sedation reported lower pain scores than patients receiving local anesthesia only and were also found to have lower levels of apprehension and anxiety. It has also been reported that patients having a repeat procedure indicated a slightly increased preference for having conscious sedation compared with patients who were undergoing it for the first time.

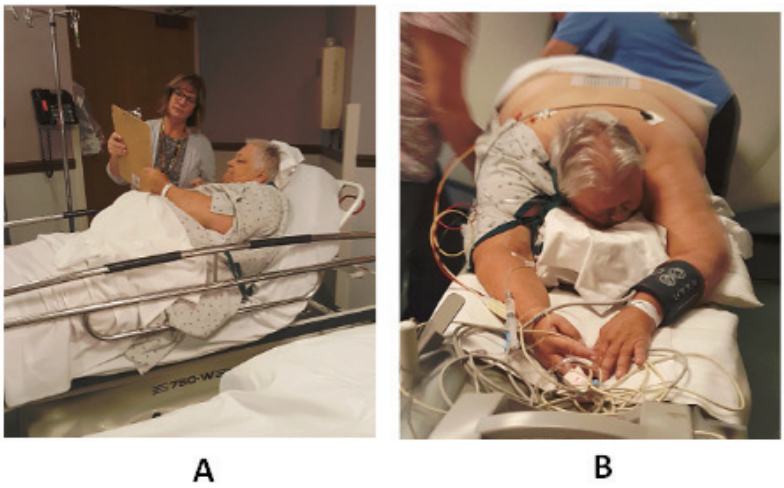


Figure 14.1 A shows a patient giving consent to the procedure. **B-** patient under conscious sedation.

Conscious sedation is not free of risk. Amnesia, drowsiness and psychomotor impairment (if the reversing agent flumazenil is used) may rarely occur in sedated patients. Drug-induced hypotension and respiratory depression requiring assisted ventilation may sometimes be required. A small percentage of patients experience post-procedure pain regardless of the type of analgesia that is used. Conscious sedation requires the attendance

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of an anesthesiologist and the availability of an operating room. This sequence is time-consuming and be costly. The patient has to recover from sedation which may take hours even if reversal of sedation is used. It has been suggested that conscious sedation is not advisable in situations where the requirements for safe sedation practice are not readily available. Although complication rates for bone marrow aspiration and biopsies appear to be very low, but there does appear to be a tangible risk present to having the procedure performed under conscious sedation.

On the other hand the procedure performed under local anesthesia alone is less time consuming, less elaborate, can be performed at a bedside or in an ambulatory setting and the time to recover is brief. The patient can be discharged within an hour. However, the pain (sometimes quite intense due to suction of marrow aspiration termed 'suction pain') during the procedure followed by protracted local discomfort may be present. Because the patient is conscious during the procedure any unusual deviation of the needle away from the anaesthetized area can evoke pain and discomfort and thereby alert the operator to avoid any serious trauma.

However, when bone marrow aspiration and trephine (core) biopsies are concerned patients should be offered the choice of having the procedure performed under a local anesthetic alone or under conscious sedation combined with a local anesthetic if the appropriate resources are available. Although it has been stated that the quality of trephine (core) biopsies obtained from patients relaxed by conscious sedation may be superior this concept is debatable.

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CHAPTER 15

BONE MARROW HARVESTING (STEM CELL COLLECTION FOR TRANSPLANTATION)



Figure 15.1

Bone marrow harvesting is the process of collecting hemopoietic bone marrow cells from a donor and transplanting some of the derived cells into the same person (autologous), or another individual (allogeneic). If the donor is the identical twin of the recipient, the process is known as a syngeneic transplant. This procedure is performed as part of the treatment for different types of diseases such as, leukemia, severe aplastic anemia, lymphoma, multiple myeloma, immunodeficiency disorders and even in some solid tumors (in rare circumstances). The harvesting procedure is usually performed on an outpatient basis in an operating room and under general anesthesia.

The amount of bone marrow harvested usually depends on the size of the patient and other factors. Typically 1.0 – 1.5 liters of marrow admixed

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with blood are harvested. Bone marrow harvesting for transplantation is usually a routine safe procedure. The donor is required to stay in the hospital recovery room for an hour or two for monitoring. Alternatively, the donors may be allowed to return home after a day to help their body to fully recover.

Bone marrow harvesting i.e., collection of multipotent hematopoietic stem cells from the bone marrow for hematopoietic stem cell transplantation (HSCT), has become a routine procedure in many cancer centers throughout the world. However, until recently, there were no instruments available that were particularly suited for this purpose. The instruments normally utilized for obtaining large quantities of marrow were the Salah or Klima needles (figure 2.3-chapter 2) or the Illinois needle (figure 15.1). The Jamshidi and Lee-Lok needles (figures 15.2, 15.3) also proved to be not ideal for bone marrow harvesting.



Figure 15.2



Figure 15.3

The Islam bone marrow harvesting needle (figure 15.4) is designed and dedicated solely for this purpose. The wider diameter, multiple side ports and the large frontal opening make it the most suitable instrument for obtaining large quantities of marrow for transplantation from the posterior ilium. It is also believed that this needle facilitates a generous yield of stem cells per milliliter of marrow and the length of time the donor has to stay in the operating room undergoing the procedure is shortened.

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Figure 15.4

Selected Reading

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Resource guide for stem cell transplant. http://www.nbmtlink.org/documents/rg.pdf

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CHAPTER 16

TECHNICAL CONSIDERATIONS

Precaution

The bone marrow biopsy needles are specially designed to obtain bone marrow biopsy specimens from the posterior iliac crest. An important feature of the Islam bone marrow biopsy needle is the fact that it has an internal core retention device which makes it possible to cut and secure the core while the needle is withdrawn with a straight pull. Because of the presence of an internal core retention device no additional parts or extra steps are necessary which is required by the newer Jamshidi or other types of needles with core capturing device. Furthermore, the gyratory movements (such as rocking or sculling) or change in the direction of the tip of the needle which are necessary while using the conventional Jamshidi or other types of needles to secure the core are not at all necessary with the Islam needles and in fact, are contraindicated as such movements will certainly damage the needle.

Although the technique of bone marrow biopsy is safe, simple and well tolerated by most patients, care must be taken while performing this procedure, particularly in obese patients. In these cases accurate localization of the posterior iliac crest may be difficult and trauma to the sciatic nerve could ensue. Patients should also be asked if they are on anticoagulation (warfarin/pradaxa/eliquis) or on anti-platelet (aspirin/clopidogrel) therapy. Appropriate measures such as stopping the therapy few days before the biopsy procedure may be necessary to avoid excessive bleeding or development of hematoma at the site of the biopsy procedure.

Size and Quality of Specimens

The object of a bone marrow biopsy is to obtain a segment of bone along with an undisturbed sample of the hematopoietic cells in its medullary cavity. In other words, to obtain a segment of marrow with its bony trabeculae and marrow architecture undisturbed. A long as opposed to a short core of bone marrow biopsy is preferred in that it may provide

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sufficient material for diagnosis when a smaller and perhaps less representative biopsy could be inconclusive. In adults, an adequate length and diameter of a marrow core is about 20-25 mm x 1.5-2.5 mm (Figures 4.1 chapter 4, 5.9a chapter 5, 10.1c chapter 10). Although an accurate diagnosis can be made from smaller biopsies when the marrow is uniformly affected, longer and larger biopsies are more useful if the lesion is more deeply placed (as detailed in the comment below and illustrated in Figures 16.1, 16.1a, 16.1b, 16.1c). Such longer and larger biopsies also provide a larger volume of tissue and a greater surface area for viewing (which may help in locating and identifying small focal lesions). The value of bilateral bone marrow biopsies in the diagnosis and management of Hodgkin's disease and non-Hodgkins lymphoma has been well established. Under ideal conditions two or three sections from each block and at different depth should be reviewed (Figures 16.2 a & b). This eliminates the necessity of making diagnoses from one single view and one plane of section. For optimal diagnostic potential, multiple sections derived from different depths within the same block should be evaluated.

Aspiration Prior versus Post Trephine Biopsy

In doing a bone marrow biopsy, an attempt should be made to obtain as much undistorted tissue as possible. Aspiration prior to coring (as detailed earlier in chapter 6) at the same site and using the same biopsy needle (as practiced by some) produces considerable distortion of the marrow and therefore should be avoided. In addition aspiration prior to coring also leaves the barrel of the needle filled with marrow and blood and results in spillage during coring and removal of the biopsy from the needle. Ideally bone marrow biopsy from the posterior iliac crest should be carried out first and aspiration attempted later. However, obtaining a biopsy before aspiration may cause the aspirated material to clot extra quickly due to generation of thrombin by the previous bone marrow biopsy procedure. Should an aspiration be performed first, the same puncture wound may be used for a core biopsy, but slightly different area of posterior iliac crest should be chosen for the latter. Preferably, to avoid all of the problems associated with combined aspiration and core biopsies performed at one locus, aspiration should be carried out from the sternum and a trephine biopsy from the posterior iliac crest immediately afterwards. Unfortunately this may not be a viable proposition because of the time and materials involved and the complications associated with the sternal puncture. It is an acceptable and useful practice to use the bone marrow biopsy specimens for making imprints if proper care is taken to avoid damage to

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the biopsied specimen. Although the cytological preparations derived from imprints are not as cellular and not as well presented as smears from aspirated samples they may prove to be confirmatory or even diagnostic at times when a bone marrow aspirate is unsatisfactory or yields a dry tap.

Long Core Biopsy

When collecting a bone marrow biopsy sample it is also important to obtain a long core biopsy as emphasized above. Biopsies of maximal length are useful particularly when the bone marrow lesion is deeply placed. This was demonstrated, for example, in a case of acute lymphoblastic leukemia which showed clinical evidence of relapse while a bone marrow aspirate sample from one site was normal and aspiration from another locus few weeks later yielded an unsatisfactory specimen. A few weeks later a long core biopsy confirmed the clinical diagnosis of relapse. The histological appearance of this biopsy specimen was different in three different areas of the same section (Figure 16.1). The outer portion of the marrow, that is, the marrow near to the cortical bone (figure 16. 1 area I), showed extremely hypocellular and grossly oedematous marrow with widely dilated sinuses and no evidence of relapse (figure 16.1a). The middle portion of the core (figure 16.1 area II) showed normal marrow with good erythroid, granuloid and megakaryocytic activity (figure 16.1b). Conversely the innermost marrow (deepest and furthest from the cortical bone) (figure 16 .1 area III), showed dense infiltration of the marrow with blast cells (figure 16.1c).

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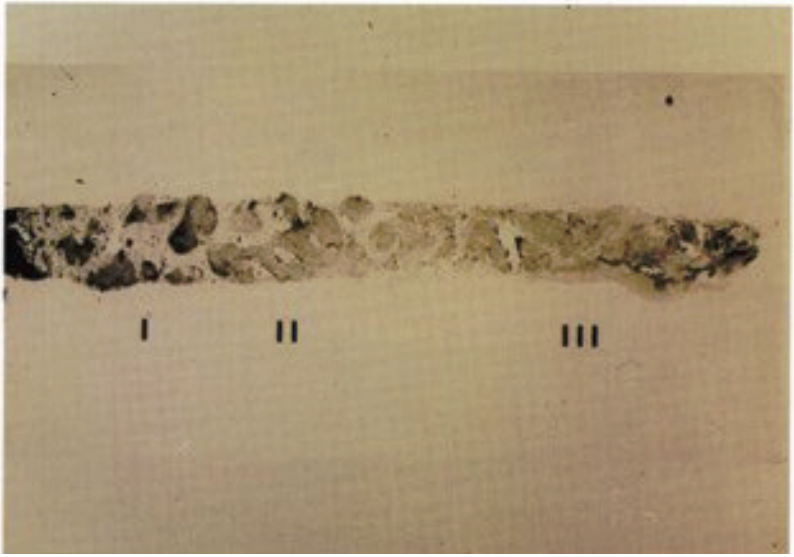


Figure 16.1 A bone marrow section of a marrow core obtained from a patient with acute lymphoblastic leukemia in relapse, demonstrating morphological discordance in three different areas of the same section.

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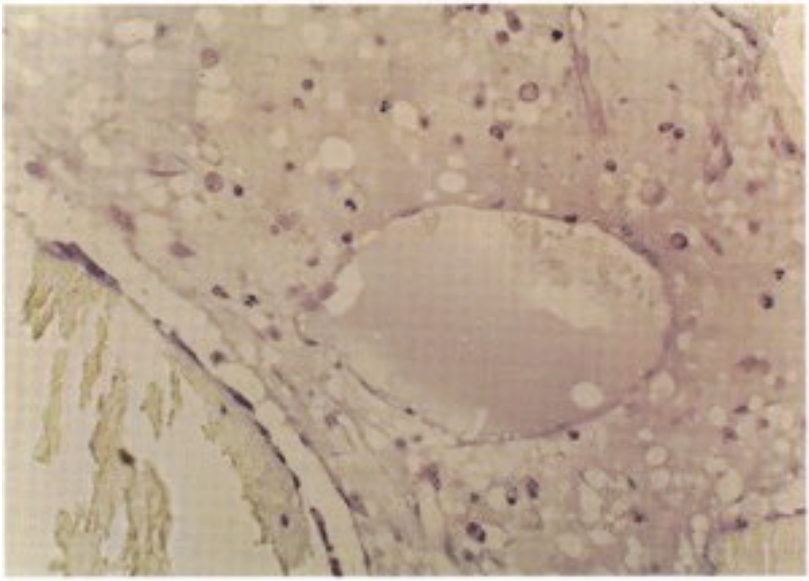


Figure 16.1a A field from the outer portion of the marrow core (figure 56, area II) showing extremely hypocellular and grossly edematous marrow with a widely dilated sinuse and no haemopoietic activity (MMA, MGG stain).

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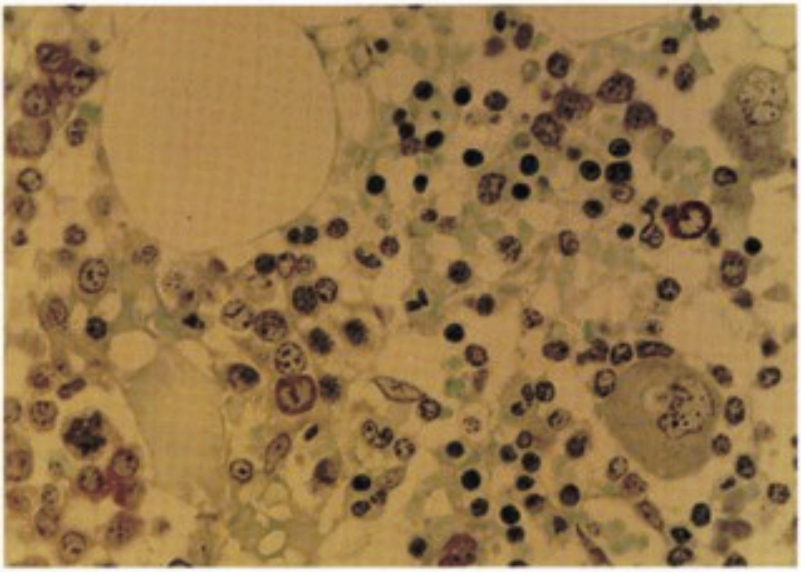


Figure 16.1b A field from the mid portion of the marrow core (figure 56, area II) showing normal haemopoietic marrow. Note the erythropoietic and granulopoietic cells as well as the scattered megakaryocytes (MMA, MGG stain).

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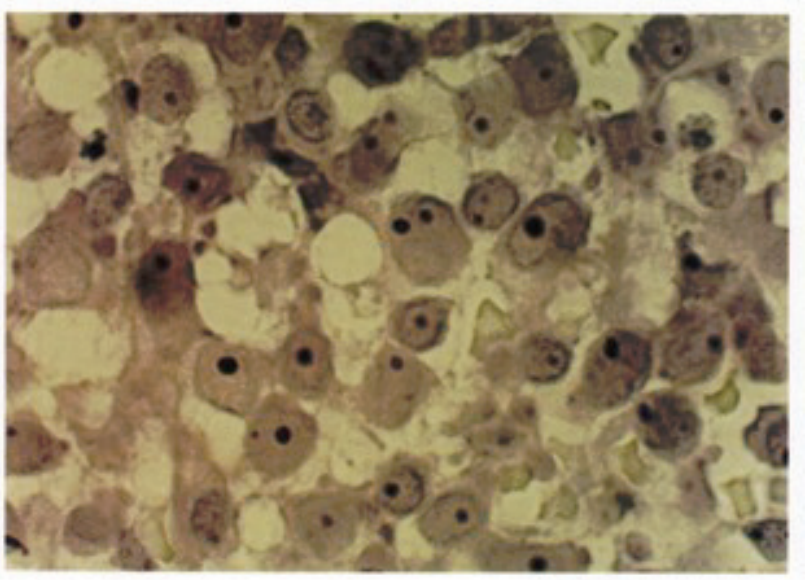


Figure 16.1c A field from the inner portion of the marrow core (figure 56, area showing dense infiltration of the marrow by blast cells (MMA, MGG stain).

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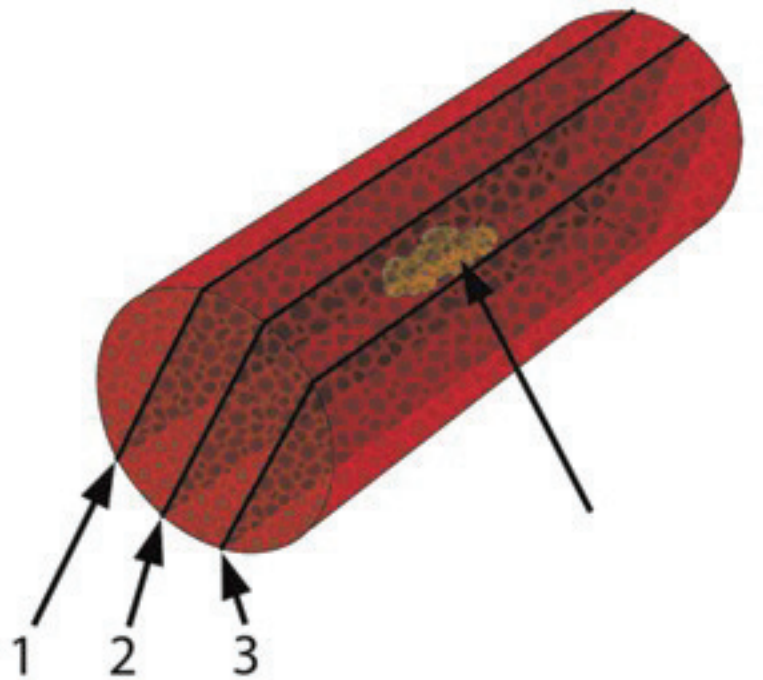


Figure 16.2a Shows a schematic representation of a cylindrical core of a bone marrow biopsy specimen illustrating a centrally placed pathological lesion (arrow). The core is sectioned at different plane/depths represented by the numbers 1, 2 and 3. The section at plane/depth 2 covers the maximum length and breadth of the specimen.

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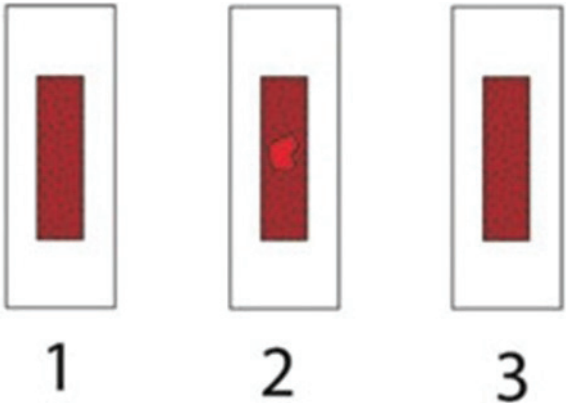


Figure 16.2b shows sections of the biopsy specimens attached on to the slides. Slide 1 demonstrate the section from plane/depth 1. Slide 2 demonstrate the section from plane/depth 2 and Slide 3 demonstrate the section from plane/depth 3. Note that the pathological lesion is demonstrable only in the section of plane/depth 2 but not in 1 and 3.

Processing of Specimens

The standard preparation of sections of bone marrow biopsy specimens requires fixation in formalin followed by decalcification and paraffin embedding (figure 16.3). Decalcification renders the study of the mineral phase of the tissue impossible while the process of fixation in formalin and paraffin embedding distorts the marrow architecture and relationships and yields poor cytological detail. Also, paraffin-infiltrated specimens are unsuitable for the thin sectioning (less than 2 /μm) that is required for detailed and precise histological analysis of a specialized multicellular tissue such as bone marrow. Furthermore, during sectioning, picking-up the ribbons of serial sections, floating them on the surface of the water in the water bath, and picking the sections out of the water bath and attaching them on to a microscope slide (figure14.4) can produce considerable damage to the sectioned tissue. There may thus be extensive loss of tissue rendering the stained section unreadable (figure 16.5). Although this is not uncommon pathologists hardly ever report this and tend to report only on whatever materials presented to them. It would be useful for clinical hematologists if they would report this condition in the following manner: 'the evaluation of the marrow core was limited due to marked loss of hemopoietic tissue'. Alternatively they could report 'the core measures (…..mm long) but cannot be further evaluated due to extensive aspiration

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artifact'. In addition, Particular disadvantages of paraffin embedding are that there is (1) pronounced cell shrinkage and distortion, (2) loss of definition of granules in maturing granulocytes and tissue basophils, (3) difficulty of obtaining semi-sections from decalcified bone and (4) hemopoietic cells are less easy to identify in sections of paraffin embedded tissues. On the other hand processing bone marrow biopsies in plastic has several advantages. The advantages of plastic embedding are that (1) semi-thin sections of 1 to 2 micrometers can be easily obtained from the undecalcified bone, (2) distortion and tissue shrinkage are minimal—only about 2% as against 10% to 50% for paraffin embedding, (3) excellent cell and tissue preservation with good morphological detail, and (4) essentially all staining techniques applicable to paraffin-embedded sections are also applicable to plastic-embedded bone marrow biopsy sections.



Figure 16.3 shows a plastic container containing buffered zink formalin and paraffin embedded bone marrow biopsies.

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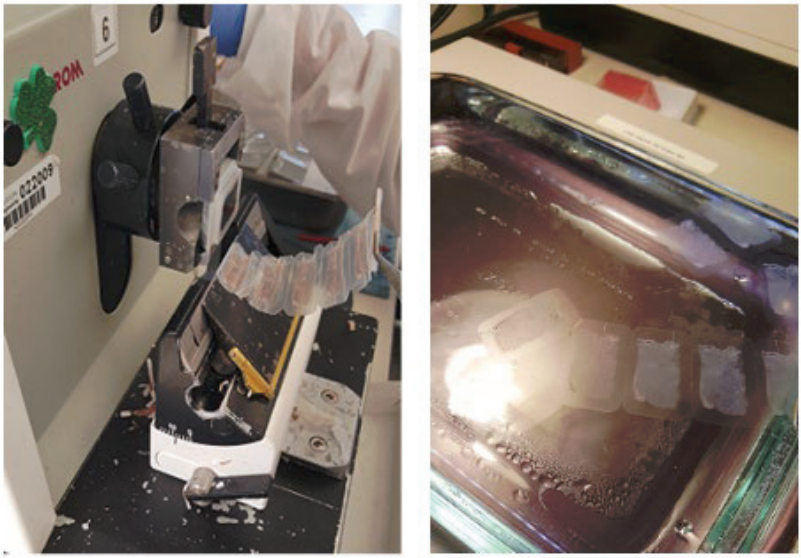


Figure 16.4 Illustrations of sectioning of a paraffin embedded bone marrow biopsy specimen (left) and floating the sections on the surface of the water in the water bath (right)

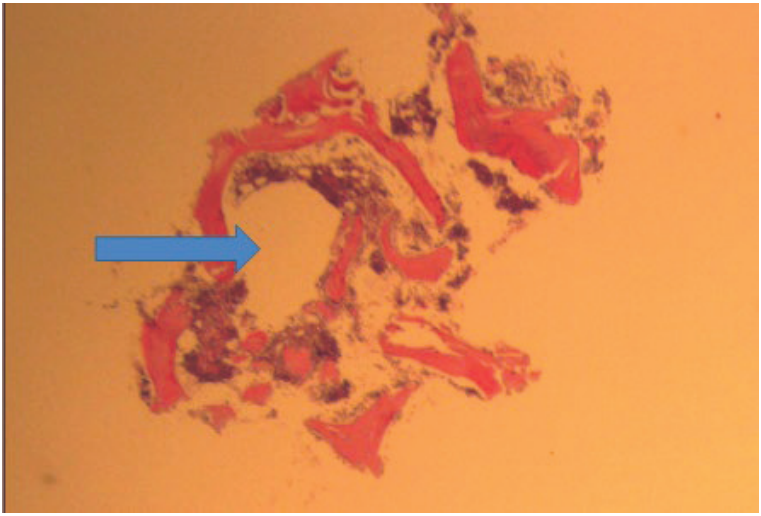


Figure 16.5 An illustration of extensive tissue loss (tissue drop out) (arrow) from a core biopsy section.

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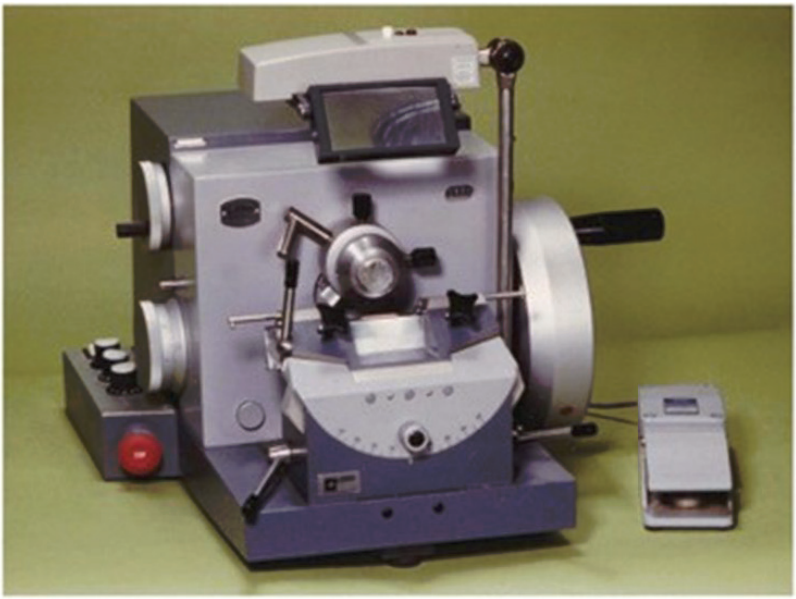


Figure 16.6 shows a Reichert Jung's heavy duty microtome (Autocut)

Plastic embedding of undecalcified bone marrow biopsy specimens provides excellent preservation of bone marrow architecture and cellular detail. The use of a special microtome (Autocut by Reichert Jung, Germany) (figure 16.6) with a tungsten carbide knife makes thin sectioning of mineralized bone possible. The result is improved microscopic resolution and enhanced cytology facilitating the identification of hemopoietic cells, the interpretation of cellular patterns and the formulation of diagnoses.

In recent years, various investigators have advocated plastic embedding for processing bone marrow biopsies because of the advantages this technique offers over softer embedding media such as paraffin. Various types of resins and plastics are now available for embedding bone marrow biopsies. The most commonly used ones are methyl and glycol-methacrylate (figure 16.7). Methyl-methacrylate (MMA) is the superior embedding material, however, it has not proved successful for enzymatic and immunohistochemical applications. The water-miscible glycol-methacrylate (GMA) embedding however, provides good morphological detail and also yields excellent enzymatic and immuno-histochemical results. Technically it also has good stretching and mounting properties.

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Some specific points in regard to the processing of bone marrow biopsies for plastic embedding and subsequent staining should be noted. An ideal fixative (figure 16.8) for morphology as well as enzyme and antigen preservation is Bouin's fixative at 4°C for 1-4 hours. Schaffer's solution (figure 16.8) is a good fixative for morphology but poor for enzyme and immunohistological studies. For morphologic detail May-Grunwald-Giemsa stain yields the best results and also has the advantage of presenting the same staining characteristics (to which hematologists are familiar) as those obtained in similarly stained bone marrow dry film smears. It is important to note that improper tissue preparation not only augments the possibility of missing the correct diagnosis but also fosters the possibility of making erroneous interpretations.

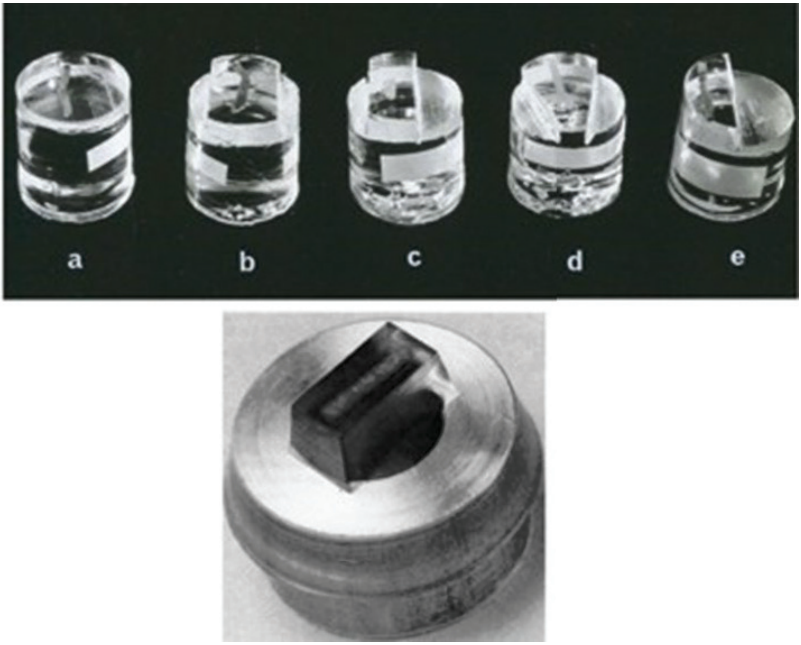


Figure 16.7 shows plastic embedded bone marrow biopsies. Top row shows biopsies embedded in methyl- methacrylate and the bottom one shows a biopsy specimen embedded in glycol-methacrylate.

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Figure 16.8 shows plastic containers containing Schaffer's solution (left) and Bouin's fixative (right).

Examination of Biopsy Sections

A bone marrow biopsy which is of adequate size (at least 1.5-2 mm in diameter and 15 to 20 mm long), satisfactorily fixed in an appropriate fixative (like Bouin's), embedded in a suitable embedding medium (like glycol-methacrylate), sectioned at 1—2 μm and stained with Romanowsky's stain (e.g. May-Grunwald- Giemsa) is essential for accurate visualization of morphology, enzyme and immunohistochemistry and for the correct interpretation of the biopsy specimen.

An inadequacy in any of the steps mentioned above may render the specimen equivocal or unsatisfactory. This should not imply that the conventional technique of processing bone marrow biopsies in paraffin and their subsequent staining with haematoxylin and eosin makes them unsuitable for study. But there is overwhelming evidence that plastic embedded bone marrow biopsy sections offer better cytomorphological and structural detail of the marrow thereby facilitating a more accurate identification of hematopoietic cells and the formulation of the diagnosis.

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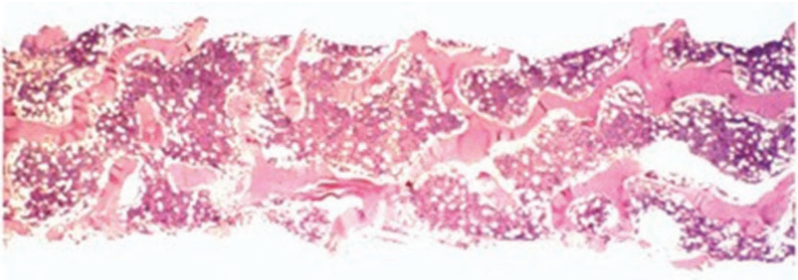


Figure 16.9 shows a paraffin embedded bone marrow biopsy section demonstrating dissociation between bone and marrow.

One of the important drawbacks of processing bone marrow biopsies in paraffin is the fact that there is always a dissociation between the bone and marrow as shown in (figure 16 .9). This endosteal region and the cells that line the bony trabeculae (figure 16.10) – the endosteal cells (EC) are perhaps the most important cells in the bone marrow. Unfortunately, because of its dissociation in paraffin embedded tissues this region has never been closely studied and the importance of EC in hematopoiesis has largely been ignored. In plastic embedded bone marrows this region is well preserved as shown in figure 16.8. In a hypothesis (Haemopoietic Stem Cell: A New Concept) studying plastic embedded sections of fetal and normal bone marrows as well as many patients suffering from various hematological disorders, it was postulated that the endosteal cells are the reminiscent of embryonal stage mesenchymal cells. Depending on the need and the circumstances, the endosteal cells can migrate either into the marrow cavity, that is intertrabecular marrow space where they proliferate, differentiate and give rise to various mature hematopoietic cells in the marrow. Alternatively, they may also become osteoblasts and osteoclasts and become responsible for the modulation of the bone (figure 16.11). Although the concept when published some years ago was quite radical, however, recent findings have shown it is not so far-fetched, as it is now known that hemopoietic stem cells can be grown from skin fibroblasts.

In order to effectively analyze a sectioned bone marrow biopsy specimen two or more sections from different depths should be examined. The initial reading should always begin with an overall assessment of the marrow section with an examination under low power (10 x objective). This insures that large cells as megakaryocytes, osteoclasts, clusters or aggregates of metastatic cells or immature haemopoietic precursor cells, macrophages, erythroblastic islets, small lymphoid nodules or lymphoid

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aggregates will not be missed or overlooked because of an inadequate survey. In most cases an accurate diagnosis can be made with the high dry (40 x) objective. When possible (in fact this should be routinely done as the technology is now available) the sections should be stained for enzymatic and immunological markers in order to obtain the maximum possible information from a given section. The oil immersion magnification (100 x objective) is not used routinely for the examination of sections from each cases. It is required only for the study of certain nuclear or cytoplasmic details.

Although it is recognized that the cytomorphological details of haemopoietic cells in sections are not as sharply delineated as they are in Romanowsky stained smears of aspirated marrow, their presentation is certainly much better in May-Grunwald-Giemsa stained plastic embedded bone marrow biopsy sections than they are in decalcified, paraffin embedded and H & E stained preparations.

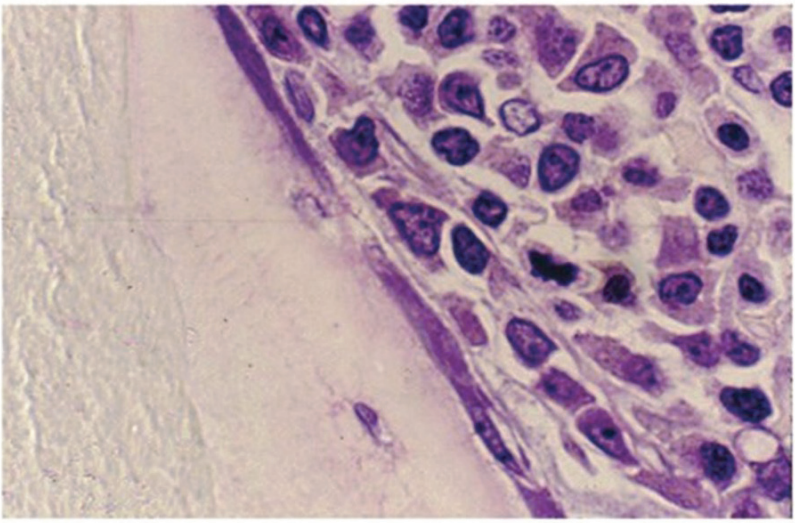


Figure 16.10 shows a section from a plastic embedded bone marrow biopsy demonstrating complete preservation of the endosteal region. Bone trabecula (left) and thin flattened endothelium like cells—endosteal cells that line the boney trabecula can be easily recognized.

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Bone marrow biopsies, particularly those from patients with hematological disorders should never be examined in the absence of available clinical information. Smears of peripheral blood and a bone marrow aspirate taken at the same time should always be examined in sequence, first the smears of peripheral blood film and then the smears of bone marrow aspirates. A study of the marrow biopsy sections is then undertaken. A full blood count, patient's history, and laboratory findings should also be at hand prior to the morphologic analysis of the marrow.

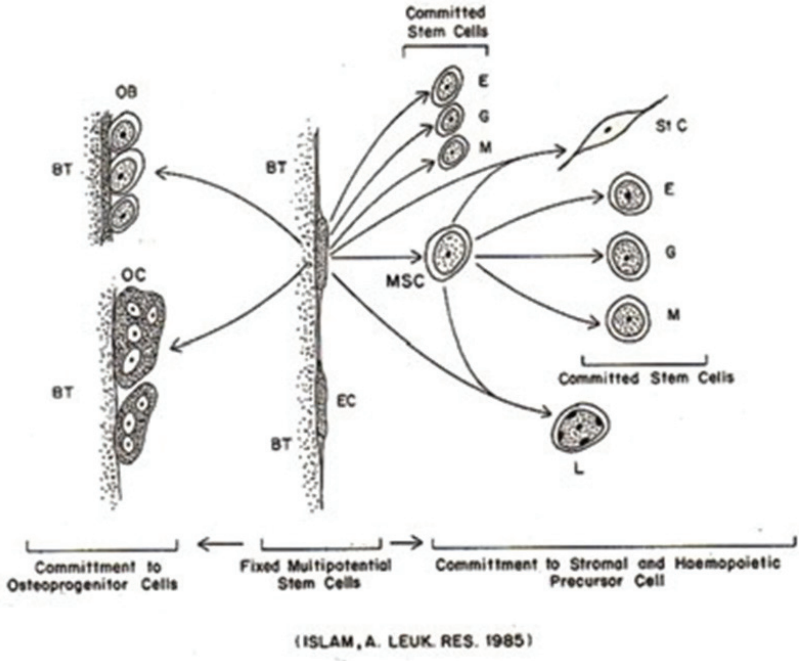


Figure 16.11 depicts the diagrammatic representation of the concept which shows that the endosteal cells (EC) are the fixed totipotential stem cells in the bone marrow and are equivalent of embryonal stage undifferentiated mesenchymal cells capable of transformation into osteoprogenitor cells (osteoblasts, osteoclasts), stromal cells (fibroblast-like cells) and precursors of all (myeloid and lymphoid) haematopoietic cells either directly or through intermediate cell cycle. BT—bony trabecular. EC—endosteal cells (fixed totipotential stem cells). MSC—mobilized stem cells (multi potential). St C—stromal cells. E—erythroid precursor cells. G—granuloid precursor cells. M—megakaryocytic precursor cells. L—lymphoid progenitor cells. OB— osteoblasts. OC – osteoclasts.

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Reporting and Interpretation of Biopsy Specimens

The microscopic analysis of a sectioned bone marrow biopsy should begin with careful and systematic assessment of the structural organization of the marrow. It initiates with the study of the bony trabeculae and their lining endosteal cells, osteoblastic and osteoclastic activity. The presence of any extravasated red cells, interstitial edema, and the number and size of sinuses should also be noted as they will affect the actual estimation of overall marrow cellularity.

The intertrabecular marrow spaces which contain the haemopoietic marrow and fat cells are examined next. In thin (plastic) sections fat cells usually appear as uniform, empty, unstained spheres. Occasionally, depending on the plane of section through a fat cell, the nucleus will be seen located in an eccentric position in its complete (or incomplete) mass of cytoplasm. The vascular structures (arteries, arterioles, capillaries and sinusoids) which are seen in between and about the fat cells, haemopoietic tissue and bony trabeculae should also be closely scrutinized. Arterioles are seen infrequently and their transition to the sinusoidal system is rarely encountered. The sinusoids are lined by a single layer of endothelial cells and vary considerably in size and shape. Mature erythrocytes are found almost exclusively in the sinusoids accompanied only by occasional normoblasts or granulocytes. Megakaryocytes are often seen close to marrow sinusoids.

The haemopoietic tissue consists of a great variety of developing and mature blood cells. These free cells are mainly granulocytic and erythroid precursors at different stages of maturation including a moderate number of diffusely distributed megakaryocytes. A lesser number of lymphocytes, plasma cells, macrophages, mast cells and reticular cells are also seen. In Romanowsky stained plastic embedded (thin) bone marrow biopsy sections virtually all cells can be identified almost as readily as they are in smears of aspirated material.

Blast cells are recognized by their relatively large size, agranular deep blue cytoplasm, nucleus that manifests very delicate chromatin strands and a prominent nucleolus. Their accurate assignment to the erythroid, granulocytic or megakaryocytic cell lines however, is not always easy, especially when they are seen in isolation and devoid of accompanying mature or partially mature cells.

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The report of a bone marrow biopsy should include an accurate assessment of the marrow cellularity. It is most accurately derived from sectioned material and is optimally reported (in percentage) as the aggregate volumetric ratio between the fat and hematopoietic cells. Further, the marrow space occupied by other elements such as edema, extravasated red cells, the number and size of sinuses should be carefully estimated and included in the non-hematopoietic segment of the marrow. (These factors are particularly pertinent in post therapy leukemic marrows where the bone marrow is usually extremely hypocellular, grossly edematous and replete with dilated sinuses.) As has been indicated previously, the cellularity of the marrow diminishes with age and this physiological variation has to be taken into account in the evaluation of a given patient's tissue. The next step in the evaluation of the bone marrow should address the qualitative and quantitative aspects of erythropoiesis, granulopoiesis, megakaryopoiesis and the presence or absence of any abnormal cells.

Then an assessment of the marrow fiber (reticulin or collagen) content should be made. If special staining procedures (enzyme and immunohistochemistry) are ran, these preparations should be examined and the findings reported. Finally a comment should be made as to the reviewer's overall impression of the marrow.

Format for an Effective and Useful Report

1. **Site:** indicate the site(s) where the biopsy was obtained. Report for example, whether the right or left posterior iliac crest was utilized. If another site was biopsied for marrow smears this should also be noted. Should a core and aspiration biopsy be obtained at the same site the sequence of the procedures should be given. List the anesthetic(s) used.

2. **Bony trabeculae:** an accurate assessment of the bony trabeculae will include for example, whether they are of normal thickness or thin (osteoporosis), very thick with a large seam of osteoid (osteomalacia) or very thick and irregular with some degree of marrow fibrosis (osteomyelosclerosis). An assessment should also be made at the same time of the endosteum, osteoblastic and osteoclastic activity.

3. **Edema and extravasation of red cells:** the presence of edema (as often seen in post-therapy marrows) and extravasation of erythrocytes (seen in leukemic as well as non-malignant conditions) should be noted and recorded when present.

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4. **Vascular structures:** the number and size of the venous sinuses can be important (they are enlarged and increased in number, for example in some myeloproliferative conditions and following chemotherapy). The status of the arteries, arterioles and capillaries should be noted (e.g amyloid deposits).

5. **Fat cells:** they normally comprise about 50% of the volume of haemopoietic marrow in the normal adult. Their presence in excess of or less than this value is an indicator of hypo and hyper haemopoietic activity. The absolute absence of adipose cells is a very significant event associated typically with malignant proliferations. Normally fat cells appear as uniform, unilocular spheres and usually are uniformly distributed throughout the marrow. They may also be seen in clusters (occasionally in large patches) and concentrated around some bony trabeculae.

6. **Overall cellularity:** in sections the hemopoietic cellularity can be quantified and expressed as a percentage of the volume of marrow. For example a leukemic marrow may be packed with malignant cells with less than 10% of the volume comprised of fat cells. Cellularity may then be described as over 90%. Whereas following therapy with the removal of the leukaemic cells the marrow may become hypocellular with less than 20% cellular elements (residual leukemia and inflammatory cells and stromal elements) while rest of the marrow may show edema, widely dilated sinuses and only a small number of developing multilocular fat cells.

7. **Erythropoiesis:** the level of activity should be indicated as normal, increased or decreased; maturation sequence (normoblastic vs megaloblastic); cytologic abnormalities such as dyserythropoietic changes, etc.

8. **Granulopoiesis:** the level of activity should be indicated as normal, increased or decreased; maturation sequence (i.e. whether all stages of maturation are represented or if there is a maturation arrest); cytologic abnormalities such as dysgranulopoiesis (giant metamyelocytes, Pelger-Huet forms etc.); the presence and localisation of the number of myeloblasts and promyelocytes.

9. **Megakaryopoiesis:** a numerical assesment should be made (increased, normal or decreased); consider the maturation sequence, platelet production, pleomorphism, cytologic abnormalities such as dysmegakaryopoiesis (small mononuclear or multinucleated forms etc.).

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10. **Plasma cell series:** a numerical assessment should be made (expressed in percentage of haemopoietic cells). Consider the maturation process, inclusion bodies, abnormalities or neoplastic changes. The distribution pattern of the plasma cells is important in reactive vs malignant conditions. Note whether they are perivascular, diffuse, scattered or clustered.

11. **Lymphocyte series:** give a numerical assessment of the lymphocytes (expressed as percentage of the haemopoietic cells in the biopsy). Indicate the presence of lymphoid nodules, germinal centers, morphologic abnormalities (large, small, cleaved cells, presence of nucleoli), their distribution should be noted e.g. diffuse, interstitial, clustered, and paratrabecular.

12. **Eosinophils and basophils:** a numerical assessment should be made (expressed in percentage of haemopoietic cells). Note any morphologic abnormalities and any infiltrative pattern if present.

13. **Iron stores:** estimate the level of content (normal, increased or decreased). The histological specimen allows more accurate evaluation of iron stores than do marrow smears, isolated spicules, or sections of bone marrow clots. The estimation of haemosiderin content is more accurately made in tissue sections because they are usually larger specimens and have a more uniform thickness than the adherent marrow units in smears. Routinely, both smears and sections should be examined for iron stores. The presence or absence of ring sideroblasts though identifiable in sections are best visualized in aspirate smears.

14. **Miscellaneous:** record the presence of macrophages, mast cells, granulomas, amyloidosis, gelatinous transformation of fat, pathologic lesions of the bone, and metastatic neoplasms etc.

15. **Differential cell count:** it is not practical to perform a standard bone marrow cell differential count on a bone marrow (paraffin or plastic embedded) section. However, the identification of essentially all cells is more effectively accomplished with plastic embedded, Romanowsky stained thin sections than with paraffin embedded, H&E stained preparations. When a bone marrow cell differential count is required it is best carried out on dry film smears. See Table 1 for the ranges of the normal bone marrow differential count.

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16. **Marrow fiber content:** indicate whether the fiber content is normal or increased. If increased, note whether the augmentation is due to reticulin or collagen or both.

17. **Enzyme and immunological marker Studies:** if carried out, they should be analyzed and reported.

18. **Conclusion:** give an overall impression as to whether the marrow is normal or abnormal. If abnormal, identify the specific abnormality whenever possible (e.g. acute or chronic myeloid leukemia, chronic lymphocytic leukemia, aplastic anemia etc). Any other studies that may be required to make a specific diagnosis should also be identified.

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CHAPTER 17

MYELODYSPLASTIC SYNDROMES

Hematological malignancies are a diverse group of neoplasms that affect the blood, bone marrow and lymphatic systems, and myelodysplastic syndromes (MDS) are considered as belonging to this group. Although it is debatable whether MDS are neoplasms of the hematopoietic system or a reflection of an underlying disorder it is recognized that some but not all do develop into acute leukemia and in that sense they can be considered as "pre-leukemia", the term that was replaced for MDS by the FAB classification.

Laboratory diagnosis of MDS is almost exclusively based on the morphology of hematopoietic cells observed in smears of peripheral blood and bone marrow and this depends solely on the presence of dysplastic changes observed in the granuloid, erythroid, and megakaryocytic cells in the absence of iron, vitamin B12 or folic acid deficiency. Hematoxylin and eosin (H&E) stained sections of paraffin-embedded bone marrow trephine biopsies are usually unsatisfactory to clearly detect such characteristic morphologic changes except perhaps demonstrating particular abnormalities in megakaryocytes, such as micromegakaryocytes, large mononuclear forms, bi or multinucleated forms and the localization of clusters immature myeloid precursor cells (blast cells) in some areas of the section. In the original and later classifications of MDS, findings demonstrated in the sections of bone marrow biopsy specimens were not taken into account, although they might have provided valuable diagnostic and prognostic information.

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Table 1: Common morphologic changes observed in erythroid, granulod and megakaryocytic cells

	DYSERYTHROPOIESIS	DYSGRANULOPOIESIS	DYSMEGAKARYOPOIESIS
PERIPHERAL BLOOD	ANISOCYTOSIS POIKILOCYTOSIS BASOPHILIC STIPPLING OVALOCYTES MACRO-OVALOCYTES DIMORPHIC PICTURE	NUCLEAR HYPOLOBULATION (pseudo-Pelger-Huet anomaly) HYPERLOBULATION HYPOGRANULATION	PLATELET ANISOCYTOSIS GIANT PLATELETS
BONE MARROW	EYTHROBLASTS WITH EXCESS CYTOPLASM NUCLEAR BUDDING IRREGULAR NUCLEAR OUTLINE INTER NUCLEAR BRIDGING INTERCYTOPLASMIC BRIDGING BI AND MULTINUCLEARITY NUCLEAR LOBULATION MEGALOBLASTOID CHANGES CYTOPLASMIC VACUOLIZATION CYTOPLASMIC INCLUTIONS NUCLEAR CYTOPLASMIC ASYNCHRONY KARYORRHEXIS MULTINUCLEATED MEGALOBLASTOID ERYTHROID PRECURSORS RING SIDEROBLASTS	NUCLEAR HYPOLOBULATION (Pelger-Huet anomaly) HYPERLOBULATION HYPOGRANULATION BIZARRE NUCLEAR SHAPE GIANT METAMYELOCYTES	MICROMEGAKARYOCYTES SINGLE SMALL NUCLEUS NUCLEAR HYPOLOBULATION SMALL BINUCLEATED FORM MULTINUCLEAR FORMS

Common morphologic findings in MDS are summarized in Table 1. For the neutrophils, hypogranularity and hypolobation may be observed in blood smears while giant metamyelocytes and bizarre nuclear forms can occur in the bone marrow (Figure 17.1). The erythroid abnormalities in the peripheral blood smear include anisocytosis, poikilocytosis, ovalocytes, macro-ovalocytes and dimorphic picture (Figure 17.2). The bone marrow aspirate smear may include members of the erythroid series displaying megaloblastoid features, altered nuclear:cytoplasmic ratios (nuclear cytoplasmic asynchrony), nuclear budding, bilobed nuclei, nuclei with an irregular outline, cytoplasmic vacuoles, inter-nuclear and inter-cytoplasmic bridging, (Figure 17.3 & 17.4) and sideroblasts including ring sideroblasts (Figure 17.5). The morphological abnormalities of the megakaryocytic series observed in the peripheral blood include giant platelets (Figure 17.2) while bone marrow aspirates and bone marrow biopsy sections may include micromegakaryocytes, excessive multinuclearity or hypolobulated megakaryocytes (Figure 17.6).

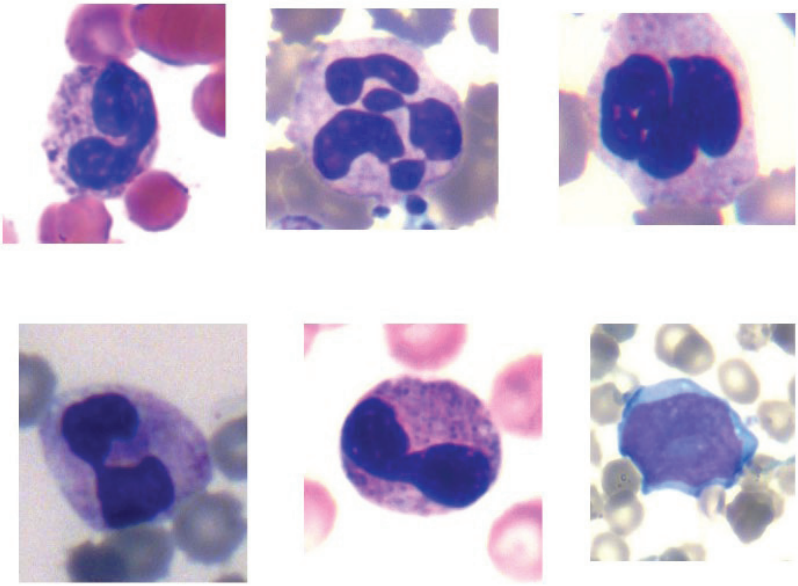


Figure 17.1. Neutrophilic dysgranulopoiesis observed in the blood and bone marrow. Note the Pelger-Huet anomaly, bilobed and 'spectacle' forms, and bizarre nuclei along with one blast cell (lower right picture).

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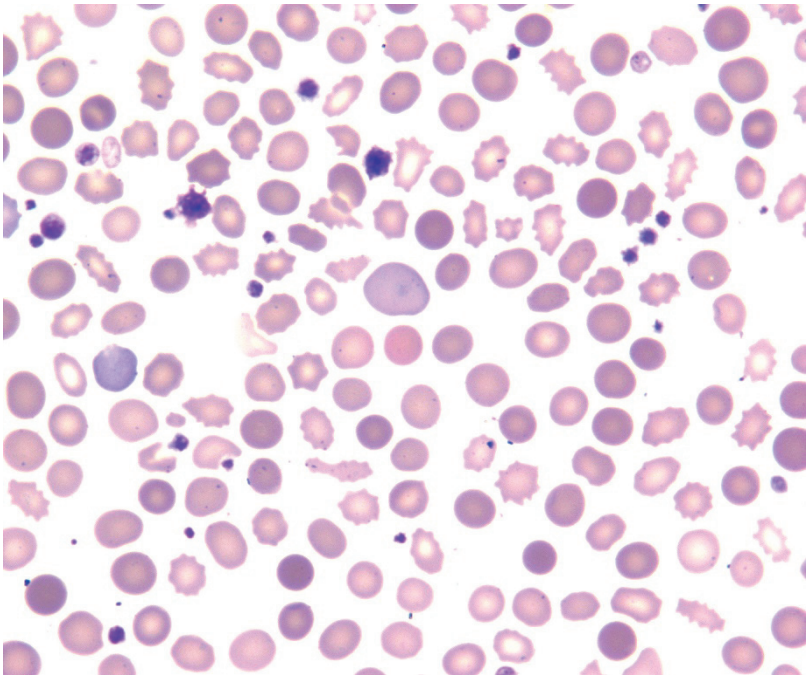


Figure 17.2. Dyserythropoiesis: peripheral blood smear showing imorphic blood picture along with anisocytosis, poikilocytosis and presence of ovalocytes, macro-ovalocytes (in the center of the picture).

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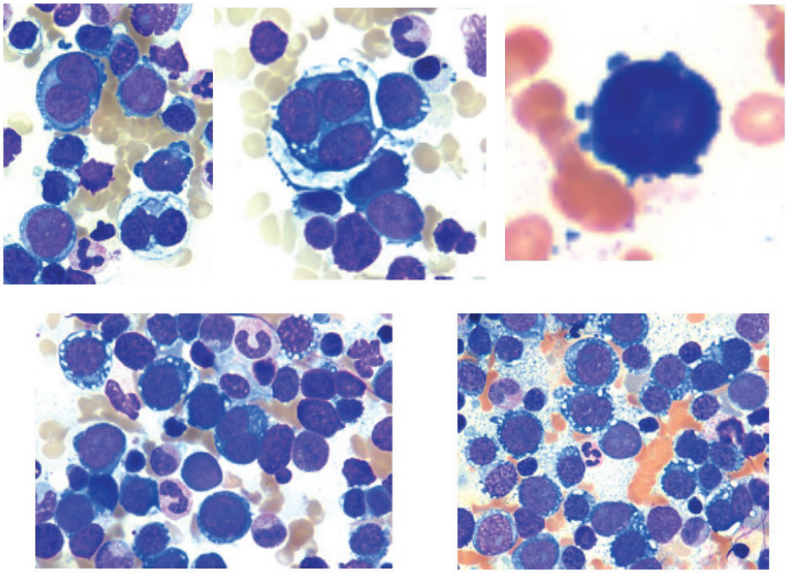


Figure 17.3. Dyserythropoiesis: bone marrow aspirate smear showing mono and multinucleated megaloblastoid erythroid precursors, cytoplasmic blebs and vacuolation.

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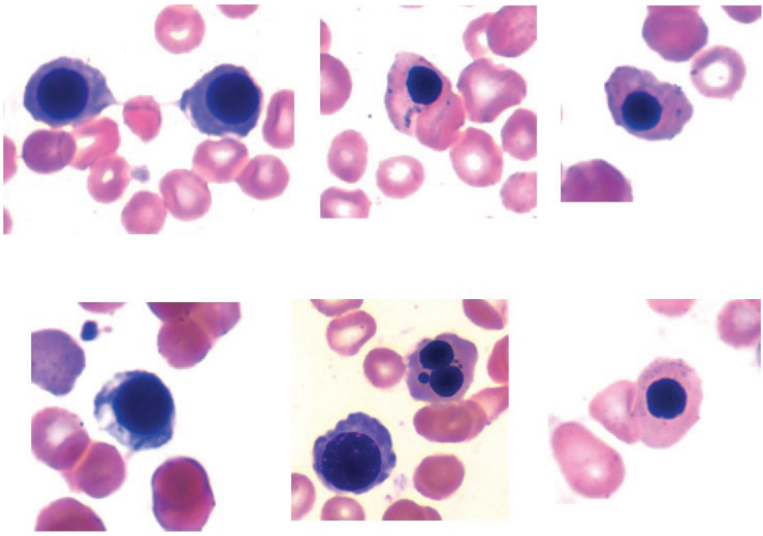


Figure 17.4. Dyserythropoiesis: bone marrow aspirate smear showing inter-cytoplasmic bridging, altered nuclear:cytoplasmic ratios, nuclear cytoplasmic maturation asynchrony, cytoplasmic vacuolation, nuclear budding.

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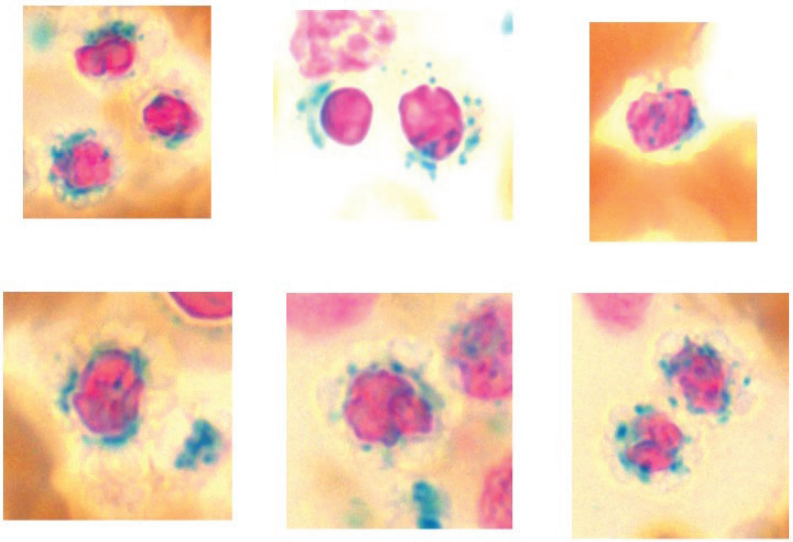


Figure 17.5. Photomicrographs showing sideroblasts and ring sideroblasts in the bone marrow aspirate smear.

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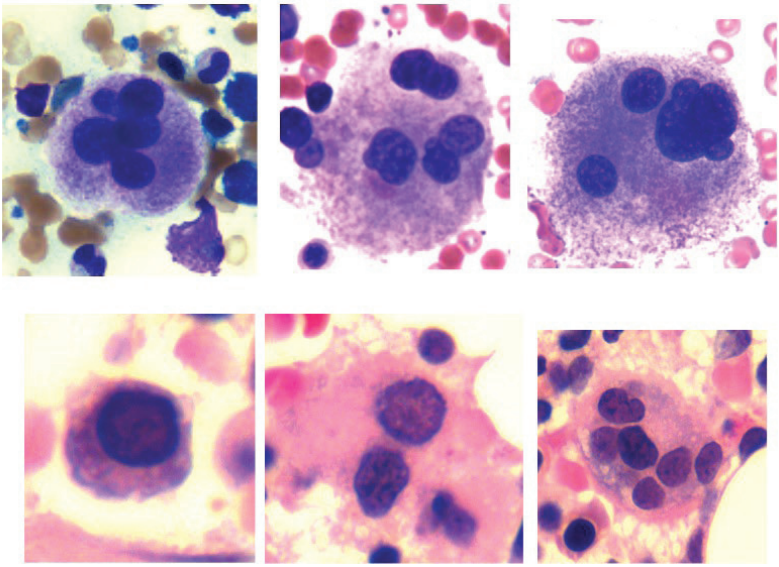


Figure 17.6. Dysmegakaryopoiesis: multi nuclear megakaryocytes, top row-bone marrow aspirate smear. Mono, bi and multi-nucleated megakaryocytes, bottom row- bone marrow biopsy section.

A diagnosis of MDS is typically made by practicing hematologists in Europe and mostly by hematopathologist in the United States by examining the smears of peripheral blood and bone marrow aspirates. Evaluation of sections of bone marrow trephine biopsy specimens does not play a pivotal role in its diagnosis. Unlike acute myeloid leukemia which might present a marrow that is heavily infiltrated with myeloblasts and is readily diagnosable, MDS is likely to display a varied picture involving one or more of the granular, erythroid and megakaryocytic populations. This profile does not lend itself to a specific, exclusive categorization. This can result in multiple varied assessments from different independent hematologists/hematopathologists. Inter-observer variation in the diagnosis of MDS and difficulty in distinguishing genuine MDS from mimics is not uncommon. For example, a group of hematologists/hematopathologists can describe one bone marrow independently in many different ways as six blind people described an elephant in many different ways. In addition, bone marrow is not always involved uniformly in pathological processes and morphological discordance is well known. This is particularly true for patients with myelodysplastic syndromes. In bone marrow biopsy sections

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from patients with MDS one could see a non-uniform involvement of the marrow with different cellular elements including localized clusters of blast cells or erythroid precursors in some areas. The latter constellation of blast cells has been termed ‘abnormal localization of immature precursors’ (ALIP) (Figure 17.7).

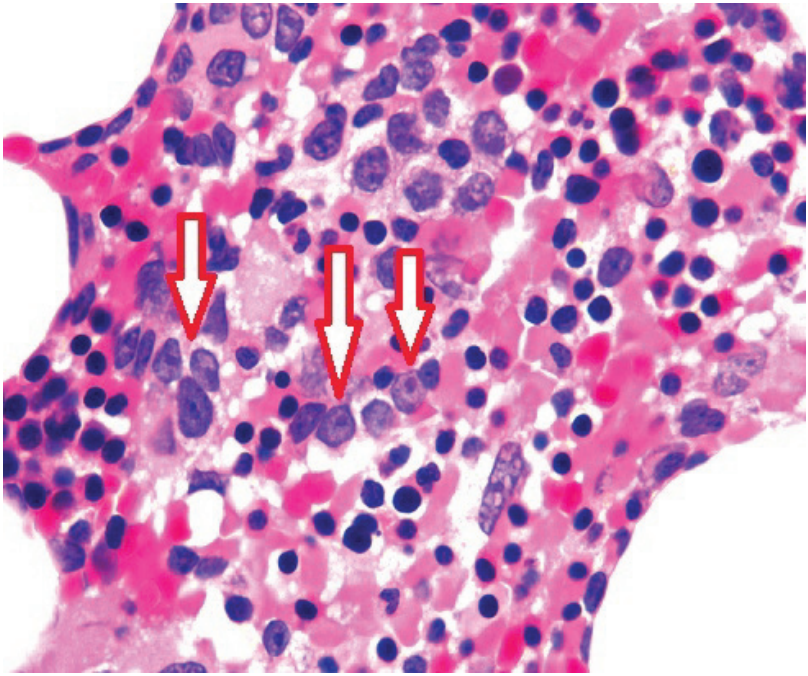


Figure 17.7. Abnormal localization of immature (blast) precursors (ALIP) (arrows) noted in the bone marrow biopsy section from a patient with MDS (H&E).

During bone marrow aspiration if the tip of the aspirating needle encounters one of these areas of ALIP’s (figure 17.8A) the aspirate may contain 15-20% or more blast cells and the patient might then be misleadingly diagnosed as high risk MDS or even de novo acute leukemia. On the other hand, during aspiration if the tip of the aspirating needle misses these areas of focal collection of blast cells (Figure 17.8B) and strikes an area containing clusters of erythroid precursors as shown in the picture (or where erythroid precursors seem to predominate) such bone marrow aspirates will definitely have few blast cells and the patient would

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be considered as of low risk MDS. Alternatively in this situation the case could be misleadingly diagnosed as erythroleukemia (FAB M6).

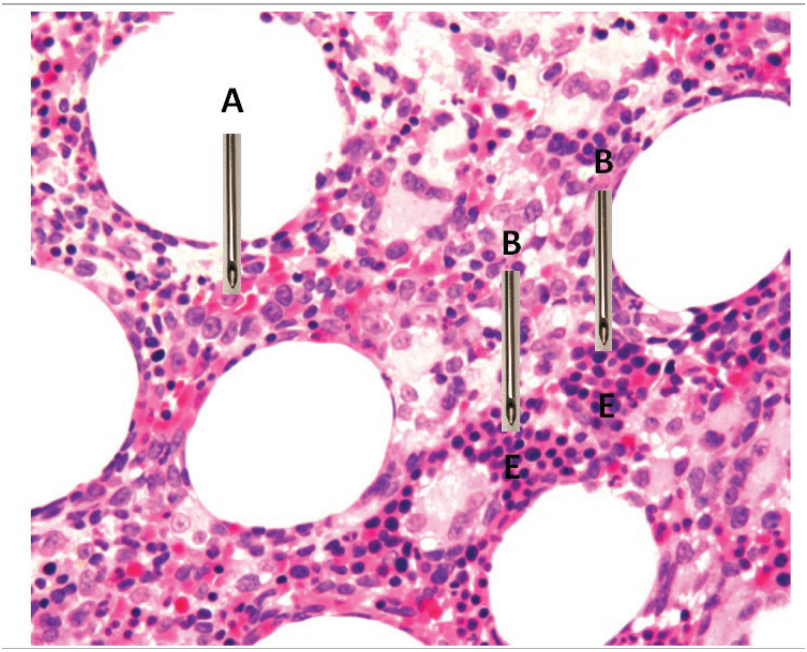


Figure 17.8. Bone marrow biopsy section from the same patient as in figure 17.7 lower magnification demonstrating **A**- the tip of aspirating needle has encountered an area where clusters of immature myeloid precursors (blast cells) are present. They can be easily identified by the presence of nucleoli. **B**- demonstrating an area where the tip of the aspirating needle has encountered an area where blast cells are absent but predominates with erythroid precursors (**E**).

MDS is primarily a disease of the elderly and most patients are at age 65 or over. The disease is characterized by ineffective hematopoiesis and bone marrow failure. Deficiencies in hematopoiesis usually result in peripheral blood cytopenias, of which anemia is the most common. However, neutropenia and thrombocytopenia, either singly or in combination may dominate the blood picture. The bone marrow usually is hypocellular but sometimes it may be normocellular or hypercellular which may lead to its interpretation or assessment as a myeloproliferative disorder and misleadingly diagnosed as myelodysplastic/ myeloproliferative neoplasm. The term Myelodysplastic/myeloproliferative neoplasm is another

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diagnostic conundrum that the international working group has led the practicing hematologist into. There is no justification of incorporating myeloproliferative disorders into the category of myelodysplastic syndromes. All patients with myeloproliferative disorder show some degree of myelodysplastic changes and it is perhaps scientifically incorrect and diagnostically ambiguous to combine these two possibly separate disease entities under one umbrella and entitle them as myeloproliferative/myelodysplastic neoplasm. MDS may arise de novo or may appear years after exposure to chemicals or mutagenic chemotherapy.

We have studied well stained bone marrow aspirate and plastic embedded BM biopsy sections from normal adults as well as from patients with various hematological disorders. Normal marrows (aspirates and trephine biopsies) were obtained from normal adults who volunteered to donate marrow for transplantation. Patients with AML, for example were studied at diagnosis, following chemotherapy, during hematopoietic regeneration following chemotherapy and at complete remission. Patients with chronic granulocytic leukemia (CGL) was studied in the chronic phase, during blast cell transformation, following autographing and during hematopoietic regeneration. Bone marrow aspirates and biopsies were also obtained from patients with aplastic anemia, chronic lymphocytic leukemia, non-Hodgkin's lymphoma and multiple myeloma.

We have observed that some degree of myelodysplastic alteration either in the erythroid or granuloid or megakaryocytic series can be observed in most of these disorders. Even in normal marrows some dysplastic changes either in the erythroid, granuloid or megakaryocytic cells could be observed but they were few and far between. In the original FAB classification it was reported that "in some patients the mere presence of these abnormalities is adequate for their inclusion in the MDS". This premise requires farther delineation because if this were to be accepted as it is then many of the newly diagnosed patients with AML's, multiple myelomas and other marrow-perturbing neoplastic conditions (where such morphologic abnormalities are not uncommon) would need to be included in MDS.

Cytogenetic abnormalities are present in many of the MDS cases (20) and are believed to have both diagnostic and prognostic significance. Prognostic groups have been proposed on the basis of cytogenetics in the revised international score (IPSS-R) scheme, which include 5 different

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subgroups including 20 different alterations. The most common cytogenetic abnormalities encountered in MDS are del(5q) [$5q^-$], -7, and -8. Cytogenetic studies are performed on spontaneously dividing cells that are typically cultured for short periods (24-72 h). MDS with hypocellular bone marrow may not provide a sufficient number of such spontaneously dividing cells and as a result cytogenetic studies in these cases may not be accurate. Karyotypic changes can also be found in many if not most hematological malignant conditions, and some are non-specific irrespective of the disease in which they are found.

In patients with a hypocellular bone marrow it can be difficult to distinguish between severe aplastic anemia and MDS due to the paucity of cells in the aspirate smear and core biopsy to assess dysplastic changes. It has been suggested that in such situations, the presence of abnormal megakaryocytes and MDS-associated cytogenetic changes may favor a diagnosis of MDS. But too often there are hardly any cells to carry out appropriate cytogenetic studies or look for specific dysplastic changes.

Another important diagnostic challenge is to distinguish MDS with bone marrow fibrosis from primary myelofibrosis. Here, the absence of Janus Kinase 2 (Jak2 V617F) mutation and the presence of MDS-associated cytogenetic changes and megakaryocytic dysplasia may be helpful factors in distinguishing MDS from primary myelofibrosis. However, in large majority of cases with essential thrombocythaemia an excessive proliferation of megakaryocytes occurs which are quite often dysplastic and associated with marrow fibrosis. These cases should be diagnosed as a myeloproliferative disorder and not MDS despite the presence of dysplastic megakaryocytes and the absence of Jak2 mutation.

Chronic myelomonocytic leukemia (CMML) was originally classified as MDS in the FAB classification. However, it has been correctly removed from the current WHO classification. MMOL truly belongs to chronic myeloproliferative disorders and the condition is very similar to chronic granulocytic leukemia (CGL) but unlike CGL where mature granulocytic precursor cells predominate in the bone marrow and peripheral blood, in MMOL it is the monocytes and pro-monocytes that predominate in these two sites (Figure 17.9).

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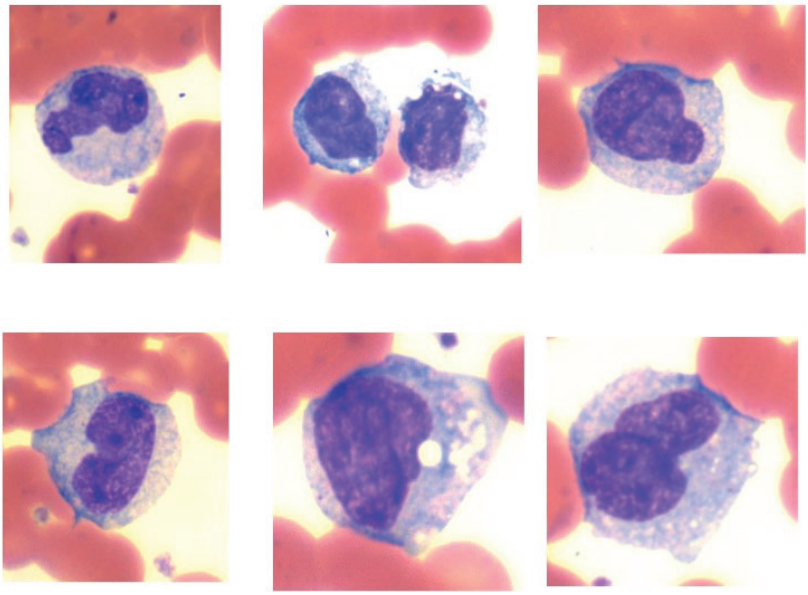


Figure 17.9. Myelo-monocytic leukemia (MMOL): Peripheral blood and bone marrow aspirate smear showing monocytes and promonocytes.

The presence or absence of ring sideroblasts plays a prominent role in the diagnosis and classification of MDS in the FAB classification. Sidereblasts are nucleated erythroid cells whose cytoplasm contain siderotic (iron positive) granules that are usually well dispersed in the cytoplasm but may also be localized adjacent to the nucleus. Ring sideroblasts display their granules in a perinuclear distribution surrounding the entire nucleus or at least one third of the nucleus. Sideroblasts are found in diverse circumstances including megaloblastic anemia. The term sideroblastic anemia has been applied to or viewed as a complication of the anemia of severe alcoholism, B-6 deficiency and lead poisoning. It is debatable whether the presence of sideroblasts or ring sideroblasts should be afforded any such prominence in the diagnosis and classification of MDS.

MDS is believed to be a group of heterogenous disorders in which the understanding of their pathogenesis is still incomplete. Recent advances have shown that immune dysregulation may contribute to the disease pathobiology in selected individuals. An analysis of the multi-subset classification of MDS [(i) MDS with single lineage dysplasia -MDS-SLD,

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(ii) MDS with ring sideroblasts - MDS-RS, (iii) MDS with multilineage dysplasia - MDS-MLD, (iv) MDS with excess blasts-1 -MDS-EB-1, (v) MDS with excess blasts-2 - MDS-EB-2, (vi) MDS unclassifiable - MDS-U, (vii) MDS with isolated del(5q), (viii) refractory cytopenia of childhood, (ix) MDS with excess blasts in transformation –MDS-EB-T], indeed leads to the conclusion that a consensus for an accurate, specific, knowledgeable diagnosis of MDS has yet to be met. Perhaps the best interim terminologic resolution of this quandary is to revert to the prior older classification of "pre-leukemia" and manage these conditions individually whether they are anemic, neutropenic or thrombocytopenic or of mixed deficiencies and not consider them as hemopoietic malignant disorder and treat them with chemotherapy. Some of these patients can be watched and observed for a long period of time with regular clinic visits and monitoring only with the CBC with differentials. For patients who require medical treatment, growth factors, such as epoietin and GCF along with a low dose steroid can be effective for those with anemia, neutropenia, or both. Even patients with excess of blasts in the marrow also responds to above therapy quite well (authors personal observation). Patients with anemia in whom erythropoietic-stimulating agents have not been effective may benefit from Luspatercept (a recombinant fusion protein that binds transforming growth factor ß superfamily ligands to reduce SMAD2 and SMAD3 signaling). Immunomodulatory drugs such as revlimid may be useful in some cases. Chemotherapy, at least as an initial treatment may be avoided. A controlled and comparative study of MDS patients with growth factors (G-CSF and erythropoietin), immunomodulatory drugs (revlimid) or chemotherapy "5-azacytidine" would be welcome. But until we are able to formulate an accurate diagnostic criteria beyond the morphological grounds (which is subject to interpretation) alone and overcome the inter-observer variation we are stuck and we will be comparing apples and oranges to formulate an accurate diagnosis and as a result therapeutic dilemmas will persist. Until we find an adequate solution to this conundrum a wise approach would be to watch and observe and treat these patients only when necessary either with growth factors or immunomodulatory drugs in combination with supportive therapy such as blood and platelet transfusions. Some of these patients do run very low platelet counts (around 20,000) and fortunately they do not bruise or bleed easily. In such circumstances an intelligent approach would be to leave them alone and not to become overly enthusiastic and aggressively treat the thrombocytopenia.

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CHAPTER 18

EXAMPLES OF DESCRIPTIONS OF BONE MARROW BIOPSY (BMB) SECTIONS FROM NORMAL AND REPRESENTATIVE HAEMATOLOGIC AND NONHAEMATOLOGIC DISEASES

Plastic (methyl-methacrylate-MMA or glycol-methacrylate-GMA) embedded bone marrow biopsy sections. MGG (May-Grunwald-Giemsa stain)

A typical morphologic description of a normal active hemopoietic bone marrow with pictorial illustrations (Figures 18.1 A & B)

A bone marrow biopsy obtained from the right posterior iliac crest using a standard Islam BMB needle. The overall cellularity is within normal limits (50% hemopoietic cells and 50% adipose cells). Erythropoiesis is active and normoblastic. Granulopoiesis is active and presents all stages of maturation. Megakaryocytes are normal in number. Gomori's reticulin stain shows a normal reticulin pattern. Iron stores are normal.

Comment: The marrow appearance is morphologically normal.

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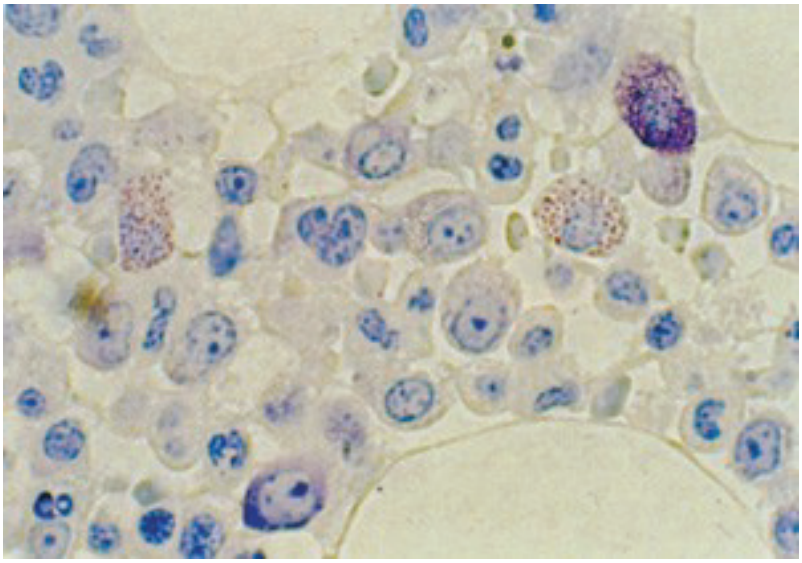


Figure 18.1 [A] A BMB section from a normal adult showing elements of granulopoiesis. Note a myeloblast (bottom left of the field), two eosonophil gralnulocytes, a basophilic granulocyte, a few neutrophilic myelocytes and their segmented forms (MMA. MGG stain.)

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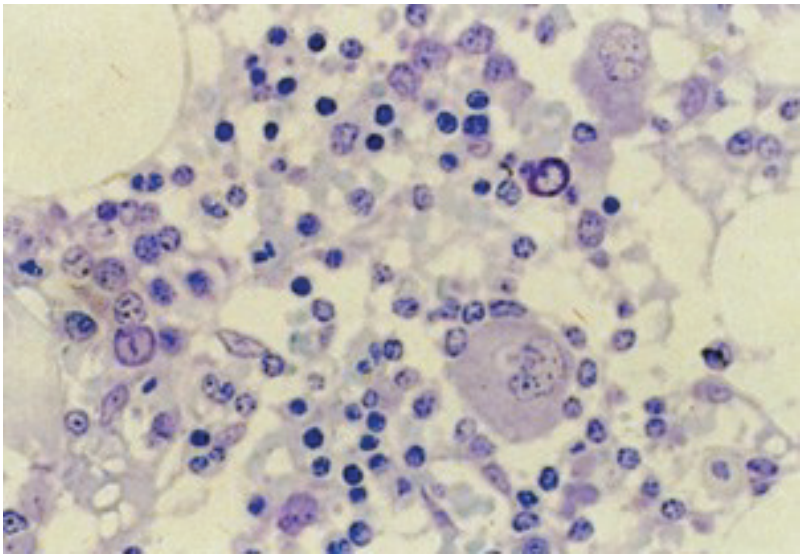


Figure 18.1 [B] A BMB section from a normal adult showing elements of erythropoiesis at different stages of maturation Two megakaryocytes and a mast cell (upper right field, cell with darkly stained cytoplasm) can also be seen (MMA, MGG stain).

A typical description of bone marrow biopsy sections from a patient with aplastic anemia with pictorial illustrations (Figures 18.2 A to D).

A bone marrow biopsy obtained from the right posterior iliac crest using a standard Islam BMB needle. The overall hemopoietic cellularity is markedly reduced (less than 15%). Fat cells (mostly unilocular and uniform in size) are markedly increased (75-80%). There is some edema, but no extravasation of red cells and vascular system (sinusoids and capillaries) are prominent. The cells present consist mostly of mature lymphocytes, plasma cells, tissue mast cells and macrophages. Erythropoiesis is markedly depressed. Only a few small clusters of erythroid precursors, mostly at the same stage of maturation (“hot spots”) are seen. Granulopoiesis is markedly depressed, only a small number of mature myeloid precursors are seen. Megakaryocytes are absent.

Comment: The marrow appearance is consistent with the diagnosis of severe aplastic anemia.

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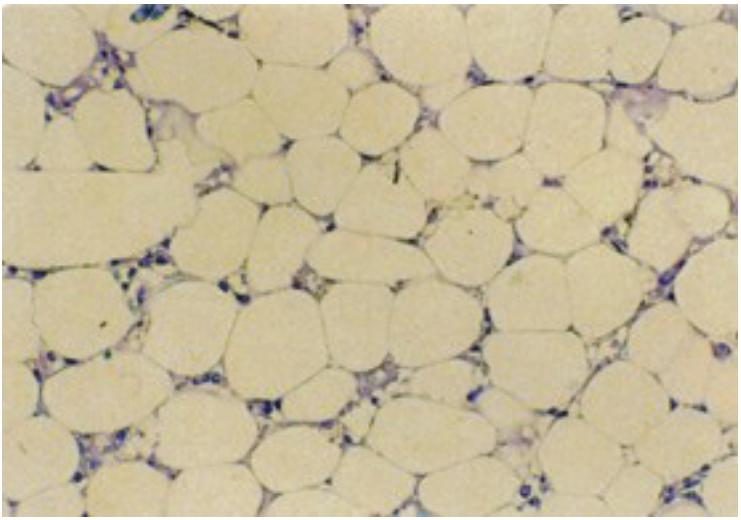


Figure 18.2 [A] A BMB section from a patient with aplastic anemia showing an extremely hypocellular and fatty marrow (MMA, MGG stain)

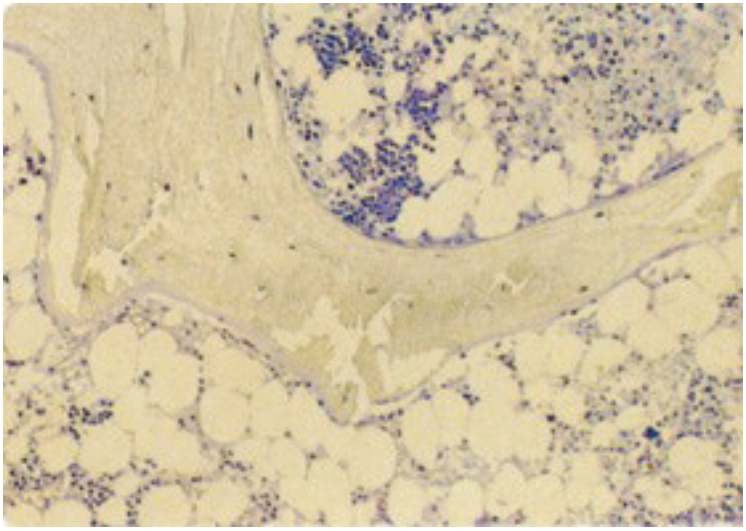


Figure 18.2 [B] BMB section from an aplastic anemia patient showing a hypocellular marrow but with residual erythroblastic clusters close to a bony trabecula; (MMA, MGG stain.)

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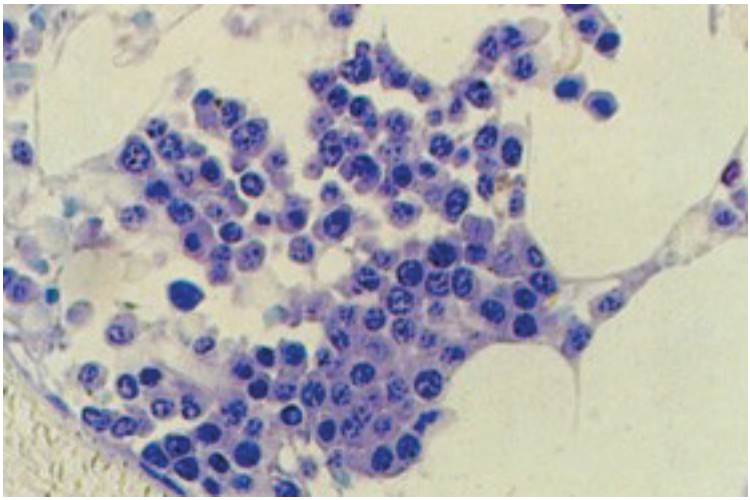


Figure 18.2 [C] The same section as in Figure 17. 2 [B] but at a higher magnification showing an erythroblastic cluster with maturation arrest. (MMA, MGG stain.)

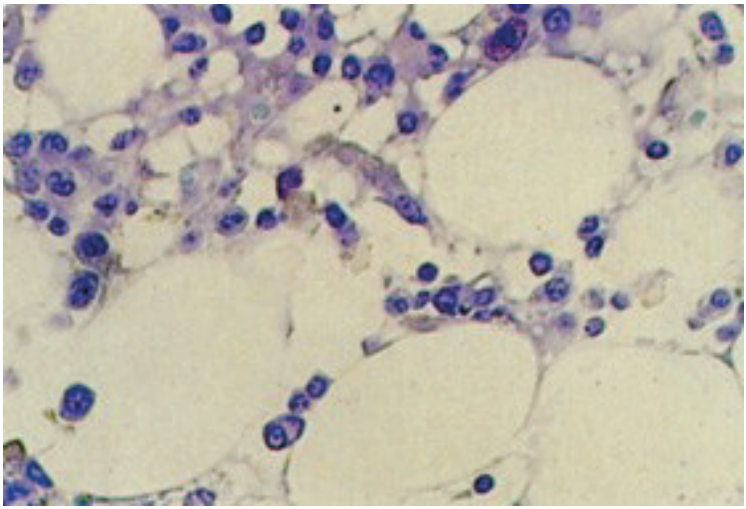


Figure 18.2 [D] The same section as in Figure 18.2 [B] showing the presence of inflammatory cells (lymphocytes, plasma cells and macrophages). (MMA, MGG stain.)

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Typical presentations of bone marrow biopsy sections from newly diagnosed patients with acute myeloid leukemia with pictorial illustrations (Figures 18.3 to 18.9).

FAB is the title of a morphologic classification of the various presentations of acute myeloid leukemia as observed in MGG stained dry film smears of blood and bone marrow. The types are designated as M1, M2 etc. The classification was formulated through the collaboration of a French, an American and a British hematologists, thus the title FAB. The British representative Professor Daniel Catovsky was a mentor for the author of this text.

Typical descriptions are:

A bone marrow core biopsy obtained from the right posterior iliac crest using a standard Islam BMB needle. The cellularity is over 90% and the fat content is less than 10%. Erythropoiesis markedly depressed, only scattered and occasional small clusters of erythroid precursors are seen. Granulopoiesis is markedly depressed, only a few mature forms are seen. Megakaryocytes are absent. There is marked infiltration of the marrow by sheets of blast cells. Gomori's reticulin stain shows no increase in reticulin or collagen fibers.

Comment: The marrow appearance is consistent with the diagnosis of acute leukemia. Morphologically the blast cells are difficult to characterize in BMB sections either as myeloblasts or lymphoblasts. However, if enzymatic and immunostainings are carried out on the sections and if majority of the blast cells are myeloperoxidase or CD13, 33 (and ± 34) positive then the diagnosis of acute myeloblastic leukemia can be made as shown in figures 18.9 A & B). Below: BMB sections from patients with AML showing different morphological types as recognized in plastic embedded BMB sections.

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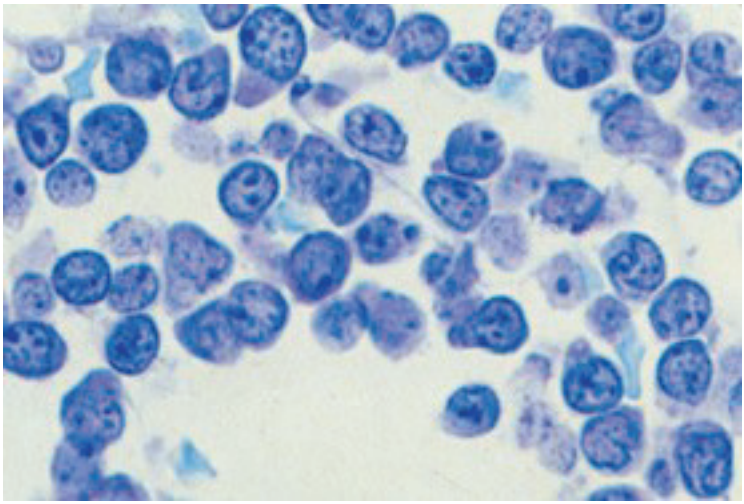


Figure 18.3 [A] A BMB section from a patent classified as FAB M1 - note monomorphic blast cells without any evidence of maturation. (MMA. MGG Stain)

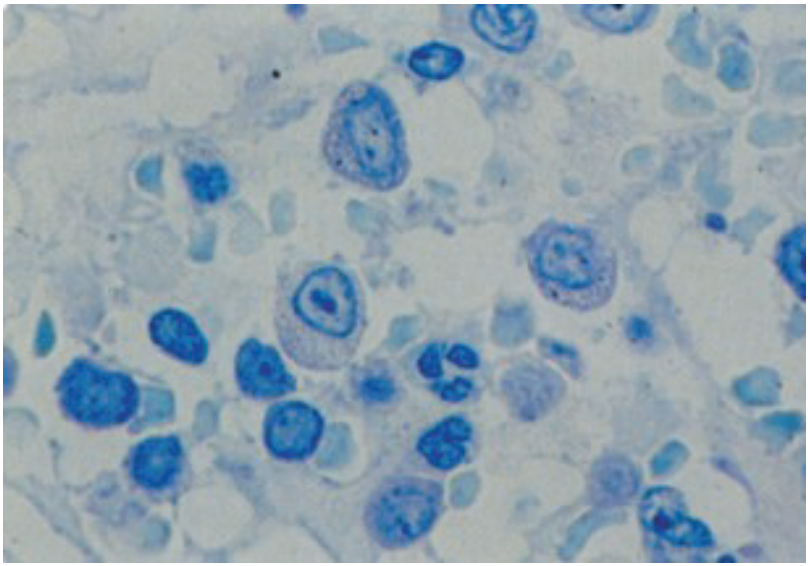


Figure 18.3 [B] A BMB section from a patient classified as FAB M2. Note the evidence of maturation. (MMA. MGG Stain)

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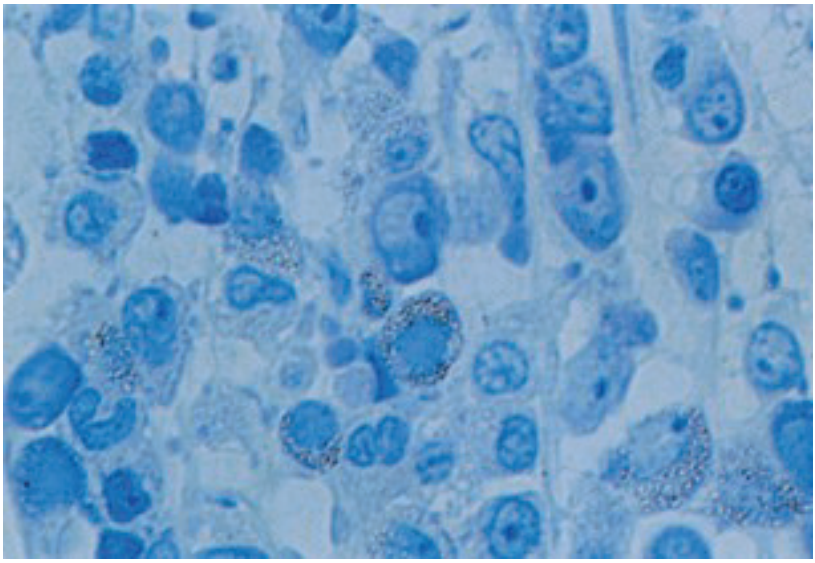


Figure 18.3 [C] A BMB section from a patient classified as FAB M3. Note the large promyelocytes with their prominent granulation. (MMA. MGG Stain)

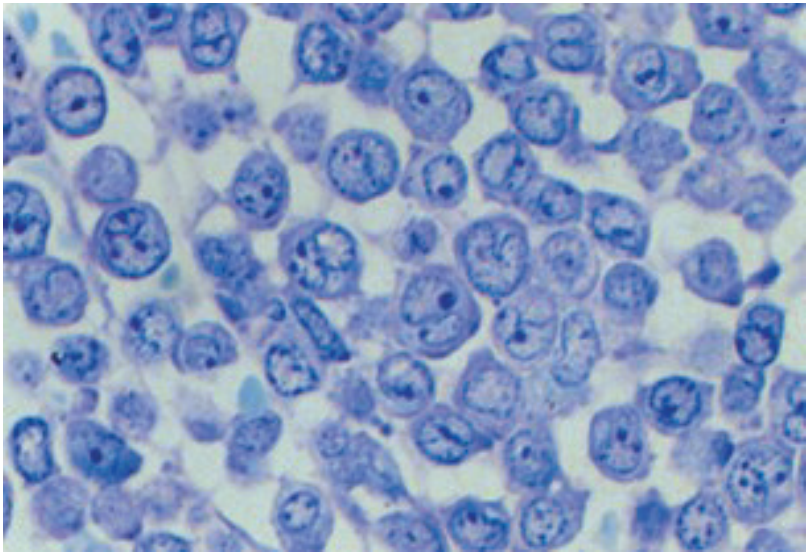


Figure 18.3 [D] A BMB section from a patient classified as FAB M4. Note the myelomonocytic feature of the blast cells (cells with folded nuclei). (MMA. MGG Stain)

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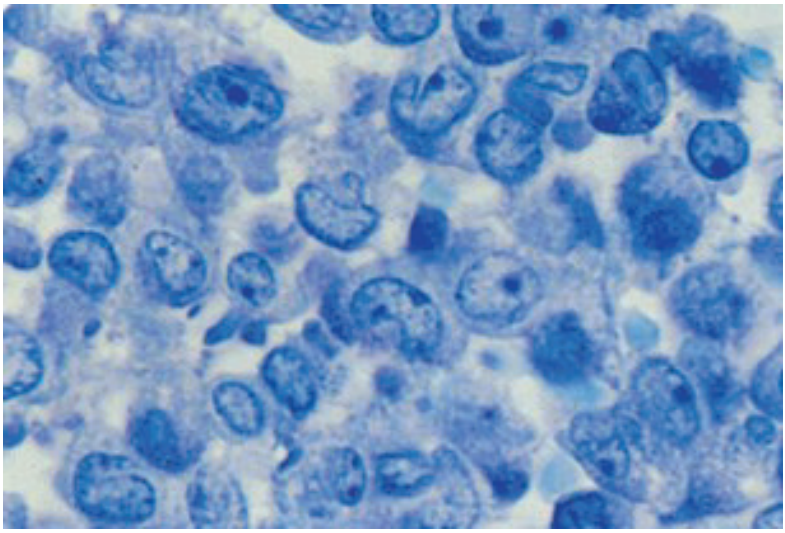


Figure 18.3 [E] A BMB section from a patient classified as FAB M5. Note the prominent monocytoid feature of the blast cells (cells with large delicate, folded nuclei). (MMA. MGG Stain)

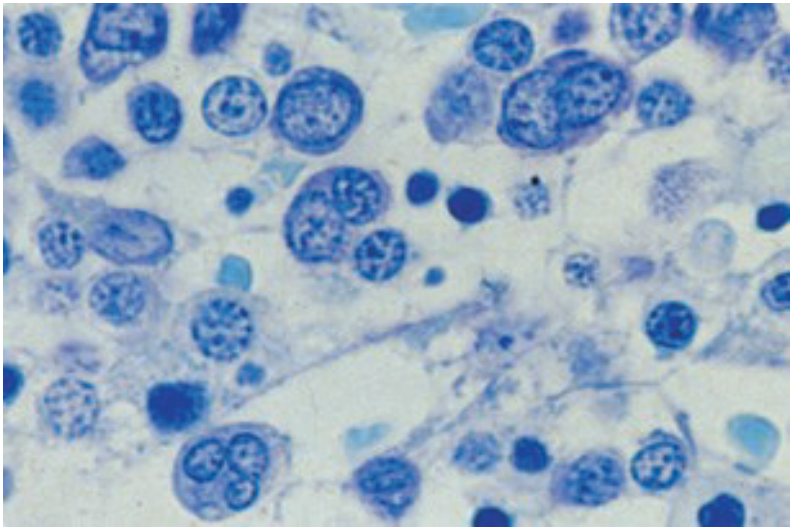


Figure 18.3 [F] A BMB section from a patient classified as FAB M6. The erythroid precursors are at different stages of maturation and are readily recognizable. They also show some degree of dyserythropoietic changes (bi and tri nucleated erythroblasts) - (MMA. MGG Stain)

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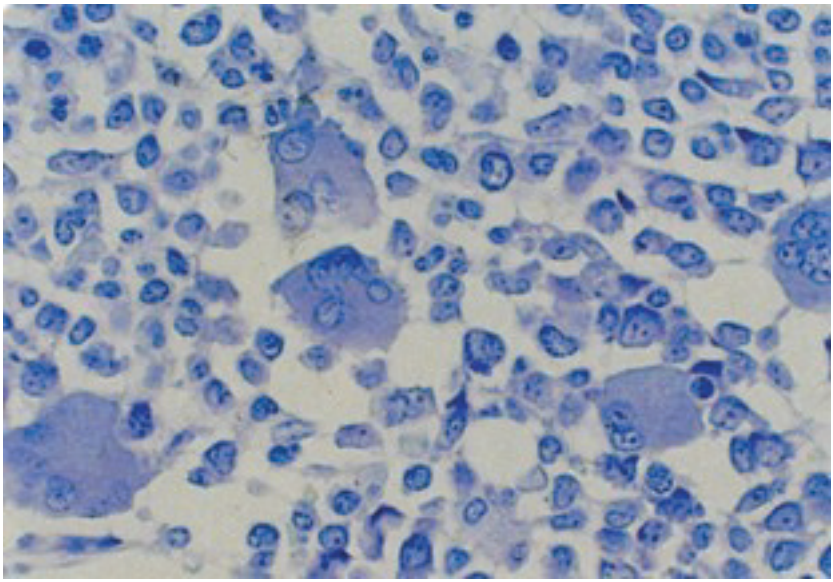


Figure 18.3 [G] A BMB section from a patient with AML showing a focal increase in megakaryocytes. (MMA, MGG stain)

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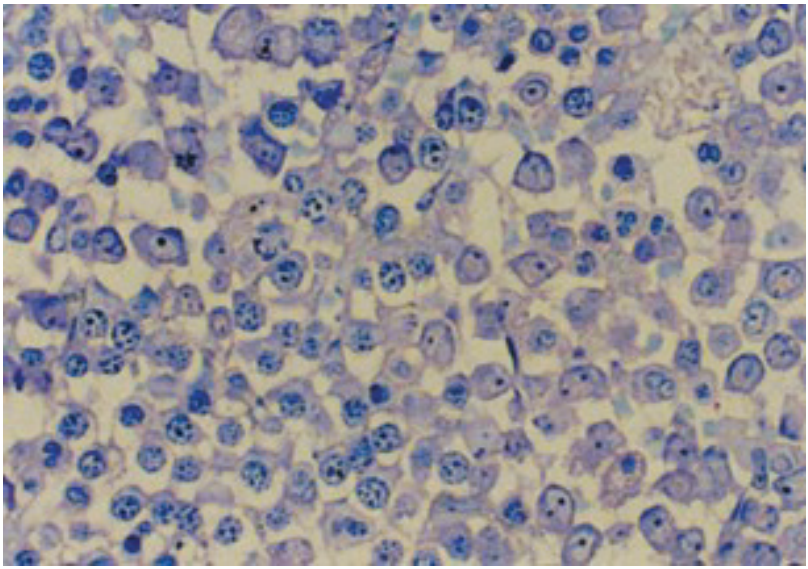


Figure 18.3 [H] A BMB section from another AML patient showing a focal increase in erythroid precursors. In both above cases the BM aspirates failed to show the extent of erythroid and megakaryocytic involvement in the marrow of these patients. (MMA, MGG stain)

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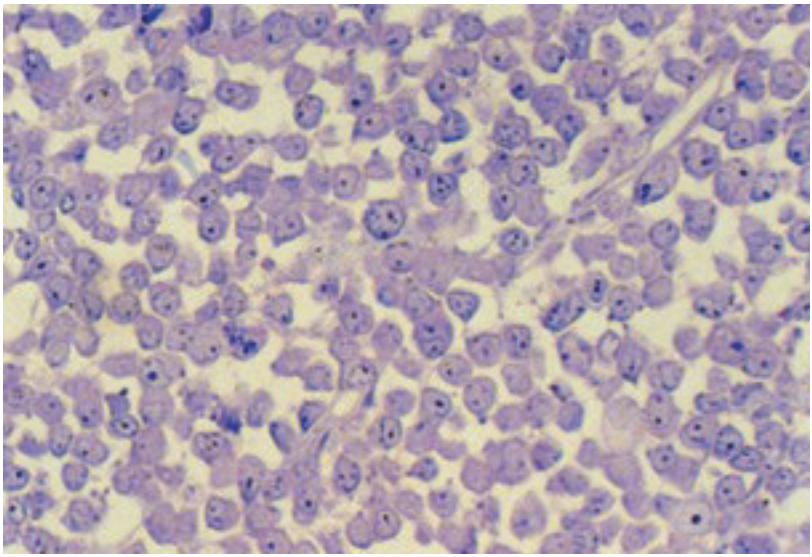


Figure 18.3 [I] A BMB sections from two cases of AML. This one presents a totally homogenous infiltration of the marrow by blast cells. (MMA, MGG stain). Observe the following photomicrograph 17.3[J] for the other case.

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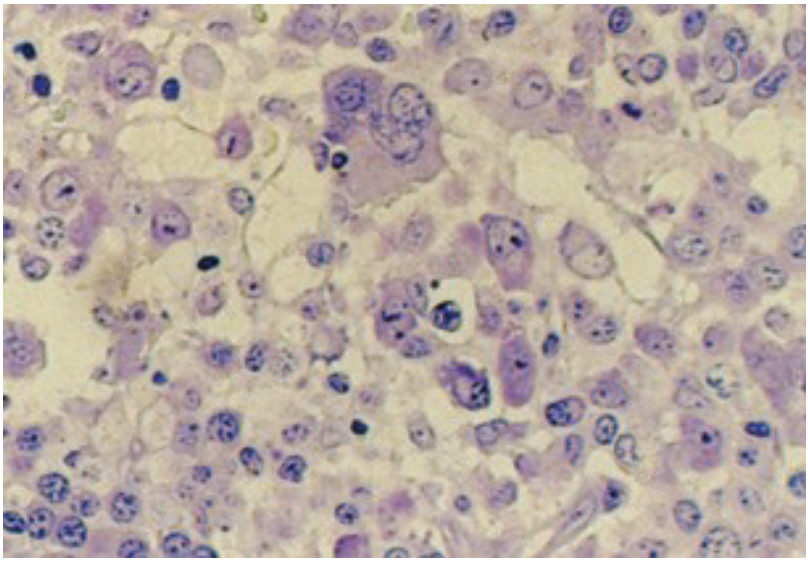


Figure 18.3 [J] A BMB section from another patient with AML showing totally inhomogeneous infiltration of the marrow by blast cells. Note the presence of a variety of other cell types in addition to the blast cells (which are the nucleolated cells). (MMA, MGG stain)

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BMB sections from two cases of AML (Figures 18.3 K & L) showing a difference in the number of cells in mitosis. These features are not well appreciated in BM aspirate smears.

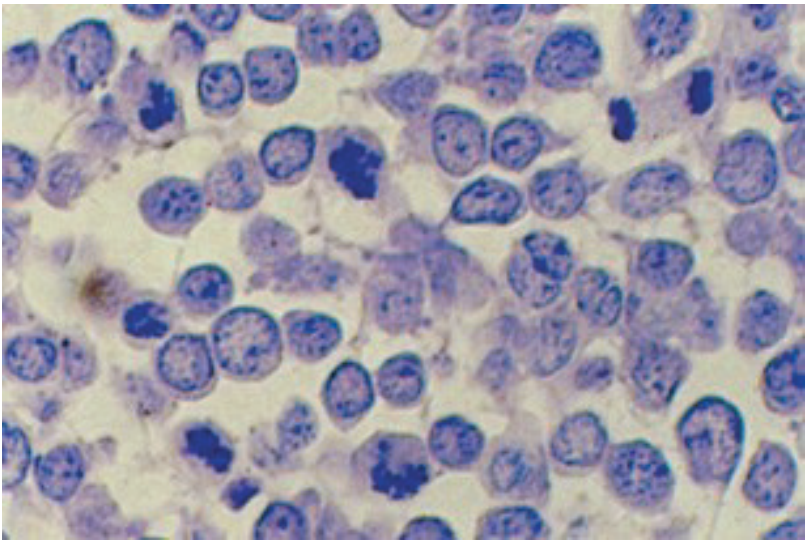


Figure 18.3 [K] A BMB section from a case of AML showing a high frequency of mitotic figures. (MMA, MGG stain)

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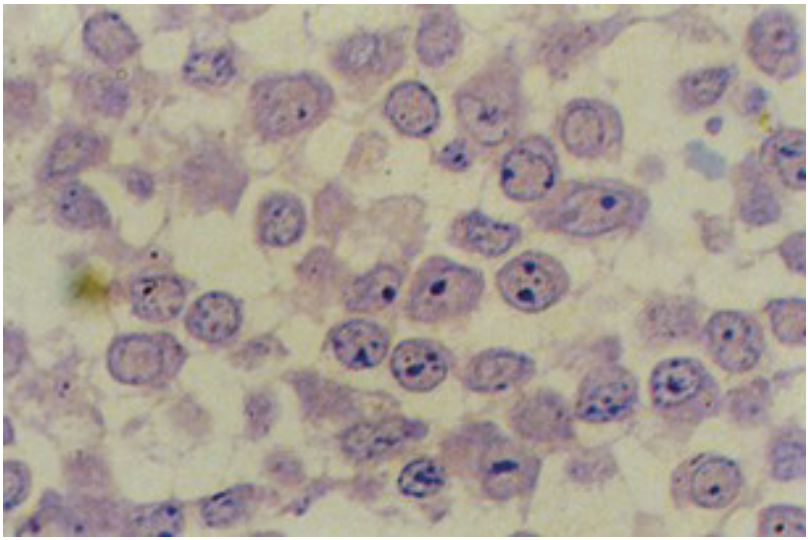


Figure 18.3 [L] A BMB section from a case of AML with infrequent mitotic figures (MMA, MGG stain). None are present in this photomicrograph, although nucleolated blast cells can be easily identified.

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BMB sections from patients with AML (Figures 18.4 A to D) showing the presence of inflammatory infiltrates: lymphocytes, plasma cells, eosinophils and macrophages. (MMA, MGG stain).

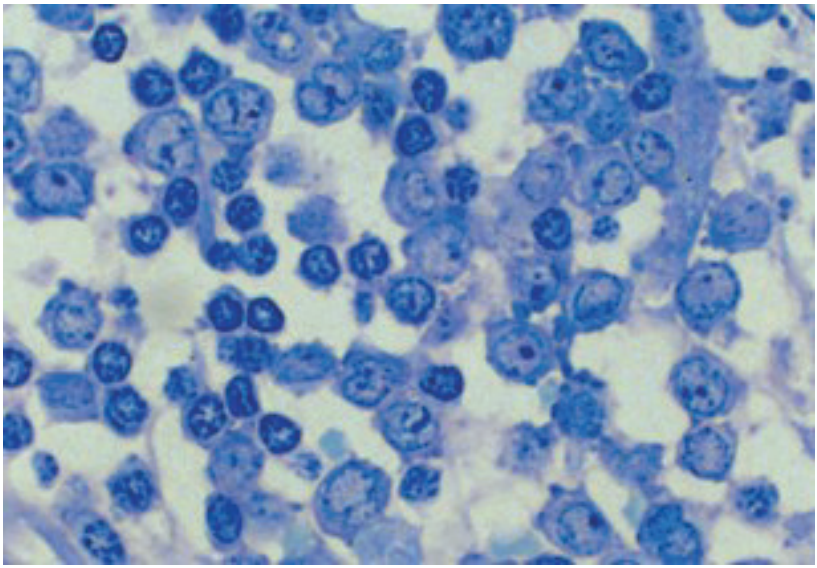


Figure 18.4 [A] A BMB section from a patient with AML illustrating the presence of a large number of lymphocytes with mature appearance. (MMA, MGG stain.)

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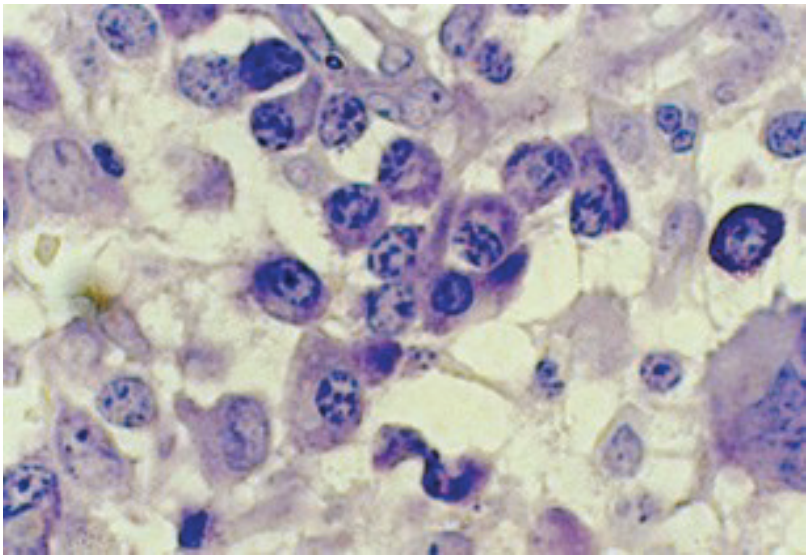


Figure 18.4 [B] A BMB section from a patient with AML showing the presence of large number of plasma cells. (MMA, MGG stain.)

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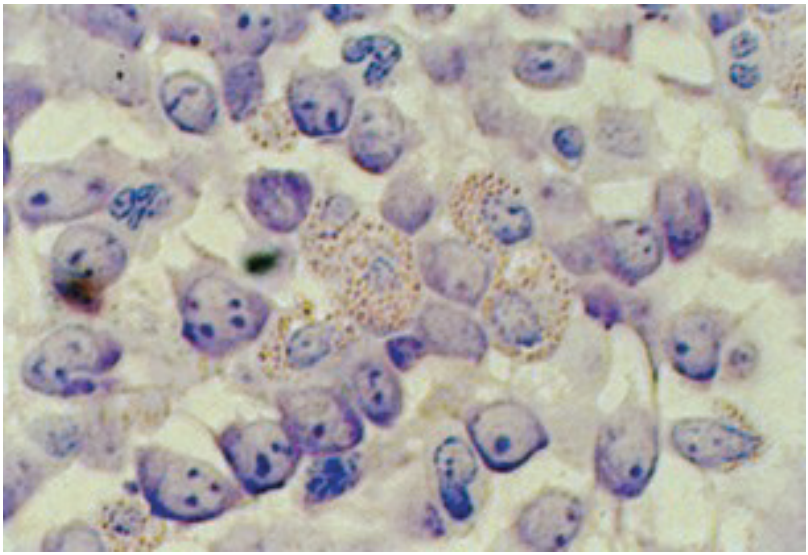


Figure 18.4 [C] A BMB section from a patient with AML showing the presence of large number of eosinophil granulocytes. (MMA, MGG stain.)

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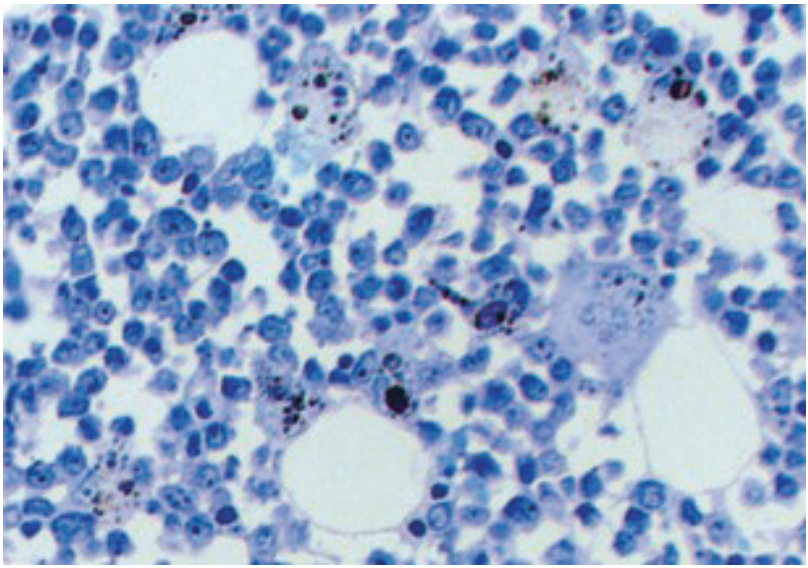


Figure 18.4 [D] A BMB section from a patient with AML showing the presence of a large number of macrophages. (MMA, MGG stain.)

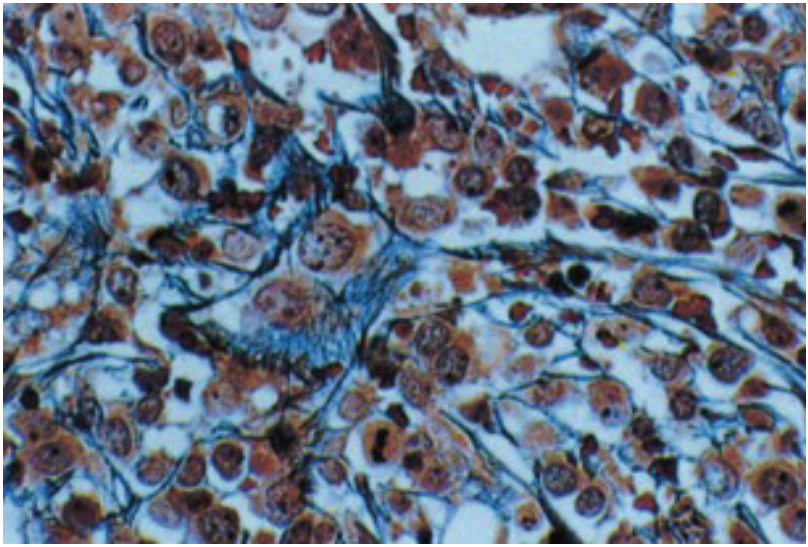


Figure 18.5 A BMB section from a patient with AML showing an increase in reticulin fibers (MMA, Gomori's reticulin stain)

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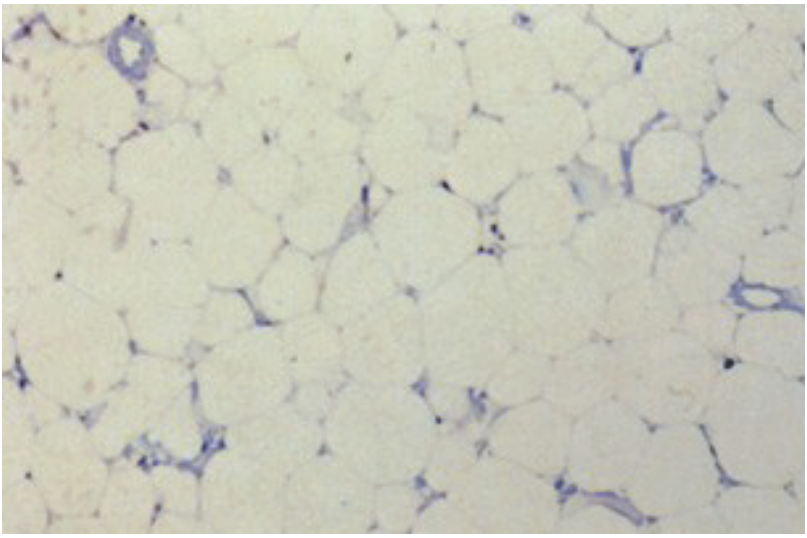


Figure 18.6 [A] A BMB section from a patient with hypoplastic AML showing a hypocellular (fatty) marrow. (MMA, MGG stain)

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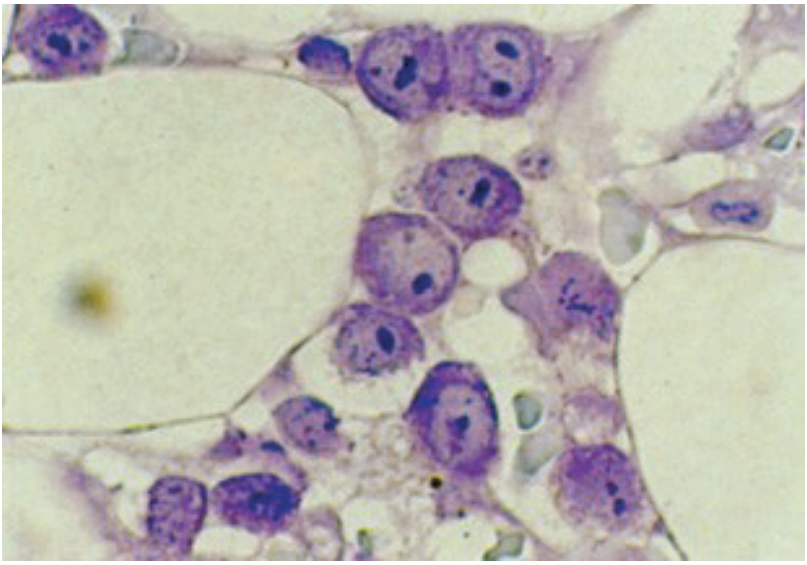


Figure 18.6 [B] The same section as in Figure 17.6 [A] but a field from another area showing a cluster of blast cells. The BM aspirate was unsatisfactory in the first attempt and while the second aspiration revealed a hypocellular marrow but no blast cells. (MMA, MGG stain).

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BMB sections from patients with AML showing myelodysplastic features (Figure 18.7 A & B)

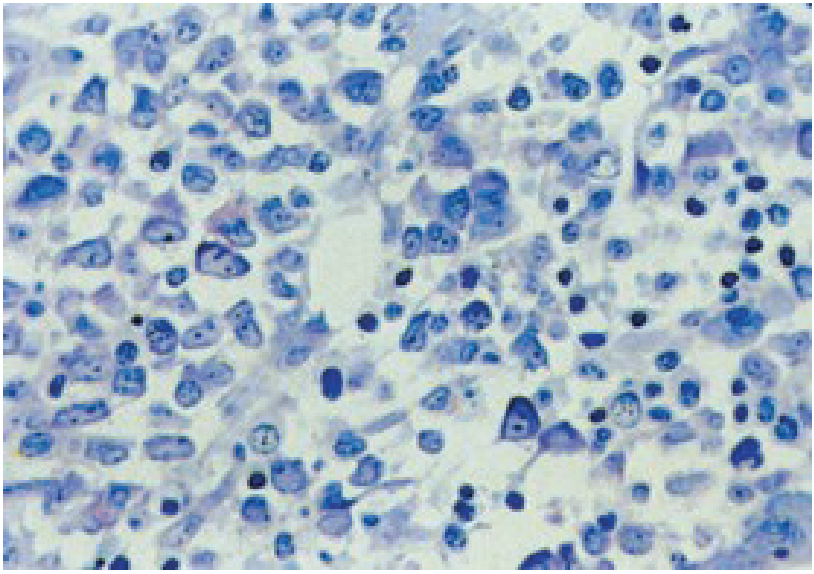


Figure 18.7 [A] A BMB section from a patient with AML showing dyserythropoietic changes. Note the megaloblastoid features, irregular shaped nuclei, lobulation and budding of the nuclei. (MMA, MGG stain)

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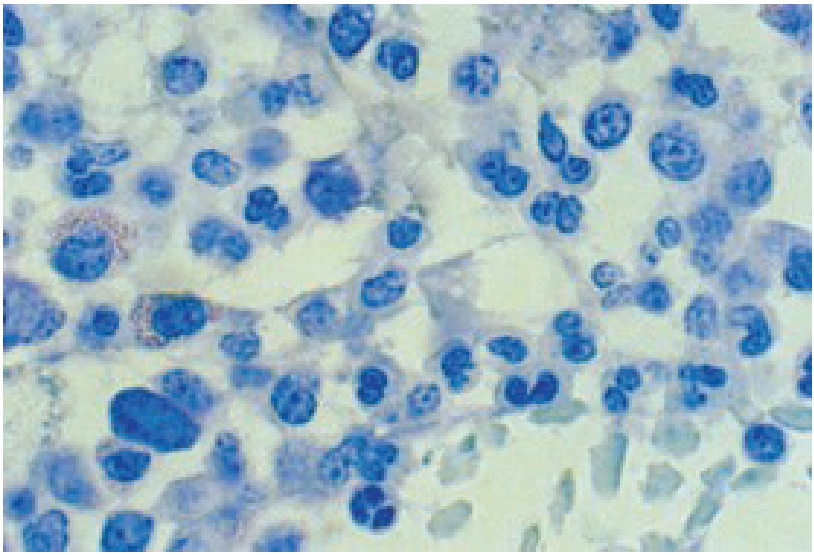


Figure 18.7 [B] A BMB section from a patient with AML showing hyposegmented neutrophils (pseudo Pelger- Huet anomaly). (MMA, MGG stain)

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BMB sections from two patients with AML following same chemotherapy but showing difference in response with regard to the elimination of blast cells from the marrow (Figures 18.8 A & B)

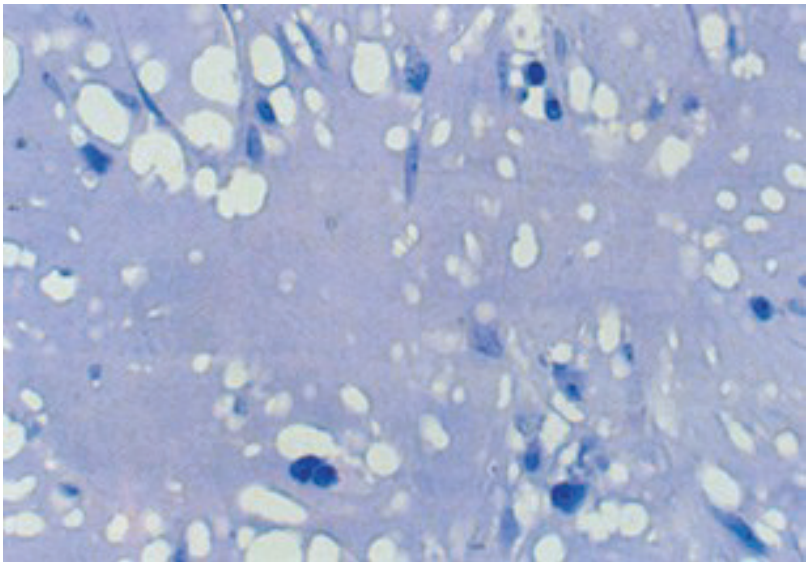


Figure 18.8 [A] A BMB section from a patient with AML two weeks after chemotherapy showing extremely hypocellular and grossly edematous marrow with almost complete elimination of blast cells. (MMA, MGG stain).

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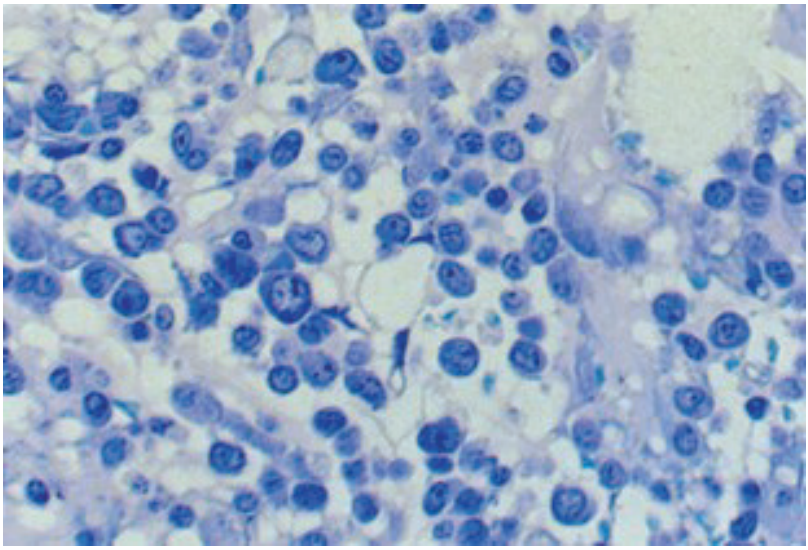


Figure 18.8 [B] A BMB section from a patient with AML two weeks after chemotherapy showing the presence of a considerable number residual blasts. (MMA, MGG stain). Bone marrow aspirates do not always provide such clear cut evidence of the presence or the extent of elimination of blast cells from the marrow.

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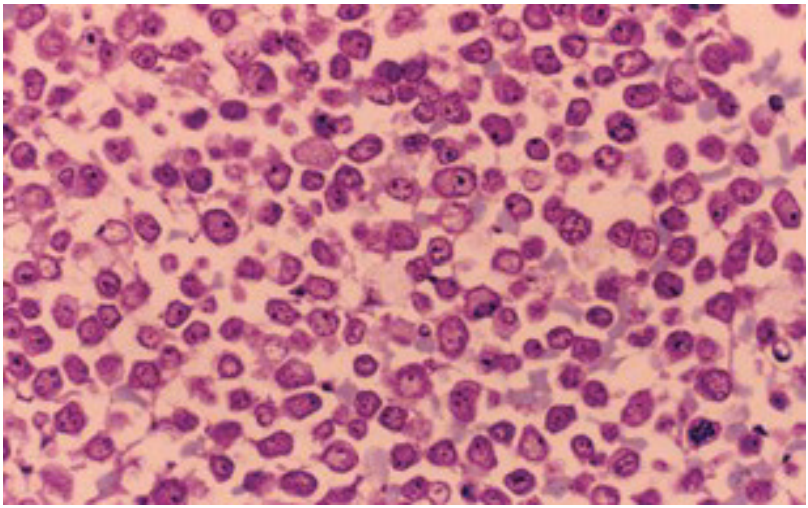


Figure 18.9 [A] A BMB section from a patient with AML showing a monomorphic infiltration of the marrow by blast cells (GMA, MGG stain).

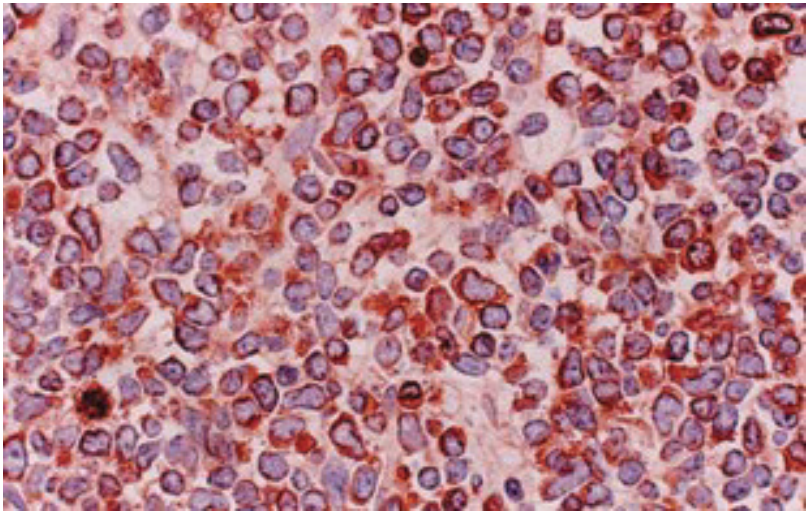


Figure 18.9 [B] The same section as 17.9A when stained for myeloperoxidase demonstrating myeloperoxidase -positive cells indicating the myeloid nature of the blast cells (GMA, PAP stain). Note a cell undergoing mitosis near the lower left corner of the field.

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A typical description of a bone marrow biopsy from patients with acute myeloid leukemia soon after chemotherapy with pictorial illustrations (Figures 18.10 A to C)

A bone marrow core biopsy obtained from the left posterior iliac crest using a standard Islam BMB needle following induction chemotherapy for AML. The overall cellularity is markedly reduced (cellularity 5-10%. Fat cells 10-15%, the remainder is edema and extravasated red cells). The cells present consist mostly of lymphocytes, plasma cells, tissue mast cells and macrophages. A few scattered and clusters of residual blast cells are seen (less than 10%). Haemopoietic activity remains depressed. An increased number of widely dilated sinuses are present. There is marked pericapillary infiltration of plasma cells.

Comment: Post therapy marrow which shows presence of a small number (< 10%) of residual blasts.

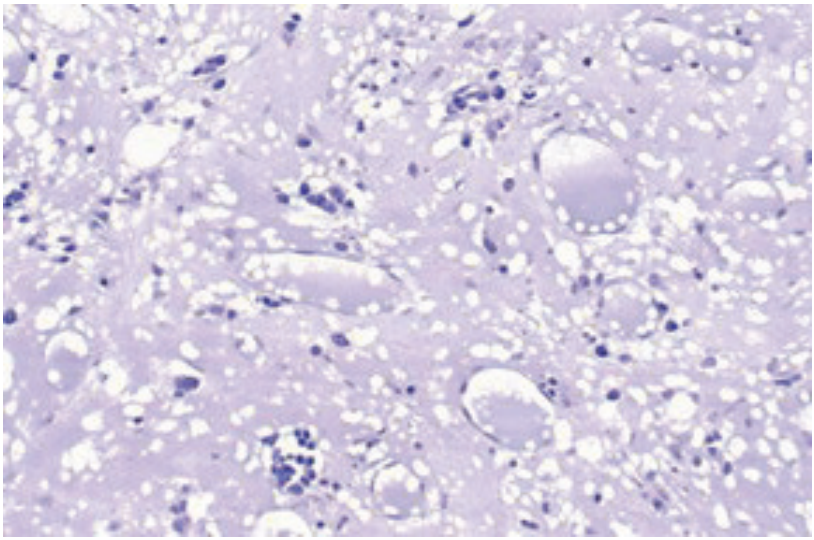


Figure 18. 10 [A] A BMB section from a patient with AML following the end of chemotherapy showing an extremely hypocellular and grossly edematous marrow with a widely dilated sinus system. The cells consist mainly of lymphocytes, plasma cells (scattered and pericapillary) and macrophages. (MMA, MGG stain).

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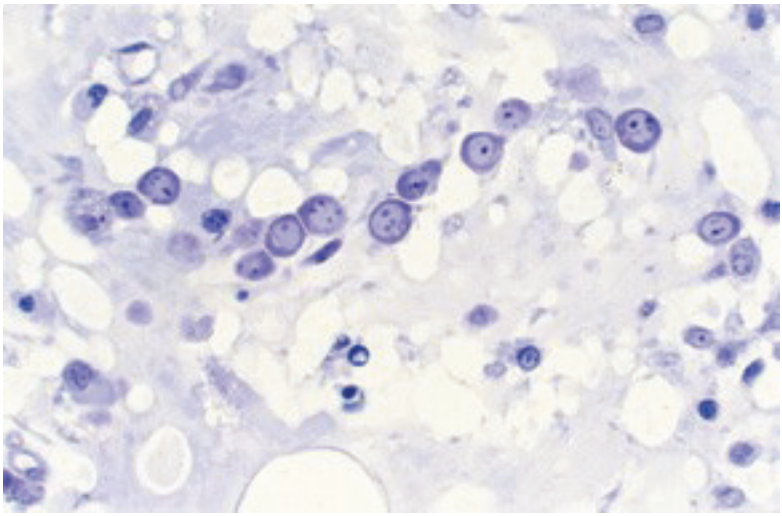


Figure 18.10 [B] The same section as in figure 17.10 A (another area, high power) showing a small number residual blast cells. (MMA, MGG stain).

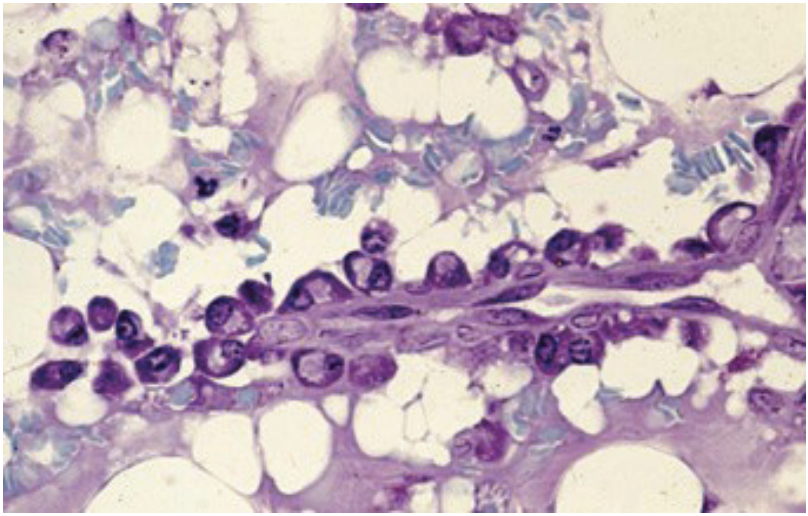


Figure 18.10 [C] The same section as in figure 17. 1 0 A (another area, high power) showing the presence of pericapillary plasma cells (MMA, MGG stain)

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A typical description of a bone marrow biopsy from patients with acute myeloid leukemia after 4 weeks of chemotherapy with pictorial illustrations (Figures 18.11 A & B)

A bone marrow core biopsy obtained from the left posterior iliac crest using a standard Islam BMB needle following induction chemotherapy for AML. Cellularity is patchy. Overall cellularity is about 30% and fat cells constitute about 50-70% in areas. There is some edema and extravasated red cells. Most of the fat cells are now unilocular (structured). Inflammatory cells (lymphocytes, plasma cells, tissue mast cells and macrophages) are very sparse. Haemopoiesis is active and mainly concentrated around the bone trabeculae and clusters of structured fat. Sinuses and pericapillary plasma cells are less evident. A Small number of blast cells (less than 5%) seen.

Comment: Post therapy marrow which shows active hemopoietic regeneration, blasts <5%.

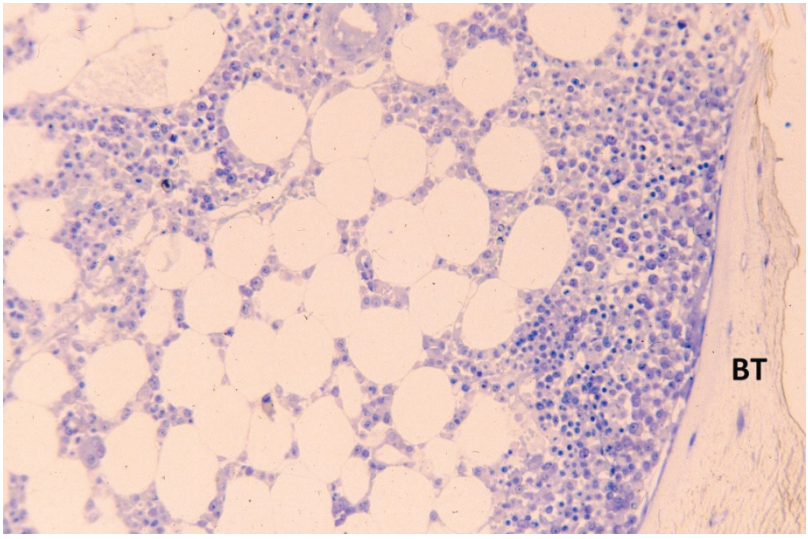


Figure 18.11 [A] A BM biopsy section from a case of AML 4 weeks after the end of chemotherapy showing active hemopoiesis. Note paratrabecular hemopoiesis consisting mostly of erythroid and granulopoietic cells. BT – bony trabecula. (Methyl-methacrylate, May-Grunwald-Giemsa stain)

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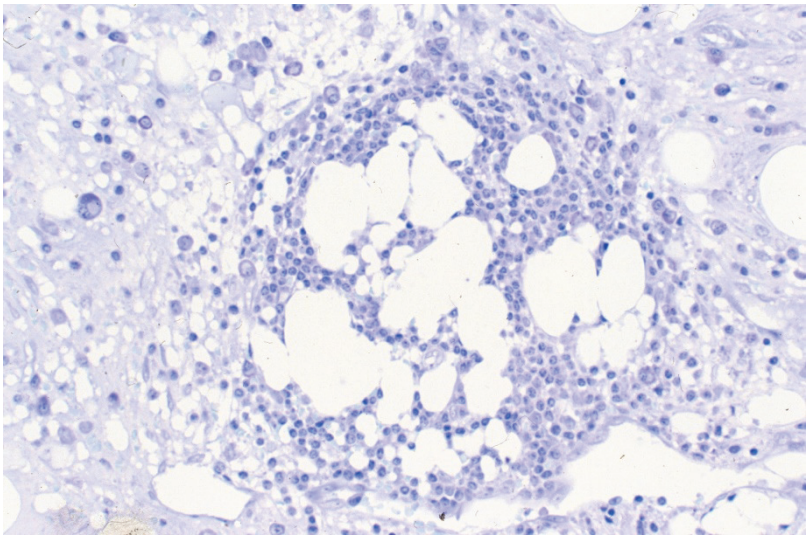


Figure 18.11 [B] A BM biopsy section from a case of AML 4 weeks after the end of chemotherapy showing hematopoiesis around the fat cells. (Glycol-methacrylate, May-Grunwald-Giemsa stain)

A typical descriptions of bone marrow biopsy section from patients with chronic granulocytic leukemia with pictorial illustrations (Figure 18.12 A to E)

A bone marrow biopsy obtained from the right posterior iliac crest using a standard Islam BMB needle. The overall cellularity is markedly increased (over 95%). Only a few scattered fat cells (less than 5%) are seen. Erythropoiesis is markedly depressed. A few scattered and small islands of erythroid precursors (mostly at the same stage of maturation) are observed. Granulopoiesis is markedly increased and consists mostly of neutrophilic myelocytes, metamyelocytes and segmented forms. Blast cells are readily indentifiable near some bony trabeculae. Occasional small clusters of blasts are also observed in the central inter-trabecular marrow spaces. Megakaryocytes (clustered and scattered) are increased in numbers and show dysplastic changes. In some areas many of the megakaryocytes are seen close to marrow sinusoids.

Comment: The marrow appearance is consistent with the diagnosis of chronic granulocytic leukemia. (Molecular and chromosomal analysis may help validate the diagnosis.)

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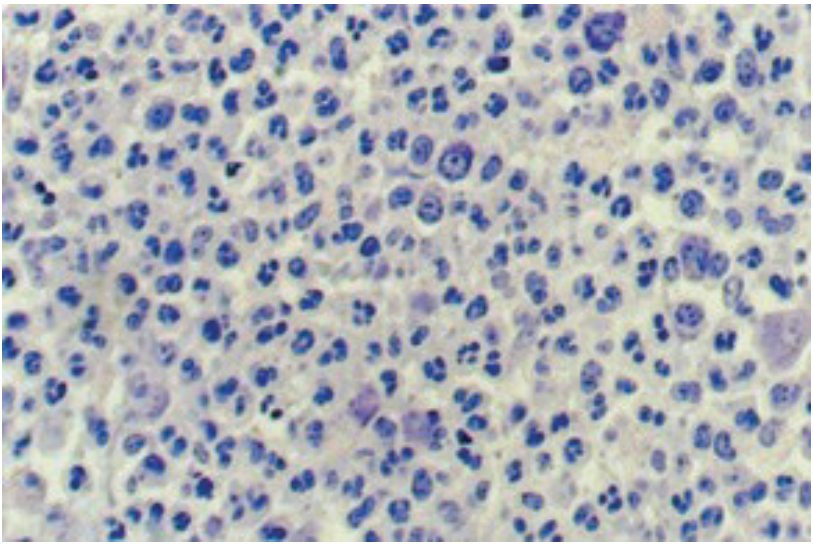


Figure 18.12 [A] A BMB section from a patient with chronic granulocytic leukemia showing a predominant accumulation of neutrophils (neutrophilic type) (MMA. MGG stain).

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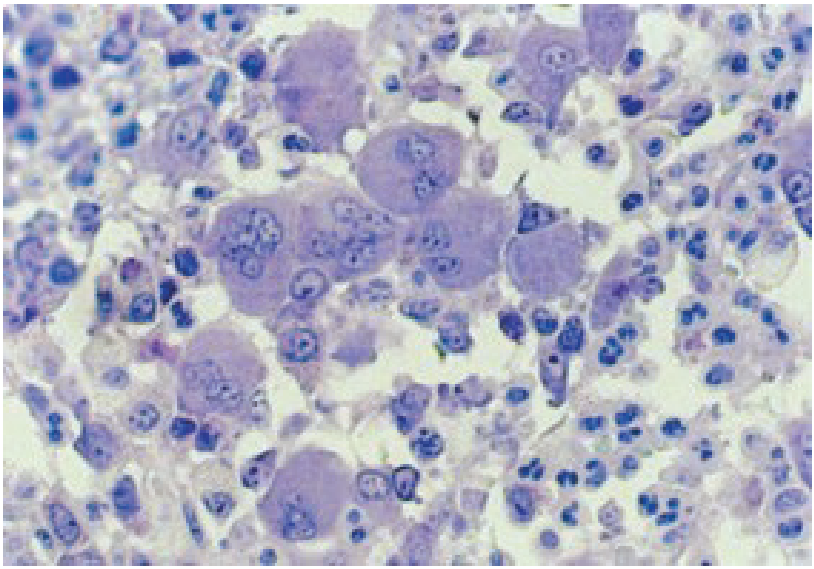


Figure 18.12 [B] A BMB section from a patient with chronic granulocytic leukemia showing a mixed granulocytic and megakaryocytic type of CML. Note the cluster of megakaryocytes in the center of the field along with mature neutrophilic granulocytes. It is only in BMB sections that such characteristic distributions of neutrophils and megakaryocytes can be appreciated. (MMA. MGG stain)

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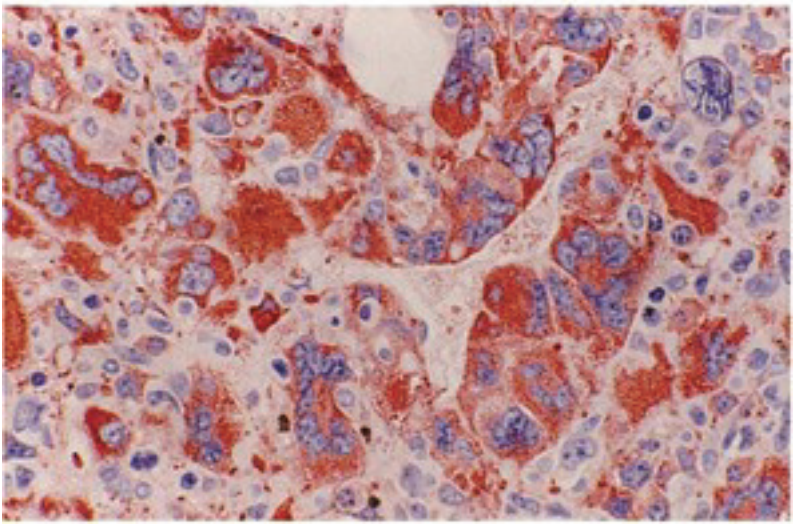


Figure 18.12 [C] A BMB section from a patient with chronic granulocytic leukemia (mixed granulocytic and megakaryocytic type) showing a large number of megakaryocytes. Some of the megakararyocytes are seen surrounding the marrow sinusoid (centrally located) as if they were shedding their platelets into the sinus. A small number of platelets can also be seen within the sinus. The section was stained for Factor VIII antibody. (GMA, PAP stain).

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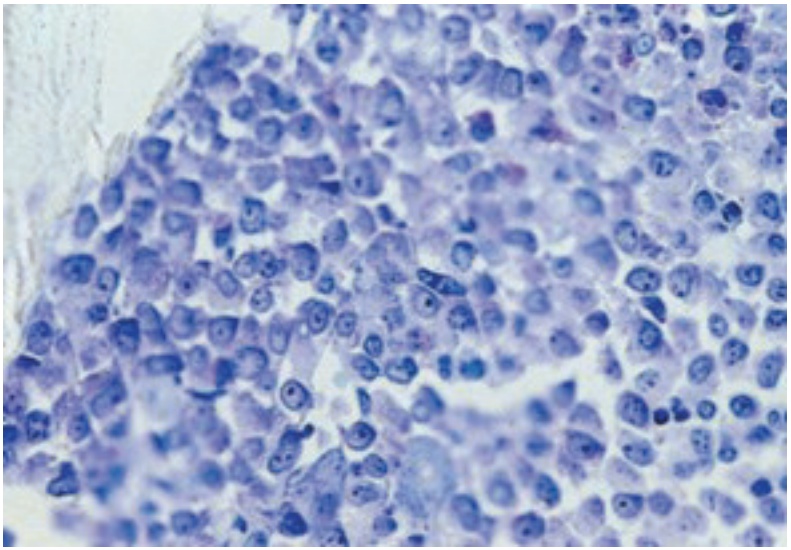


Figure 18.12 [D] A BMB section from a patient with chronic granulocytic leukemia in the chronic phase of CML showing features of early blast cell transformation. Note the marked paratrabecular infiltration by early granulopoictic cells (blasts and proyelocytes). It is only in the well fixed and well stained plastic embedded BMB sections that such characteristic features of high significance can be well appreciated. MMA, MGG stain).

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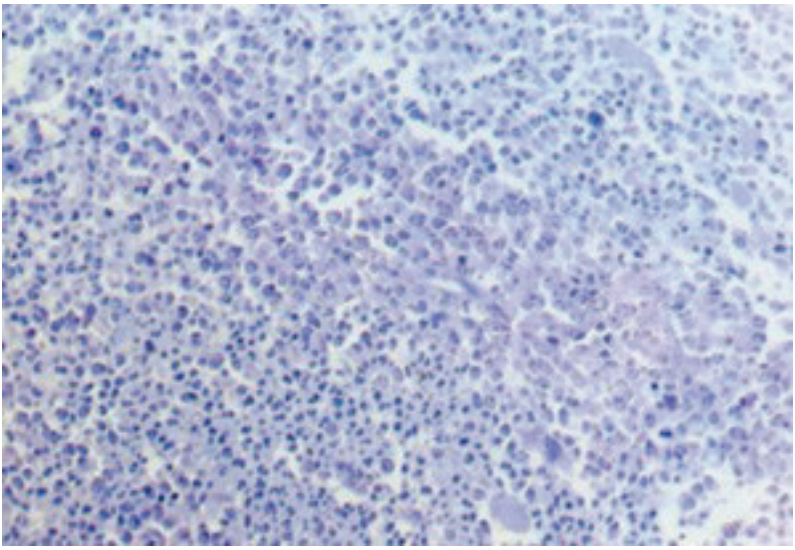


Figure 18.12 [E] A BMB section from a patient with chronic granulocytic leukemia in the chronic phase showing features of early blast cell transformation. Note the marked perivascular infiltration with early granulopoietic cells (blasts and promyelocytes) that is identifiable in the plastic embedded BMB sections. (MMA, MGG stain).

A typical description of a bone marrow biopsy section from a patient with chronic lymphocytic leukemia with pictorial illustration (Figure 18.13)

A Bone marrow biopsy obtained from the right posterior iliac crest using a standard Islam BMB needle. The overall cellularity markedly increased (80-90%). There is a reciprocal reduction of the fat cells which now constitute about 10-20% of the marrow. There is diffuse infiltration of the marrow with mostly mature- appearing small lymphocytes. The infiltration is particularly dense in the perisinusoidal regions. A variable number of mast cells and plasma cells are seen. Erythropoiesis is normoblastic but its activity is reduced. Granulopoietic activity is also reduced but presents all stages of maturation. Megakaryocytes are seen but reduced in number. Gomori's reticulin stain shows a fine network of reticulin fibers present mostly in and around the lymphoid nodules and in the densely infiltrated areas. Iron stores are normal.

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Comment: The marrow appearance is consistent with the diagnosis of chronic lymphocytic leukemia. (This can be further substantiated if the lymphocytes are CD 5 and CD 19/20 positive.)

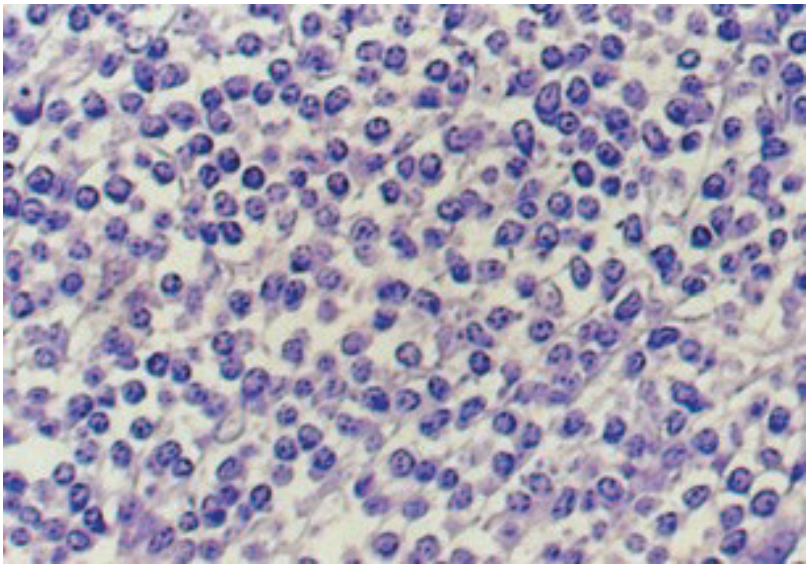


Figure 17.13 A BMB section from a patient with chronic lymphocytic leukemia showing dense infiltration of the marrow with mature-looking small lymphocytes. Unlike the hairy cell leukemia (Figure 17.13) the lymphoid infiltrate is very dense (MMA, MGG stain).

A typical description of a bone marrow biopsy section from a patient with hairy cell leukemia with pictorial illustrations (Figure 18.14)

A bone marrow biopsy obtained from the right posterior iliac crest using a standard Islam BMB needle. There is diffuse infiltration of the marrow with loosely arranged mononuclear cells which are widely spaced from each other. There are very few fat cells but numerous interstitial erythrocytes and a few plasma cells are seen. Erythro and granulopoietic activity is markedly reduced. Megakaryocytes are seen but reduced in number. Gomori's reticulin stain shows a diffuse increase in fine network of reticulin fibers.

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Comment: The marrow appearance is consistent with the diagnosis of hairy cell leukemia. (This can be further substantiated by immunohistological studies.)

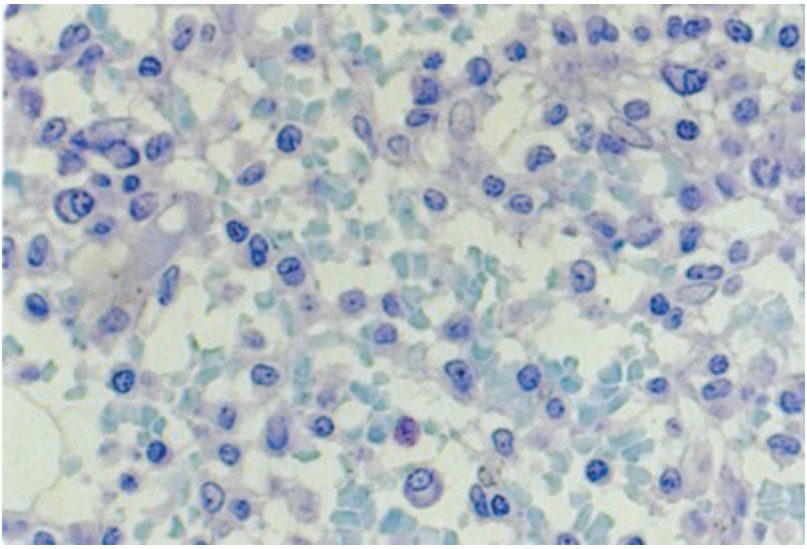


Figure 18.14 A BMB section from a patient with hairy cell leukemia showing infiltration of the marrow by loosely arranged mononuclear lymphoid cells. Note numerous interstitial erythrocytes and a few plasma cells (MMA, MGG stain).

A typical description of a bone marrow biopsy section from a patient with multiple myeloma with pictorial illustrations (Figures 18.15 A & B)

A bone marrow biopsy obtained from the right posterior iliac crest using a standard Islam BMB needle. The overall cellularity is markedly increased (80-90%). There is a reciprocal reduction of the number of fat cells which now constitute about 10-20% of the marrow. There is diffuse infiltration (over 30%) of the marrow with plasma cells. Some of the plasma cells show nuclear aberration with bi and tri-nuclear forms. Immuno-histology of the section revealed that the majority of the infiltrating cells to be positive for the lambda light chain. Erythropoiesis is normoblastic but greatly reduced in activity. Granulopoietic activity is also reduced but represents all stages of maturation. Megakaryocytes are seen but reduced in number. Gomori's reticulin stain shows no increase in reticulin fibers.

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Iron stores are normal in this case. (GMA, PAP staining.)

Comment: The marrow appearance is consistent with the diagnosis of multiple myeloma. This can be further substantiated with immunohistological studies (CD 138 and CD 38).

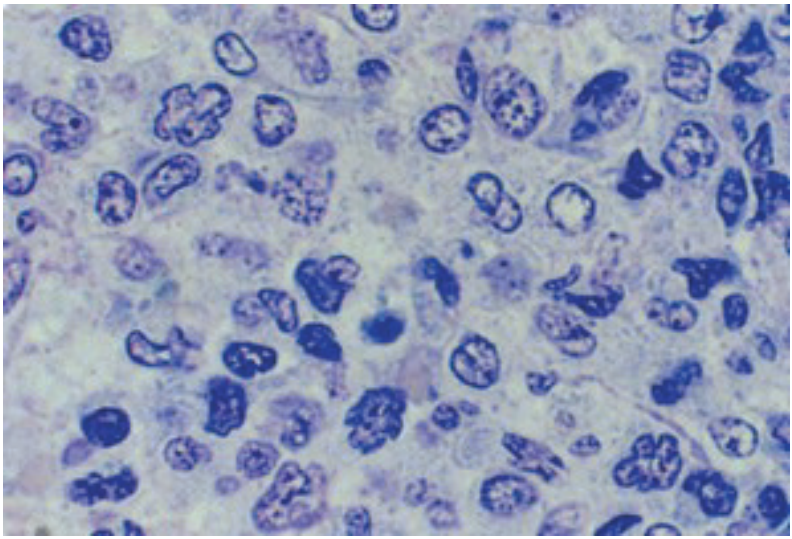


Figure 18.15 [A] A BMB section from a patient with multiple myeloma showing marrow infiltration by atypical plasma cells. (GMA, MGG stain)

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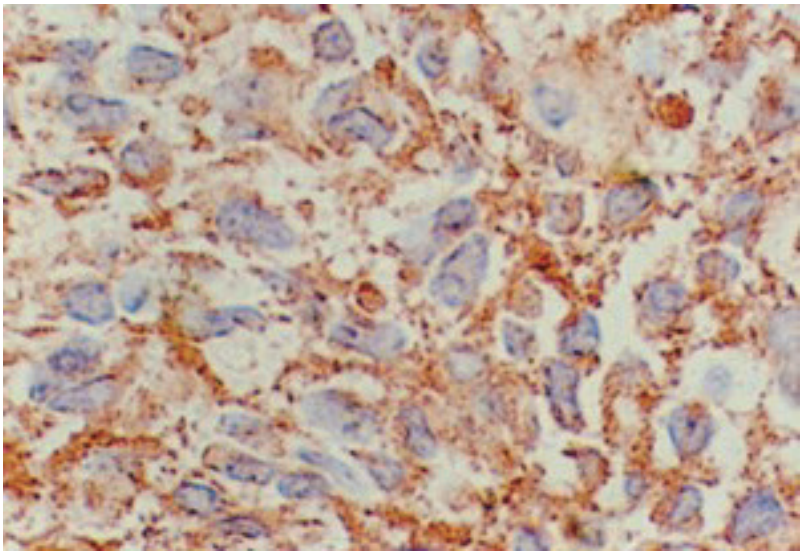


Figure 18.15 [B] The same bone marrow as in Figure 18.15 [A] immunohistologically stained for a light chain. This section showed that the majority of the infiltrating cells to be positive for the lambda light chain. (GMA, PAP staining.)

A typical description of bone marrow biopsy section from a patient with Hodgkin's disease with pictorial illustration (Figure 18.16)

A bone marrow biopsy obtained from the right posterior iliac crest using a standard Islam BMB needle. The overall cellularity is markedly increased (70-80%). There is a reciprocal reduction of the number of fat cells which now constitute about 20-30% of the marrow. There is focal infiltration of the marrow with typical Reed-Sternberg cells and their mononuclear variants along with mature-appearing small lymphocytes. A variable number of mast cells and plasma cells are seen. Erythropoiesis is active and normoblastic. Granulopoiesis is active and represents all stages of maturation. Eosinophil granulocytes are prominent. Megakaryocytes are seen in normal number. Gomori's reticulin stain shows an increase in reticulin fibers mostly in and around the malignant infiltrates. Iron stores are normal.

Comment: The marrow appearance is consistent with the diagnosis Hodgkin's disease.

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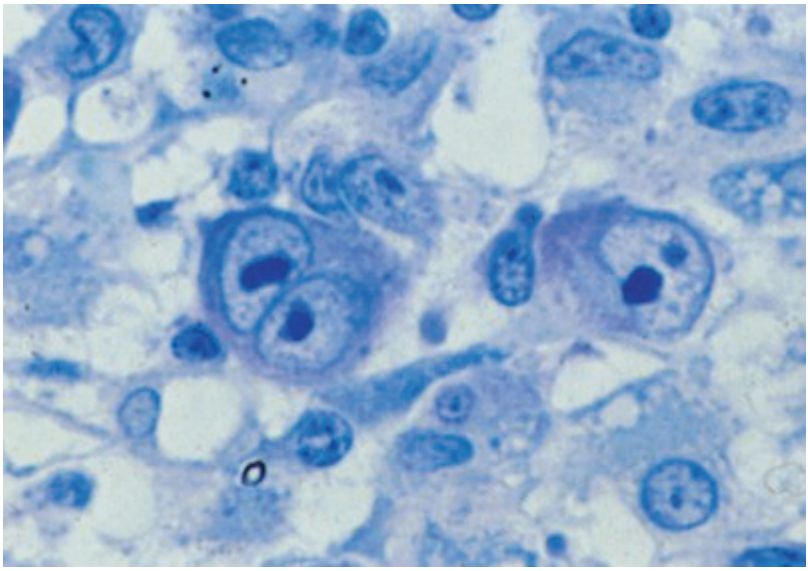


Figure 17.16 A BMB section from a patient with Hodgkin's disease showing marrow infiltration with typical Reed-Sternberg cells and its mononuclear variant. (MMA, MGG stain)

A typical description of a bone marrow biopsy section from a patient with non-Hodgkin's lymphoma with pictorial illustrations (Figures 18.17 A to F)

A bone marrow biopsy obtained from the right posterior iliac crest using a standard Islam BMB needle. The overall cellularity is markedly increased (80-90%). There is a reciprocal reduction of the fat cells which now constitute about 10-20% of the marrow. There is diffuse (interstitial infiltration of varied density) and nodular infiltration of the marrow with mostly mature-appearing small lymphocytes. A variable number of mast cells and plasma cells are seen. Erythropoiesis is normoblastic but its activity is reduced. Granulopoietic activity is also reduced but represents all stages of maturation. Megakaryocytes are seen but reduced in number. Gomori's reticulin stain shows a fine network of reticulin fibers present mostly in and around the lymphoid nodules and in the densely infiltrated areas. Iron stores are normal.

Comment: The marrow appearance is consistent with the diagnosis of small lymphocytic lymphoma/chronic lymphocytic leukemia. This diagnosis

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can be further substantiated by immunohistochemistry and flow cytometric studies on the bone marrow aspirate sample (CD 19/20 positive).

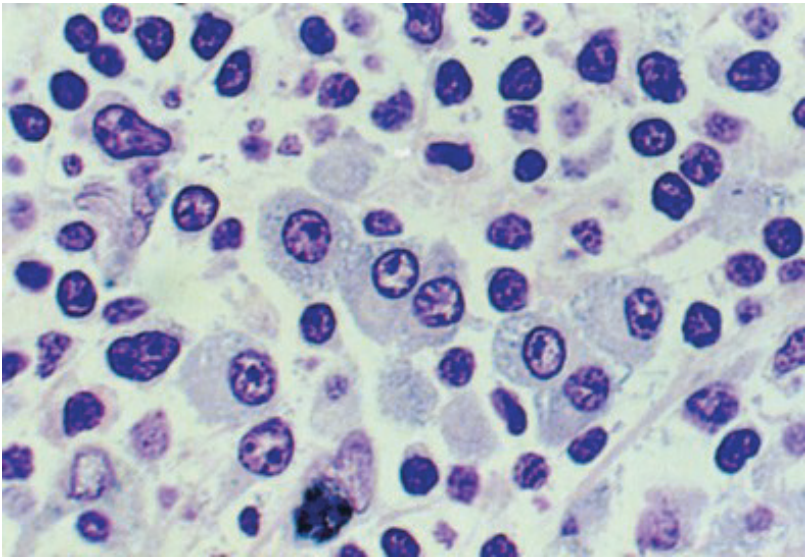


Figure 18.17 [A] A BMB section from a patient with non-Hodgkins lymphoma showing: lympho-plasmacytic infiltrate (GMA, MGG stain)

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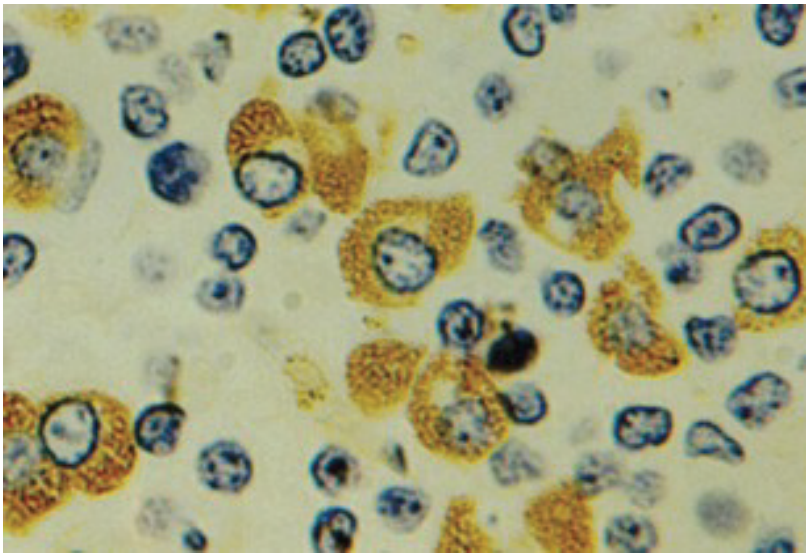


Figure 18.17 [B] The same bone marrow as in figure 17.16[A] immunohistologically stained for immunoglobulins. The plasma cells show a strong positive reaction for immunoglobulin IgA. (GMA, PAP staining)

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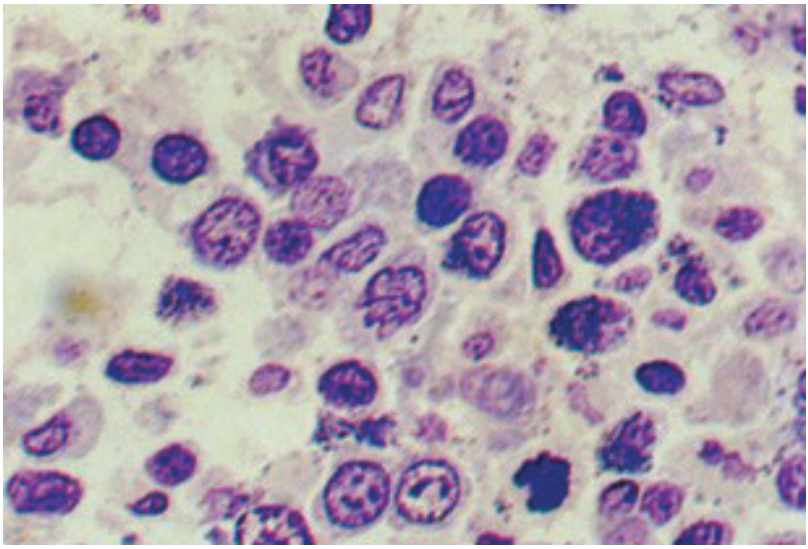


Figure 18.17 [C] A BMB sections from a patient with non-Hodgkin's lymphoma showing a cerebriform cell (center of the photomicrograph). (GMA, MGG Stain)

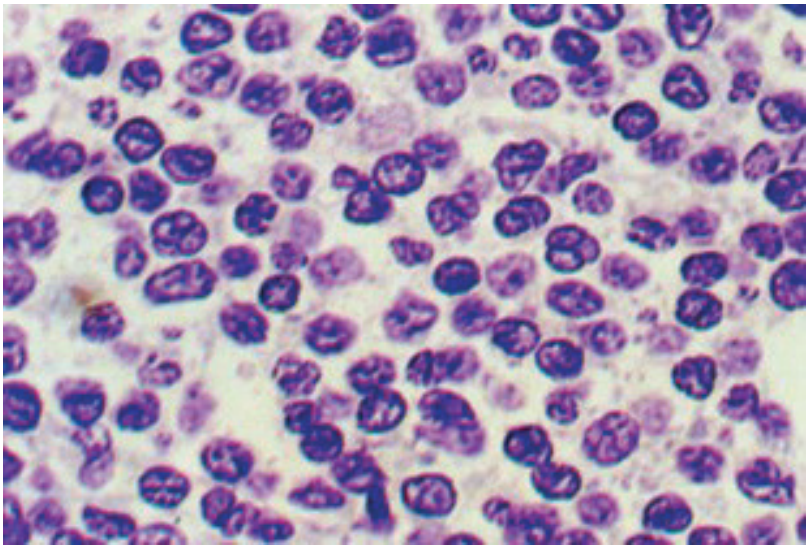


Figure 18.17 [D] A BMB section from a patient with non-Hodgkin's lymphoma showing cleaved, non-cleaved and hyperlobated lymphoma cells. (GMA, MGG Stain)

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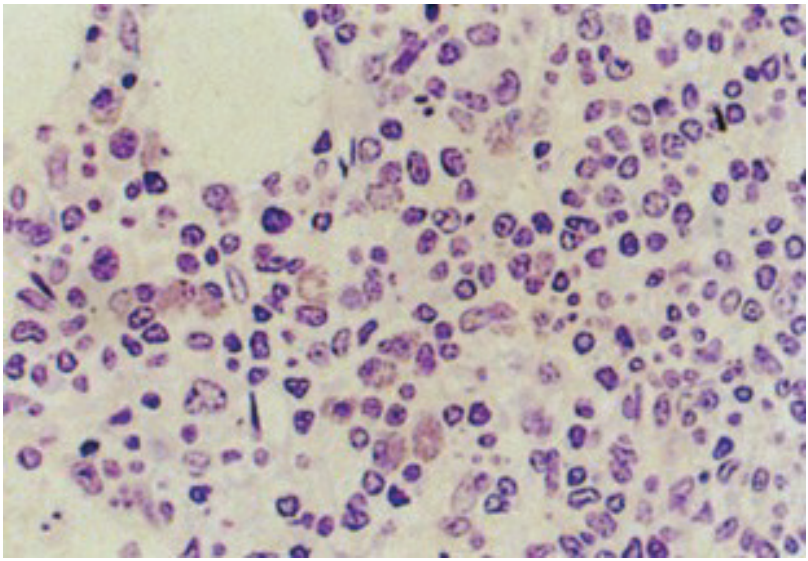


Figure 18.17 [E] A BMB section from a patient with non-Hodgkin's lymphoma showing a concentration of eosinophil granulocytes at the periphery of the lymphoid infiltrate. (GMA, MGG stain)

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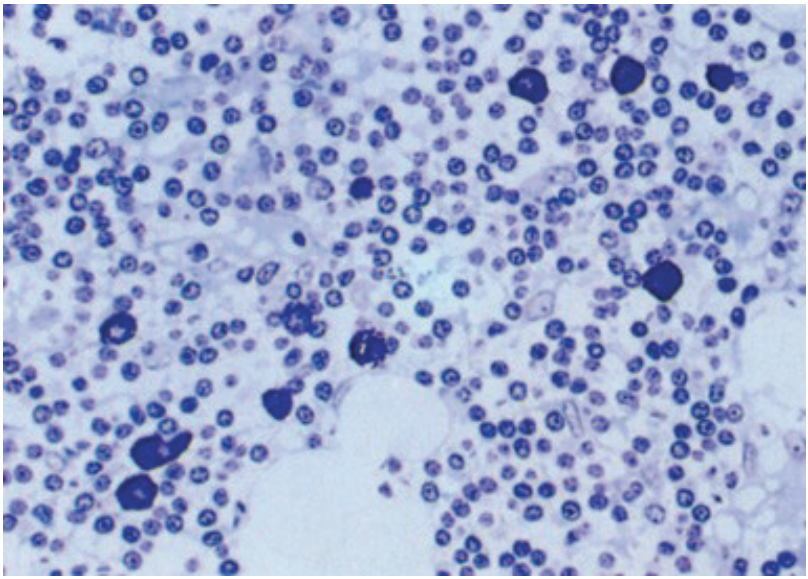


Figure 18.17 [F] A BMB section from a patient with non-Hodgkin's lymphoma showing the presence of an increased number of mast cells. (GMA, MGG stain)

A typical description of a bone marrow biopsy section from a patient with carcinoma of the breast with metastasis to the bone marrow with pictorial illustration (Figure 18.18)

A bone marrow biopsy obtained from the right posterior iliac crest using a standard Islam BMB needle . The overall cellularity is markedly increased (90-100%). There is a reciprocal reduction of the number of fat cells which constitute about 0-10% of the marrow. There is massive infiltration of the marrow with sheets of metastatic breast cancer cells. Erythropoiesis and granulopoesis are markedly depressed. Only occasional erythroid and granulocytic precursors are seen. Megakaryocytes are absent. Gomori's reticulin stain shows a mild increase in reticulin fibers. Iron stores are absent.

Comment: The marrow appearance is consistent with the diagnosis carcinoma of the breast with metastasis to the bone marrow.

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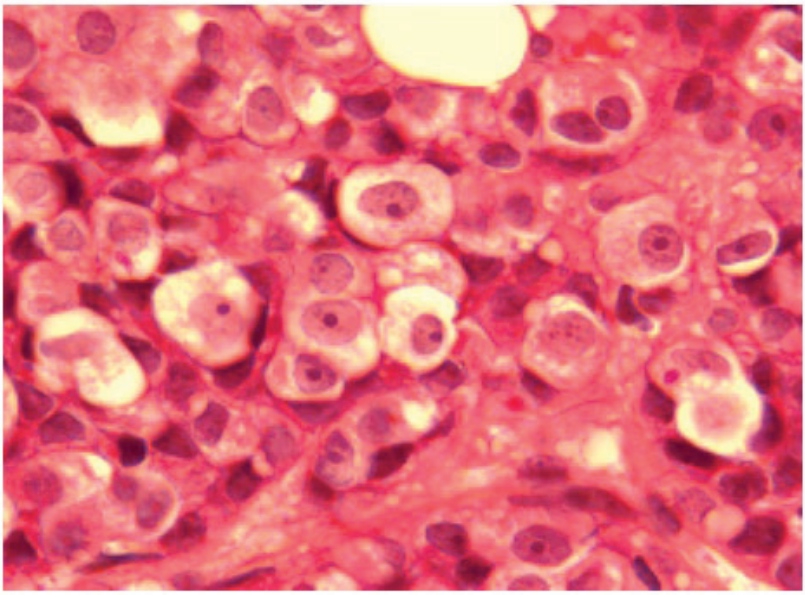


Figure 18.18 A paraffin embedded bone marrow biopsy section from a patient with carcinoma of the breast showing infiltration of the marrow with metastatic breast cancer cells (H&E stain).

A typical description of a bone marrow biopsy section from a patient with carcinoma of the prostate with metastasis to the bone marrow with a pictorial illustration (Figure 18.19)

A bone marrow biopsy obtained from the right posterior iliac crest using a standard Islam BMB needle. The overall cellularity is about 50 %. There is some edema and extravasation of the red cells. Fat cells constitute about 30% of the marrow volume. There is infiltration of the marrow with atypical cells suggestive of a metastatic process. The cells were positive for NKX 3 (a marker for prostate cancer cells) and prostate-specific antigen (PSA). Erythropoiesis and granulopoiesis are markedly reduced. Only occasional erythroid and granulocytic precursors are seen. Megakaryocytes are absent. Gomori's reticulin stain show a mild increase of reticulin fibers. Iron stores are absent.

Comment: The marrow appearance is consistent with the diagnosis of carcinoma of the prostate with metastasis to the bone marrow.

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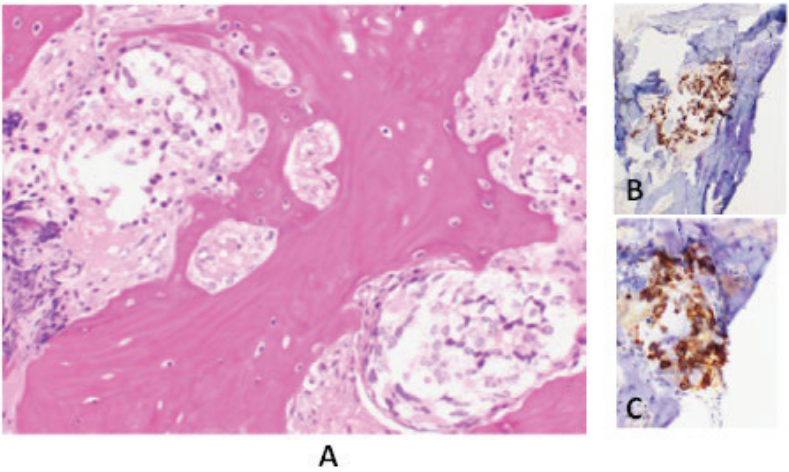


Figure 18.19 [A] A paraffin embedded bone marrow biopsy section from a patient with carcinoma of the prostate showing infiltration of the marrow with metastatic prostate cancer cells (H&E stain). **[B]** The same section stained for NKX3 a marker for prostate cancer cells and **[C]** same section stained for prostate-specific antigen (PSA) by immunohistochemistry. (Courtesy Dr. Kelly Garner).

A Detailed Protocol of a Clinical Bone Marrow Report

1. Submitted specimens:

Bone marrow aspirate (in EDTA)	Yes	No
Bone marrow aspirate (in Na heparin)	Yes	No
Bone marrow aspirate smears	Yes	No
Bone marrow core biopsy in formalin	Yes	No
Bone marrow clot in formalin	Yes	No
Bone marrow biopsy touch preparations	Yes	No
Bone marrow aspirate for flow cytometry	Yes	No
Bone marrow aspirate for cytogenetics	Yes	No
Bone marrow aspirate for molecular studies	Yes	No

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2. Clinical Information (an example)

Clinical History: This is a 73 year old white male being evaluated for lymphocytosis to rule out chronic lymphocytic leukemia. CBC data from 00/00/00 shows WBC count 17.4 $X10^9$/L, hemoglobin 14.9 g/dL, and platelet count 236 $X10^9$/L. The differential is notable for lymphocyte 65% Neutrophil 30% , eosinophil 3%, Monocyte 2% . Absolute lymphocyte count of 12.7 k/ul. The patient is noted to have had an absolute lymphocyte count of 7.5 k/ul on 00/00/00.

3. *Peripheral blood smear:* demonstrates the presence of a large number of mostly mature lymphocytes with many smear (smudge) cells.

4. *Bone marrow aspirate smear:* The aspirate smears are satisfactory with numerous smeared marrow spicules. The aspirate is slightly hypocellular. All normal hematopoietic elements are decreased. However, megakaryocytes are observed in normal numbers and they appear to be morphologically normal. Red cell maturation is progressive. Myeloid maturation is progressive.

The majority of the marrow elements are small lymphocytes. The lymphocytes are small and round. They appear to comprise at least 50-60% of the total hemopoietic nucleated marrow elements. The M-E ratio is about 1:1. Scattered plasma cells are seen.

In order to better quantitate and evaluate this lymphoid process, the following immune stains were done: Pax-5: About 40-50% of the marrow cells express this marker.

CD3: About 3-5% of the marrow cells express this marker.

Cycline D1: Negative

An iron stain done on the aspirate smear shows 2+/4+ iron stores. No ringed sideroblasts are seen. Comment: The marrow appearance is consistent with a diagnosis of chronic lymphocytic leukemia (CLL)

5. *Bone marrow biopsy:* The core biopsy is of generous length. However, there is a prominent subcortical zone of hypocellular marrow in two of the three biopsy sections. The third biopsy section shows about two thirds of the marrow being totally acellular with the remaining one-third having a cellularity of about 30%.

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6. *Clot section:* Many marrow spicules are observed. The cellularity again is variable, ranging from less than 5% to 25%, overall less than 10% cells. Hemopoietic activity appears reduced. The cells present consist mostly of small lymphocytes.

Comment: Moderate to markedly hypocellular bone marrow involved by chronic lymphocytic leukemia

7. *Flow cytometry*: An abnormal population of B-lymphocytes is noted expressing CD19, dim CD20, HLA- DR, CD5, CD23, dim CD11c, with dim lambda light chain restriction. These lymphocytes are small judging by forward scatter. No expression of CD10, CD34, CD25, FMC7, CD38 or CD103 is noted.

Comment: The immunophenotype is consistent with chronic lymphocytic leukemia (CLL), involving about 30% of the isolated marrow cells.

Instead of individualized comments, summation of the diagnosis can be made at the end of the report and written as one comment.

8. *Additional note:* As stated earlier in chapter 5 sometimes when the bone marrow aspiration is performed before obtaining the core biopsy using the same bone marrow biopsy needle, this procedure can yield a biopsy specimen devoid of all marrow elements making it impossible to make an adequate study of the specimen. In such circumstances the bone marrow biopsy can be reported as follows:

The core measures 10 mm in length but is insufficient for morphological evaluation due to aspiration artifact.

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CHAPTER 19

COMMON PROBLEMS AND THEIR RESOLUTION

Loss of or Failure to Obtain a Core Biopsy

Although a satisfactory sample of bone marrow can be obtained without much difficulty from the posterior iliac crest (the site most commonly used at the present time) with the use of unimproved, standard bone marrow biopsy needles, occasionally a core sample may slip out of the needle during its withdrawal and remain inside the patient. This problem is often encountered with Jamshidi and somewhat similar types of needles as they do not have a biopsy (core) retention device. In such circumstances it is necessary to re-insert the needle with its stilette in place and advance the needle into the bone in a slightly different direction in order to secure another sample. Sometimes, however, especially in cases of severe myelosclerosis or osteoporosis or when the marrow is packed with malignant cells (e.g., metastasis from carcinoma of lung/breast/prostate) a marrow sample remains unobtainable even with repeated attempts. In such circumstances a needle with a core securing device such as the Islam bone marrow biopsy needle or newer Jamshidi (with core acquisition cradle) or other types of needles (with a single or double sleeve) which address this problem may prove to be useful. In patients with osteoporosis the needle should be introduced very carefully into the bone and marrow cavity and should be cored with slow, steady, controlled and clockwise and counter-clockwise rotary motion with a gentle forward thrust. Otherwise, the soft osteoporotic bone will crumble and little or no marrow tissue or only a small crushed sample may remain within the lumen of the needle upon its withdrawal from the patient.

Indications for a Hemopoietic Assessment

The indications for bone marrow biopsies are manifold. The information obtained from the combined study of bone marrow aspirate and bone marrow biopsies is markedly enhanced over that obtained when only one of the procedures is elected. Indeed, because the combination of both procedures has become so convenient, and practical, as well as yielding

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tissue with excellent histologic and cytomorphologic detail that any patient undergoing a bone marrow aspiration should concomitantly have a bone marrow biopsy.

Bone marrow biopsies yield significant information: for the diagnosis and differential diagnosis of hypoplasias and aplasias, for the diagnosis, differential diagnosis, and classification of myelo- and lymphoproliferative disorders, for the documentation of ontogeny and evolution of a disease process, for monitoring therapy and detection of residual disease, evaluation of factors of prognostic significance, and for the assessment of hematopoietic tissue and stromal response at diagnosis, post chemotherapy and before and after autografts and transplants.

Specific indications for a core bone marrow biopsy in hematological disorders are all cases of acute and chronic leukemia, hypoplasia and aplasia, myelodysplastic syndromes, cytopenias and conditions with potentially increased marrow reticulin and/or collagen. The need for biopsy in other conditions such as Hodgkin's disease, non-Hodgkin's lymphoma and multiple myeloma has already been established.

In internal medicine bone marrow biopsy is useful in many endocrine disorders, in disturbances of renal function, for the detection of amylodosis, in autoimmune disorders particularly for the assessment of the walls of blood vessels, for the diagnosis of granulomatous diseases and various other non-specific conditions.

Bone marrow biopsy is diagnostic in storage diseases such as Gaucher's disease and may be useful in histoplasmosis, toxoplasmosis, Q fever, giant cell arteritis, in mesenchymal and collagen disorders, and in rare metabolic disturbances such as hypophosphatasia. Bone marrow biopsy is also indicated in any condition involving alterations in the formation and resorption of bone which may occur in a wide variety of diseases either primarily or secondarily, e.g. Paget's disease, osteoporosis in intestinal malabsorption, in vitamin and mineral deficiencies, and in certain congenital disorders.

In non-hematologic malignancies a bone marrow biopsy can provide evidence of metastases and information useful in the evaluation of marrow function and reserve before, during and after cytotoxic therapy, and the early recognition of dysplastic changes which may herald the development of a hematologic malignancy (often as a consequence of cytotoxic therapy).

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Information Obtainable from a Well Fixed, Well Processed, Well Stained, Long and Uncrushed Bone Marrow Biopsy Sample

The information that is obtainable from a satisfactory (15-20 mm in length, devoid of loss of marrow tissue and crush artifact) core bone marrow biopsy specimen that is adequately processed and properly stained has consistently been impressive. As indicated previously, in hematological disorders in which the marrow is either hypocellular (as in cases of aplastic anemia) or hypercellular (as in cases of leukemia and other myelo- and lymphoproliferative disorders) a bone marrow biopsy provides critical information. In cases where there is an increase in marrow reticulin and/or collagen, the results of aspiration are usually unsatisfactory (dry tap), and a bone marrow biopsy not only becomes mandatory but is the only available vehicle which can yield a morphologic diagnosis. In sections of bone marrow biopsy specimens overall cellularity as well as quantitative and qualitative cytologic features can be accurately assessed for their diagnostic and prognostic significance.

Aplastic Anemia

In patients clinically suspected of having aplastic anemia, a bone marrow biopsy is essential not only to exclude other causes (such as refractory anemia, hairy cell leukemia, myelofibrosis, malignant lymphoma, metastatic carcinoma) that might be responsible for the clinical presentation but also to establish the definitive diagnosis. In patients with aplastic anemia a bone marrow dry film smear alone is rarely sufficiently diagnostic.

In aplastic anemia a bone marrow biopsy demonstrates a drastic reduction in hematopoietic tissue with a corresponding increase in fat cells. A small number of (residual) erythroblastic islands (aggregates of erythroid precursors which are at the same stage of maturation), so-called “hot spots”, are seen located close to the marrow sinusoids and near the bony trabeculae (personal observation). These hot spots and some additional features of possible prognostic significance such as an increase in inflammatory cells (plasma cells, lymphocytes, tissue mast cells and macrophages) are more accurately visualized and quantified in a bone marrow biopsy sections than in dry film smears.

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Acute and Chronic Myeloid Leukemia

In some instances of these conditions definitive pathological features may exist that can only be identified and documented in bone marrow biopsy sections. A new classification of AML (with possible prognostic implications) has recently been proposed on the basis of observations on plastic embedded sections of solid tissue specimens. The evaluation of a bone marrow biopsy is also the most effective means of validating the presumptive induction of a complete remission and monitoring the effects of therapy as compared with the examination of peripheral blood or bone marrow aspirates alone. Sectioned biopsies may also provide assistance in the understanding of the role of the marrow microenvironment during reconstitution of the marrow following therapy. In AML following chemotherapy and in CML after autografting, micro-anatomic relationships have been observed between the regenerating hematopoietic cells and the stromal cells (fat, fibroblast-like and endothelial cells). Haemopoietic regeneration has been seen to occur preferentially within areas of structured fat (areas consisting of large uniform unilocular fat cells in close apposition) and in close vicinity of vascular endothelial cells suggesting the existence of a functional role (through the elaboration and interaction of cytokines). The biopsy sections also provide means of exploring and understanding the ontogeny and etiology of these disorders.

Chronic Lymphocytic Leukemia

In the early stages of chronic lymphocytic leukemia (CLL) there may be an absence of or only minimal diffuse infiltration of the marrow by small round (mature) lymphocytes, with or without the development of nodular aggregates. With progression of the disease both forms of CLL (diffuse and nodular) encroach upon the normal hematopoietic population until it is completely replaced by the lymphoid cells. Statistical analysis of untreated patients with CLL have shown that the histologic pattern of bone marrow involvement has prognostic significance with a shorter median survival for the diffuse and a longer survival for the nodular variety.

Myelodysplastic Syndromes (MDS)

Myelodysplastic Syndromes are characterized by qualitative and quantitative defects in haematopoiesis. Abnormalities usually occur in all three cell lines and are observed in smears of aspirates, in bone marrow biopsy sections and by electron microscopy. There is usually a single or combined

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cytopenia and the bone marrow may be normo-, hypo- or hypercellular. One of the characteristic features of these conditions is the abnormal clustering of immature myeloid precursor cells popularly termed "ALIPs" (abnormal localization of immature precursors). This particular feature of possible prognostic significance can only be identified in sections of bone marrow biopsy specimens. If during bone marrow aspiration such areas containing ALIP's are hit then the aspirate may demonstrate over 20-30% blast cells and a erroneous diagnosis of acute leukemia may be made.

Chronic Myeloproliferative Disorders (MPD)

In these conditions [e.g. polycythaemia vera (PV), chronic myeloid leukemia (CML), idiopathic thrombocythaemia (IT), myelofibrosis (MF) and osteomyelo-sclerosis] distinctive morphologic and structural features exist that warrant examination of a sectioned biopsy specimen. Recent studies indicate that CML is not a single entity and based on the findings of bone marrow biopsy sections the disease can be morphologically classified into two categories: granulocytic and mixed granulocytic-megakaryocytic types, according to the nature and predominance of the cellular proliferation. Sections may also reveal characteristic cellular proliferations of immature myeloid (hematopoietic) precursor cells adjacent to bony trabeculae (paratrabecular accumulation of blast cells). The extent of such infiltrations may also help predict the transformation of CML into an acute blastic phase.

Hairy Cell Leukemia (HCL)

In this malignancy a bone marrow biopsy is usually diagnostic and presents a typical picture. It shows the characteristic cytologic features of hairy cells (round, oval, or kidney shaped nuclei whose chromatin, unlike that of small lymphocytes, shows little clumping). Unlike CLL and other lymphoid infiltrations of the marrow, hairy cells appear loosely arranged, widely separated (an appearance probably due to their large cytoplasmic volume) and are enmeshed in a reticulin network which also contains plasma and mast cells and numerous free erythrocytes. Bone marrow aspiration is usually difficult due to presence of marrow fibrosis and as a result it often yields either an unsatisfactory specimen or a dry tap.

Multiple myeloma (MM)

This hematologic malignancy is characterized by multifocal neoplastic proliferations of plasma cells. Bone marrow examination still remains the

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cornerstone in establishing the diagnosis. In classic cases, the morphologic diagnosis of MM is straightforward and not difficult to identify. In such cases the bone marrow aspirate and/or biopsy sections show the presence of large clusters or infiltrates of plasma cells (mature, intermediate, immature or plasmablastic type) that replace the normal hematopoietic elements. However, in other cases the diagnosis can be extremely difficult. This may be due to several reasons. First, the plasma cell infiltration may be associated with significant marrow fibrosis. The marrow aspiration in these cases is often very difficult and results in an unsatisfactory (nondiagnostic) sample, whereas a bone marrow biopsy section may prove to be diagnostic in this situation. Second, because of the multifocal nature of the disease process a bone marrow aspirate may fail to provide a diagnostic specimen; in such instances there is a greater likelihood, that a bone marrow biopsy will provide the required atypical tissue for diagnosis. Further, because sectioned specimens offer an insight into the undisturbed distribution of bone marrow cells, such preparations are more likely to permit the recognition of (normal) perivascular location of plasma cells versus the irregular distribution of pathologic proliferations. Third, in cases where the bone marrow aspirate and/or section contain abnormal cells that cannot be definitely identified as belonging to the plasma cell series, it may still be possible to reveal their plasmacytic identity through the immunoperoxidase staining of plastic embedded bone marrow biopsy sections.

Hodgkin's Disease (HD)

Although the importance of bone marrow biopsies in the diagnosis and management of patients with Hodgkin's disease (HD) has been debated, they are still conducted in most centers as the detection of marrow involvement not only affects the level of pathologic staging but also influences the approach to therapy. In addition, a positive marrow biopsy obviates the need for a staging laparotomy. Although the incidence of bone marrow involvement in HD (as reported in the literature) varies considerably (2-32%), in a significant number of cases, typical Reed-Sternberg cells or their mononuclear variant can be identified in marrow sections. The extent of marrow involvement in a given bone marrow biopsy can vary from small focal lesions to almost complete replacement of the marrow. Of the patients that do demonstrate medullary infiltration the pattern of involvement in the section is diffuse in 70-80% of the cases and focal in the remainder. In some studies marrow involvement has been shown to be one of the most important factors in predicting an unfavorable

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course of the disease. Nevertheless it has also been shown that in a large majority of cases with negative biopsies various nonspecific alterations were present in the marrow. These findings had predictive value; hypoplasia, exudative and leukemoid reactions indicated a poor prognosis, while epithelioid cell granulomas and lymphocytic aggregates constituted more favorable signs.

Non-Hodgkin's Lymphoma (NHL)

A bone marrow examination is now considered an integral part of the initial diagnosis and staging of patients with non-Hodgkin's lymphoma. Bone marrow (core) biopsies are essential for this as aspirates have a high incidence of false negatives. Bilateral biopsies are generally believed to be superior to unilateral biopsies because the increased volume of marrow that is obtained enhances the likelihood of finding a focal lesion. Some other benefits are also derived from examining tissues obtained from two anatomically distant sites. Bone marrow biopsies are useful for evaluating patients' responses to chemotherapy and for following previously treated patients for evidence of recurrent disease.

Bone Disease

Bone marrow biopsies are critical for histomorphometric analysis of metabolic and non-metabolic bone disorders which are characterized by alterations in the amount and structure of cortical and trabecular bone; the amount, extent, and width of osteoid seams, and the extent of osteoclastic resorption of surfaces. The abnormalities of bone formation, resorption and mineralization (osteoporosis, osteomalacia, osteodystrophy, Paget's disease etc.) may be diagnosed by bone marrow biopsy long before their effects are evident on X-ray films. For the performance of bone histomorphometry, undecalcified bone marrow biopsy sections are essential because of the conservation of the differences between calcified and uncalcified bone (osteoid) which is required for the recognition of bone abnormalities.

Non-hematologic Malignancies

Documentation of the presence or absence of metastases to the skeletal system is an important step in the evaluation of the patient with a malignancy. It has long been appreciated that the red, well-vascularised hematopoietic marrow is one of the sites most commonly involved with

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metastases of non-hematologic malignancies (solid tumors). In patients with cancer of the breast or prostate, as well as those with neuroblastoma or small cell carcinoma of the lung, metastatic disease is initially documented in the marrow more frequently than in any other site. It is unfortunate that marrow biopsies are not routinely performed on most patients with solid tumors. It has been reported, for example, that patients with evidence of metastatic carcinoma of the breast in the marrow had a significantly higher relapse rate than did patients whose marrow did not have this manifestation. Clearly the demonstration of bone marrow metastasis in such patients will profoundly influence the choice of the therapeutic approach.

Marrow infiltrated with tumor tissue, including malignant lymphoma, can be difficult to aspirate and consequently a dry tap occurs relatively frequently. The sensitivity of histologic diagnosis of breast cancer from bone marrow (core) biopsies when compared with that obtained from aspirates or clot sections, was found to be superior, however, maximal success was obtained when both the core biopsy and the aspirate were examined. Bilateral bone marrow biopsies are perhaps more sensitive in this regard because of the larger volume of tissue and the fact that two sites are examined.

Newer Developments and Future Directions

The development and application of enzymatic and immunological techniques (e.g. immunoperoxidase) to decalcified (paraffin-embedded) and undecalcified (plastic-embedded) bone marrow biopsy sections continues to improve the hemato-pathologist's diagnostic capabilities. The use of monoclonal antibodies that react selectively with normal and abnormal hematopoietic cells as well as metastatic tumor cells in the marrow has further improved the diagnostic possibilities. In addition, the molecular genetic techniques, such as *in situ* mRNA hybridization, interphase cytogenetics and PCR amplification of DNA for evaluation of minimal residual leukemia/lymphoma in bone marrow biopsies are opening up new frontiers in the etiologic and diagnostic evaluation of bone marrow biopsies in various hematologic and non-hematologic malignant conditions.

The detection of molecular and chromosomal abnormalities plays an important role in the diagnosis, assessment and management of patients with hematologic malignancies. The most common mutations in acute myeloid leukemia (AML) are: ITD, FLT3-ITD, TKD, FLT3-TKD, and NPM1. Incorporation of such molecular studies in regular bone marrow

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diagnostics has proven of use for patients with certain types of acute myeloid leukemias and in some cases they are successfully treated with oral medication on the basis of their molecular mutations. Currently available medications for such treatments are: Rydapt (midostaurin) for the treatment of adult patients with newly diagnosed FLT3+ AML, Xospata (gilteritinib) for the treatment of relapsed or refractory FLT3 mutation-positive AML, and IDHIFA (enasidenib) for the treatment of adult patients with relapse or refractory acute myeloid leukemia with an IDH2 mutation. In chronic lymphocytic leukemia (CLL) chromosomal abnormalities are now detected in up to 80% of the patients. Among them deletions of 11q, 13q, 17p and trisomy 12 have a known prognostic value and play a vital role in pathogenesis, evolution, prognosis and therapeutic strategies. The detection of cytogenetic abnormalities in multiple myeloma (MM) has also received more importance in recent years for risk stratification and the new risk-adapted treatment strategies. It has been suggested that conventional G-banding analysis should be included in a routine bone marrow procedure at the initial diagnostic workup for patients suspected of MM.

Conventionally, hematologists and oncologists perform bone marrow aspiration and trephine biopsies relying heavily on external anatomical landmarks and palpation which is known as the “blind approach” for bone marrow aspiration and trephine (core) biopsy (see chapter 9). This technique has an inherent problem as the site (posterior iliac crest) may be missed resulting in an inadequate or unsatisfactory specimen. If the needle does not penetrate the bone at the correct angle, this may result in a tangential biopsy containing mostly bone and very little marrow tissue. Furthermore, if the needle veers too much to the right or to the left, or in any other direction, or misses the posterior ilium completely, this can cause serious complications, including damage to the sciatic nerve or a massive thigh and buttock hematoma. These complications, although rare, have been reported.

Another new entry into bone marrow diagnostics includes the use of a smart phone for ultrasound (image) guidance (chapter 12) to permit precise identification and localization of the entry point of the needle on the surface of the body (over the posterior iliac crest) and its accurate guidance and safe passage towards the desired marrow-rich intramedullary site (posterior iliac crest) while avoiding damage to important surrounding structures.

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A new design and future direction of the bone marrow aspiration and bone marrow biopsy needles (figures 19.1 and 19.2): all conventional single-use bone marrow aspiration and biopsy needles have two components; one made of plastic (handles etc.) and the other made of stainless steel (needle and the stilette). The surface of the plastic handles can be slippery. It may therefore be appropriate to provide at least part of these surfaces, those which come in contact with the operator's hand, with a non-slip finish or non-slip surface elements as shown in figures 19.1 and 19.2. Addition of such non-slip surfacing for easy grip may provide more comfortable handling of the needle and improve its maneuverability during the biopsy procedure. Manufacturing of such needles is in progress.

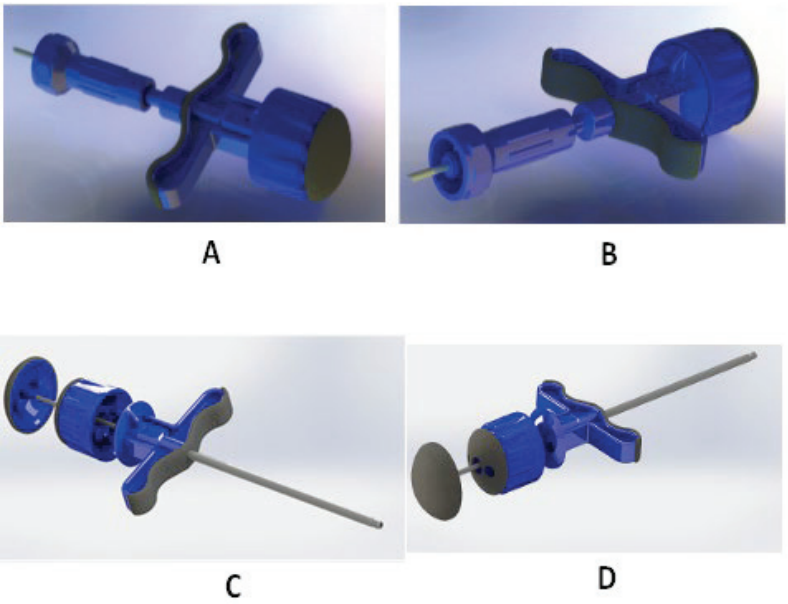


Figure 19.1 demonstration of an Islam single use bone marrow biopsy needle with attached non-slip surface elements. A & B are the sternal/posterior iliac puncture needle. C & D depict the bone marrow trephine (core) biopsy needle.

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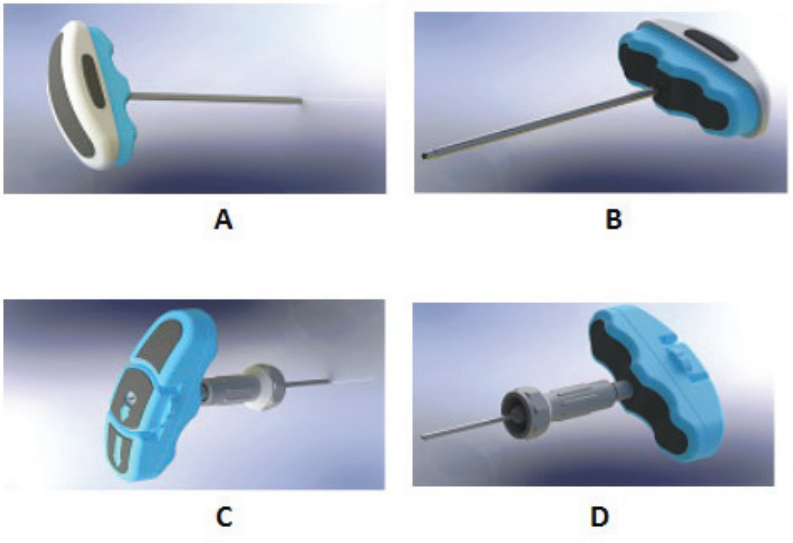


Figure 19.2 demonstration of a third generation Islam single use bone marrow aspiration and biopsy needle with attached non-slip surfaces. A & B depict the core retention bone marrow trephine biopsy needle. C & D demonstrate the sternal/posterior iliac puncture needle.

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APPENDIX

PATIENT INFORMATION

Bone marrow aspiration and biopsy procedures although minor are considered surgical interventions and as a result patients are often apprehensive, nervous and afraid of undertaking the procedure. They may have questions with regard to the procedure, which have to be adequately answered before they undergo the procedure. In general patients have to be made comfortable to undertake the procedure and any questions they might have must be adequately and appropriately answered; their burden of fear and apprehension must be removed. With this in mind the following patient information has been prepared which the reader might find handy and useful.

Bone Marrow Aspiration and Biopsy Procedures Patient Information and Handout

What are bone marrow aspiration and biopsy procedures?

Bone marrow aspiration and biopsy procedures are diagnostic procedures that involve the removal of tissue - either liquid marrow or a solid cylindrical core of marrow tissue (in which both bone and marrow architecture remain undisturbed) from the bone marrow cavity. These procedures are necessary to initiate, follow-up or complete examinations of patients suspected of having or suffering from certain hematological or non-hematological disorders.

How are they done?

Bone marrow aspiration and biopsy procedures are simple and straightforward. They are usually performed in an operating room (OR), Interventional radiology suite, in an outpatient clinic or in a doctor's office. The procedures may also be performed at a patient's bedside if he or she is already hospitalized. The entire process takes only 10 to 15 minutes; however, you will need to stay an additional 15 to 20 minutes for observation afterwards.

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Here's how the procedures are done:

Following cleaning with alcohol and sterilization with an iodine solution, the area to be tested (usually hip bone) is draped with a sterile cloth. The skin is then anesthetized using a small (25 gauge X 5/8") needle to prevent pain. The anesthetized skin site is then used to introduce a slightly larger and longer (22 gauge X 2") needle to anesthetize the soft tissue, muscle and periosteum to numb the area so you do not feel any pain during the procedure.

After the anesthetic has taken effect, a small, delicate incision is made in the skin to facilitate the entry of the bone marrow aspiration and biopsy needles. A bone marrow aspiration needle is inserted to aspirate the fluid marrow. During the initial stages of the aspiration, you may feel slight discomfort or pain. This is known as "suction pain." This sensation is a good sign – it indicates that the aspiration needle is precisely situated in the marrow cavity and the biopsy procedure is being properly carried out.

Following the bone marrow aspiration, a biopsy needle is immediately inserted at the same site, but directed towards a slightly different area in order to obtain a solid, cylindrical core biopsy sample (the second step of the test). Once an adequate core biopsy sample is secured within the lumen of the needle, the needle is withdrawn. The sample is then removed and placed in a preservative for processing and examination.

Once the entire procedure is completed a pressure dressing will be applied and you will be asked to lie flat on your back for 15 to 20 minutes to avoid bleeding. You should keep the pressure dressing in place for at least 24. If you experience excessive discomfort, pain or bleeding, or if you have any questions, please call (tel: 000-0000)

Is there any risk involved?

These procedures are virtually risk free. In rare cases, complications such as bleeding, swelling or pain may occur. If necessary, you will be given painkillers.

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Instructions for you on the day of your procedure

- Follow your normal eating and drinking habits. Fasting is not necessary.
- You may take your regular medications, with the exception of Coumadin, lovenox, aspirin, aspirin-containing medication, or platelet aggregation inhibitors such as dipyridamole or aggrenox or an antiplatelet agent like plavix. If you are taking lovenox, aspirin, a platelet aggregation inhibitor, anti-platelet agent or an oral anticoagulant such as coumadin, pradaxa or eliquis, please inform your doctor in advance, as you may be advised to stop taking them a day or two (may be more) before your biopsy procedure. You will be able to resume taking them soon after your procedure is complete.
- Please arrive at hospital about 30 minutes before your scheduled appointment. At the Admissions Department in the main lobby, register for the Department of……. When you have completed the registration process, please proceed to the outpatient/ ambulatory surgery department on the …… floor and report to the nursing staff.

You will be able to resume normal activities within a few hours however, if you wish, you may have someone accompany you.

Some patients feel some tenderness at the procedure site for a day or two. To alleviate this tenderness, you may take one or two Tylenol tablets every four to six hours as needed.

Your biopsy has been scheduled for _____ (day and date) at _____a.m./p.m.

If you need to cancel or reschedule your appointment, please call at 000 0000.

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A SAMPLE REQUEST FORM USED IN OUR HOSPITAL

BONE MARROW HEMATOPATHOLOGY REQUISITION 1 of 2

Patient ID Area

PATIENT INFORMATION	REQUESTING PHYSICIAN
SH # _____ Date _____	
Address _____	Signature X _____
City _____ State _____ Zip _____	Office location if more than one:
ICD-10 Code _____	_____
History _____	Additional chart copies to:
If bone marrow is submitted, please attach CBC data	

REQUIRED BILLING INFORMATION

☐ Bill Insurance ☐ Bill Account

PRIMARY INSURANCE CARRIER

☐ Medicare ☐ Medicaid ☐ Other _____

ID#	Group #	Plan Code

Name of Subscriber

Patient's Relationship to Subscriber:
☐ Self ☐ Child ☐ Spouse ☐ Other _____

SECONDARY INSURANCE CARRIER

ID#	Group #	Plan Code

Name of Subscriber

Patient's Relationship to Subscriber:
☐ Self ☐ Child ☐ Spouse ☐ Other _____

INSURANCE ADDRESS REQUIRED FOR COMMERCIAL INSURANCE

Street City State Zip

PERSON TO BE BILLED IF OTHER THAN PATIENT

Name (Last, First, MI) Phone

Street City State Zip

PATIENT / AUTHORIZED SIGNATURE & DATE

I AUTHORIZE THE RELEASE OF ANY MEDICAL INFORMATION NECESSARY TO PROCESS THIS CLAIM TO MY INSURANCE CARRIER.

X _____ Date _____

***ABN (below) needed if frequency of order or diagnostic information does not meet Medicare guidelines**

Advanced Beneficiary Notice (ABN)
I have been informed that Medicare will only pay for services that it determines to be "reasonable and necessary" under Section 1862 (a)(1) of the Medicare law. I understand that Medicare will deny payment for my laboratory work if the frequency of the order/diagnostic information does not meet Medicare guidelines (*see above). If Medicare denies payment, I agree to be personally and fully responsible for payment.

Signature (Medicare Beneficiary) X _____ **Date** _____ **Time** _____

SPECIMENS SUBMITTED:

Date/time collected _____

Peripheral blood: ☐ For morphology ☐ CBC/diff ☐ Smears (stained/unstained)

Bone marrow: Site: Posterior Iliac (Indicate left or right) Other (indicate) _____

☐ Aspirate (anticoagulated, EDTA) ☐ Aspirate (smears ___) ☐ Clot (in fixative) ☐ Core biopsy in fixative ☐ Touch preparations

Fluid: Site/comments: _____

Lymph node: (fresh preferable, receive within 1 hour, call in advance) Site _____

Other tissue/material: _____

Slides for consultation/review: (attached previous report) _____

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BONE MARROW HEMATOPATHOLOGY REQUISITION 2 of 2

Patient ID Area

TEST REQUESTED: (Cytogenetics, FISH, and Molecular Genetics are all send out tests)

☐ **Morphology/Interpretation:**
For bone marrow interpretation
Iron studies done routinely, unless not needed: ☐ No iron stain
Aspirate smears interpreted unless not needed: ☐ Aspirate for correlation only

☐ **Flow Cytometry:** Work up will be guided by the history given above.
Specimen requirements: Keep at **room temperature, 18 to 25 degrees Celcius**, transport ASAP, within 8 hours. If testing is expected to occur in greater than eight hours, specimens must be handled and transported with cold packs to maintain specimens between 2 and 8 degrees Celsius prior to testing. Do not place specimens directly on ice pack to freeze.
-- Blood/marrow anticoagulated EDTA, heparin, or ACD;
-- Lymph nodes/tissue: Sterile container with RPMI/Hanks/normal saline

Specimen submitted _____
☐ Morphologic interpretation/correlation requested

LAB USE ONLY

Accession # _____
RECEIVED ☐ Core ☐ Clot
Aspirate
_____ # Smears
_____ # Tubes (list types)
SENT (where and type of tube sent)
Flow _____
Cytogenetics _____
FISH _____
PCR _____
OTHER _____

☐ **Cytogenetics:** (Call in advance to notify)
Specimen requirements: Sterile media or green top tube, transport ASAP, preferably within 12 hours
Specimen/comments _____

☐ **Microbiologic Cultures:**
☐ Routine bacterial – Bactec Peds plus (blood culture tube) ☐ Mycobacterial – (ACD) yellow or (heparin) green tube
☐ Fungal – Bactec Peds plus (blood culture tube) ☐ Other _____

☐ **FISH and Molecular Genetics: (Send out tests)**
Specimen requirements:
Blood/bone marrow/fluids: Fresh (Anticoagulated ACD/EDTA) for FISH and PCR - Transport on ice
Tissue: Fresh/Frozen for PCR; fixed or paraffin block (FISH and PCR on selected tests)

Specimen submitted _____
☐ Tests can be ordered upon pathologist's discretion
☐ FISH Tests:

FISH Panel:
☐ CLL panel (6q-, MYB, ATM, Trisomy 12, 13q-, p53, CCND1/IgH)
☐ Multiple myeloma/MGUS panel (1q+, -3, +9, +6, 13q-, p53, FGFR3/IgH, CCND1/IgH, IgH/MAF)
☐ MDS panel (5q-/-5/+5, 7q-/-7, +8, 20q-/-20, MLL)
☐ AML panel (5q-/-5/+5, 7q-/-7, +8, MLL, RUNX1/RUNX1T1, PML/RARA, CBFB)
☐ ALL panel (TCF3/PBX1, Trisomy/Tetrasomy 4,6,10,17, MYC, BCR/ABL1, MLL, IgH)
☐ Eosinophilia panel (PDGFRA, PDGFRB, FGFR1)
☐ High-Grade/Large B-cell lymphoma panel (MYC, BCL-2, BCL-6)

Individual Probe:
☐ BCR/ABL1 t (9;22) ☐ CCND1/IgH t (11;14) ☐ IgH/BCL-2 t (14;18) ☐ BCL-6 ☐ MYC
☐ ALK (2p23) ☐ API2/MALT1 t (11;18) ☐ IgH/MAFB t (14;20) ☐ PML/RARA (15;17)
☐ Other _____

☐ PCR Tests:
☐ Myeloproliferative neoplasm (MPN)
☐ MPN reflex panel (JAK-2 with reflex of JAK-2 exon 12, MPL, CALR mutations)
☐ JAK-2 V617F with reflex of JAK-2 exon 12-14
☐ B-cell receptor gene rearrangement (IgK and IgH)
☐ T-cell receptor gene rearrangement (TCR-β and TCR-γ)
☐ MYD88 mutation (lymphoplasmacytic lymphoma)
☐ MPL mutation ☐ CALR mutation ☐ BCR/ABL1 ☐ BRAF mutation
☐ FLT3 mutation ☐ NPM1 mutation ☐ CEBPA mutation ☐ c-KIT mutation
☐ Other _____

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