Tutorials in Surgery 4

Surgical Pathology I

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Preface

Accurate diagnosis is the most important and challenging facet of medical practice since without it treatment is ineffective. This book is intended to help both prospective and established surgeons to understand the basic pathology of the diseases which present for surgical treatment. A surgeon is a physician who treats a pathological condition, where thought necessary, by operation. A pathologist is a physician who, because of his knowledge of disease processes, plays an essential role in accurate diagnosis. Both should be concerned with the sick individual as a whole who is liable to suffer the protean problems which can arise in any pathological situation. It is, therefore, imperative that the pathologist is given full access to all the relevant clinical information about a particular patient. The pathologist employs a microscope and not a crystal ball. Rapport between the surgeon and pathologist must be complete, not only for the help they can give each other but for the benefit of the patient.

Because this text is aimed at the practising surgeon rather than the 'pure' pathologist, an attempt has been made to describe the clinical effects of each pathological condition before passing on to a consideration of the gross and microscopic pathology.

We have tried, albeit perhaps imperfectly, to produce a text after the fashion of the father of the Leeds School of Surgery, Lord Moynihan, who coined the phrase 'the pathology of the living.'

F G Smiddy
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Leeds 1984

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A handwritten folio must be converted into typescript and, as always, Mrs P M Docherty gave her whole-hearted attention to this matter. Finally the typescript must be edited in such a way that it becomes a textbook, and knowing the expertise required for this task the authors gratefully acknowledge the work of Mrs Susan Brown.

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Contents

1 Infections of surgical importance

1.1 Erysipelas (erythros pele = red skin)

This cutaneous infection is mainly caused by the beta-haemolytic *Streptococcus pyogenes* of the Lancefield Group A and occasionally Group C.

Clinically the disease is rare before the age of 20 and chiefly occurs in middle age. It develops as a rapidly spreading, erythematous, oedematous, cutaneous infection usually beginning on the face. The condition spreads producing a brawny erythema which has a sharp, well demarcated serpiginous border. The skin of the affected part is thickened but gross areas of suppuration are uncommon. Red streaks, indicating lymphangitis occasionally spread from the affected area to the local lymph nodes which are enlarged and tender.

Histologically there is an acute oedematous, interstitial reaction in the dermis and epidermis with some reaction in the deeper subcutaneous layers. An intense infiltration with neutrophil leucocytes occurs particularly around the blood vessels and skin appendages. Whilst microabscesses may form, tissue necrosis is minimal and only occasionally do large abscesses accompanied by gross tissue destruction occur. It is because of this lack of tissue destruction that resolution results in apparent complete recovery of the normal tissue architecture. Should, however, infection spread deeply to involve the subcutaneous connective tissues cellulitis is produced.

The spreading nature of streptococcal lesions is due to the production of hyaluronidase which liquefies the mucinous ground substance of the connective tissue thus allowing the organism to spread. Also involved are fibrinolysins

which dissolve fibrin, the natural barrier to infection, and leucocidins which kill the polymorphonuclear leucocytes.

1.2 Boil, furuncle

This lesion which most commonly occurs in the dense dermal connective tissue on the back of the neck is caused by the *Staphylococcus aureus* which invades the dermis via a hair follicle and sets up an acute inflammatory swelling. The infection spreads locally in the dermis and produces an area of skin necrosis in the centre of the lesion which is caused by toxins liberated from the organism. Additional factors are the decreased blood supply of the infected part caused by a combination of inflammatory oedema and thrombosis of small surrounding blood vessels. An intense polymorphonuclear infiltrate surrounds the lesion and with digestion at the periphery, the necrotic core separates and is eventually discharged leaving an ulcer lined by granulation tissue (Fig. 1.1) which will organize. A pitted scar may be left depending upon the size of the local reaction.

If the 'resistance' of the patient is low, for example as in the patient receiving immunosuppressive drugs, in whom a leucocytosis may not occur, or in dia-

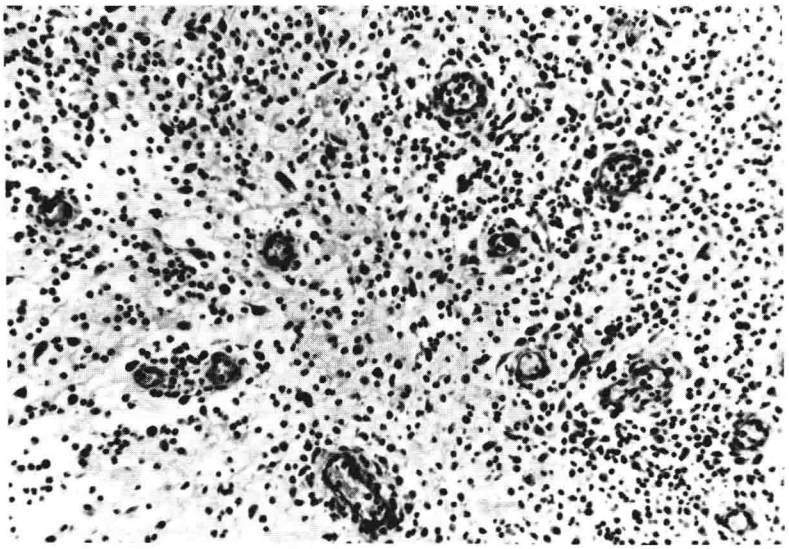

Fig. 1.1 Granulation Tissue
This consists of capillaries in an oedematous stroma of fibroblasts, strands of fibrin and mixed inflammatory cells (polymorphs, histiocytes and lymphocytes). The capillaries are newly-formed, as indicated by thick endothelial cells, and contain numerous marginating polymorphs ready to pass out of the vessels.

betes mellitus, which is associated with a specific malfunction of the leucocytes, the infection may spread through the dermal and underlying soft tissues giving rise to a carbuncle; a complex loculated and ill defined abscess usually associated with multiple discharging sinuses.

1.3 Gas gangrene

Two varieties of gas gangrene are recognized, clostridial cellulitis and clostridial myositis, the latter being the more serious.

The cause of gas gangrene is the group of obligate Gram-positive anaerobes belonging to the genus Clostridia, the most common being *Cl. perfringens* (*welchii*), *Cl. oedematiens* and *Cl. septicum*. All or only a few varieties of the clostridia may be present in an individual case.

Clinical presentation

The disease is most commonly contracted after severe, deep, soft tissue injuries have occurred which have been contaminated by soil in which the spores of the organisms are present. Infection with aerobes such as the staphylococcus and proteus aid in the production of the necessary degree of anaerobiosis by causing active inflammation and suppuration. In addition, if a compound fracture has occurred in the depth of the wound the bony splinters liberate small amounts of calcium which lowers the oxidation-reduction potential. Spore contamination of a wound is of little importance if the degree of oxygenation is such that it prevents germination. However, once germination has occurred the clostridia are highly invasive and the presence of an active infection usually becomes manifest within 1 to 3 days of injury. Oedema of the underlying tissues causes the skin to become pale and tense. Necrosis and rupture of the skin may follow the formation of large bullous vesicles and large amounts of serosanguinous, faintly foul-smelling exudate is discharged from the wound. As the condition progresses, gas is formed and spreading crepitus occurs. The absorption of a variety of toxins causes severe systemic upset, chiefly manifested by a rapid rise in the pulse rate which may be remarkedly out of step with the rise in temperature. Haemolysis causes profound anaemia and finally the patient becomes 'shocked' and dies.

Pathological changes

The spreading characteristics of the clostridial infections are due to the elaboration of a number of enzymes and toxins, the most important of which are fibrinolysins, hyaluronidases, collagenases, haemolysins, cytolysins and lecithinase.

The infected muscles first appear swollen and pink in colour due to the release of blood pigment from the lysed red cells. Microscopically, unless suppuration has preceded the onset of the disease, there is minimal migration of leucocytes into the affected tissues. Gas is formed by *Cl. welchii* fermenting sugars, thus producing carbon dioxide which collects in the dead and dying tissues causing the typical crepitation. As the infection progresses the inflamed muscle becomes soft, blue black, friable and sometimes almost semifluid because of the potent proteolytic bacterial enzymes.

If death occurs, all the tissues of the body may contain large numbers of clostridia, in particular the liver, which may be filled with gas bubbles. It should be noted that in some patients dying from other causes, particularly bowel disease, the terminal blood-borne dissemination of clostridia may produce similar gas filled spaces in the liver or brain, Swiss cheese brain. This is agonal and histology shows the clostridia lining the spaces are unaccompanied by any tissue reaction.

1.4 Wound sepsis

Wound sepsis has been defined by the National Research Council as the presence of pus in a wound which has either spontaneously discharged or has had to be released by the removal of sutures or re-opening the incision. This strict definition excludes a stitch abscess and erythema, both of which may spontaneously resolve.

Wound sepsis is related to two specific factors, the degree to which the wound is contaminated by intestinal contents at the time of the operation and the type of bacterial flora in the intestinal tract. In addition other factors may, in some patients, play an important part in the development of wound sepsis; such factors include diabetes, agranulocytosis and the administration of immunosuppressive drugs such as glucocorticoids.

The incidence of wound sepsis following abdominal operations varies in different series, according to the indications for and the type of operation performed. Thus, in clean abdominal operations, an incidence of wound sepsis of 2 per cent can be expected, whereas when pus is already present in the abdominal cavity, the incidence of wound sepsis may reach nearly 40 per cent if no attempt is made to anticipate the complication by the administration of antibiotics. In colo-rectal surgery a significant reduction in the incidence of wound sepsis can be achieved by oral antibiotic therapy together with the complete evacuation of the bowel contents by means of an elemental diet and preoperative whole gut irrigation.

The most numerous bacteria in the appendix, colon and rectum are the anaerobes, particularly Peptostreptococcus spp., Lactobacillus spp., *Cl. welchii* and Bacteriodes spp. Anaerobes, since they exceed the number of aerobic micro-organisms by a factor of 10,000 are, therefore, more likely to be the infecting organisms. The commonest aerobic organisms are *Streptococcus faecalis*, Staphylococcus spp. and *Escherichia coli.*

It is thus obvious that any reduction in wound sepsis following intestinal surgery requires the administration of drugs which not only diminish the number of aerobic organisms but also the anaerobes. The introduction of metronidazole which is specifically effective against *Bacteroides fragilis*, the major anaerobe, together with which the cephalosporins are effective against the aerobes has been shown markedly to reduce wound sepsis in many prospective trials when used in combination. In addition, of considerable importance in controlling the incidence of wound infection are various technical manoeuvres, such as the avoidance of wound contamination by methods including isolating the site of the anastomosis and a change of gown and gloves before wound closure.

1.5 Tetanus

This is a highly fatal disease characterized by convulsive contractions of voluntary muscles due to CNS stimulation by the exotoxins liberated by the *Clostridium tetani*. This organism is a Gram-positive slender motile rod up to 5 μm in length. Large terminal spores develop which give the organism a drumstick appearance. However, unlike the clostridia of the gas gangrene group the *Cl. tetanus* does not invade the tissues and unless the amount of trauma or superadded infection produces the necessary degree of anaerobiosis the spores may lie dormant in the tissues for many months.

Clinical presentation

The normal incubation period is between 1 and 2 weeks and the onset of the disease is ushered in by stiffness of the voluntary muscles which is then followed by widespread tetanic muscular contractions which tend to follow minimal stimulation. When the muscles of the face are affected trismus develops giving rise to the term 'lockjaw' which is sometimes accompanied by a sardonic smile, the 'risus sardonicus'. Involvement of the spinal muscles produces opisthotonus, and painful convulsions and involvement of the respiratory muscles or possibly the respiratory centre leads to terminal respiratory failure.

Pathological changes

Although the neurotoxins liberated by the *Cl. tetani may* cause such severe clinical effects, the morphological changes found at autopsy are often minimal and non-specific. The local injury which resulted in the infection may well have healed prior to the onset of symptoms. If this is not so, all that may be found is a non-specific inflammatory reaction associated with some tissue necrosis from which a mixed bacterial flora may be isolated.

In the nervous system inconsistent and non-specific changes are found including swelling of the anterior horn cells in the cord accompanied by nuclear swelling and chromatolysis.

It is generally believed that the exotoxin, produced at the site of infection, passes up motor trunks of the local nerves to reach the cord where normal inhibitory activity on anterior horn cells of the affected segment suffers interference. The exact site of action of the toxin and how it arrives there are still not completely understood.

1.6 Tuberculosis

This disease, which is now relatively rare in the native communities of Western Europe and North America, is chiefly caused by two types of tubercle bacillus, the *Mycobacterium tuberculosis* or human type and the *Mycobacterium bovis*, the bovine type. In recent years 'atypical' or 'anonymous' tubercle bacilli have been found to produce low-grade infections resistant to antituberculous drugs. The reasons given for the greatly reduced incidence of this disease which was in the recent past a major cause of death in youth and middle age are as follows:

1 better living standards associated with better nutrition, particularly among industrial workers;

2 the elimination of milk herds infected with the bovine type of organism thus diminishing the chances of infection of the very young;

3 protection by immunization with the Bacille Calmette-Guérin at an early age;

4 the control of the disease by a variety of antituberculous chemotherapeutic drugs.

It is not always appreciated that the mycobacterium may lie dormant in a lesion for many years without any clinical manifestations developing and then become active again due to reduced resistance, for example, by the development of a debilitating disease, e.g. diabetes, the administration of corticosteroids or immunosuppressive drugs, or even malnutrition. This accounts for the majority of cases seen in the middle aged and elderly in Great Britain today.

Another important aspect of infection by the mycobacterium is that once infection occurs, cell-mediated immunity develops. This is due to the production of primed T-lymphocytes which are capable of reacting directly with the antigenic protein of the tubercle bacillus, and it develops within two to three weeks. Once the primed lymphocytes have reacted with the antigen, soluble factors known as lymphokines are produced which, among other properties, are able to induce an acute inflammatory reaction and to influence the behaviour of the mononuclear phagocytes. It is assumed, however, that the immune response invoked by the organism leads to its elimination and hence the cure of the disease in some patients. However, it is probable that most of the tissue damage which occurs in a tuberculous infection is due to this response since the organism itself does not produce any specific toxins. Furthermore, mycobac-

teria can survive and multiply within histiocytes in tissue culture without harm to the cultured cells.

Two types of lesion are recognized; the primary response which occurs on first contact with the organism and the secondary response, which occurs when an individual who has been immunized by BCG or who has had a primary infection which has healed becomes reinfected.

The primary response (primary tuberculosis)

In the primary response, a lesion, the primary, develops at the portal of entry of the organism which is usually the lung, tonsil or small intestine and whilst this usually rapidly heals, early spread occurs to the draining lymph nodes which enlarge. The combination of the lesion and the enlarged lymph nodes is known as the primary complex and both caseate to some extent. Involvement of the lymph nodes gives the organism an opportunity to invade the blood stream, and when large numbers disseminate through the tissues acute miliary tuberculosis follows. Miliary lesions are commonest in the lungs, liver, kidneys, spleen and meninges, the last producing a tuberculous meningitis which is rapidly fatal if untreated.

The histological changes associated with the primary response can be followed with ease in an experimental animal such as the guinea pig. In the first day or two following the injection of the mycobacterium a local infiltration with neutrophil polymorphonuclear leucocytes occurs which rapidly disappears to be replaced in the next few days by macrophages of the mononuclear phagocyte system. These migrate into the area and ingest the organisms without destroying them. After approximately 10 days lymphocytes gather to surround the infected area, the combined cellular aggregation being the beginnings of the subsequent granulomatous lesion. Some of the macrophages enlarge and because they bear some resemblance to epithelial stratum spinosum cells, they are known as epithelioid cells. Some of these fuse together to form the Langhans' giant cells. The normal tissue in the centre of this process becomes necrotic and forms a creamy white and crumbling mass which resembles cream cheese. The process is, therefore, described as caseation and the necrotic material is caseous. A tubercle consists of a caseous centre with surrounding epithelioid and Langhans' cells and lymphocytes surrounding the whole.

The further course of the lesion depends upon many factors particularly the resistance of the host and the virulence of the invading organisms. Should the organisms continue to multiply numerous tubercles will form which, as they enlarge, become confluent so that eventually a lesion several centimetres in diameter is formed. Subsequent liquefaction of the central caseous zone produces a lesion known to the clinician as a 'cold' abscess because of the lack of the acute inflammatory features which follow infection by pyogenic organisms. A cold abscess may complicate any developing tuberculous lesion but it used to be particularly common in the lymph nodes of the neck, the lymph nodes of the mediastinum and in the psoas sheath following tuberculous involvement of the spinal column.

The early pathological changes described in experimental animals parallel the

changes in the human. However, in the human the lesion at the portal of entry usually remains small and disappears on healing or leaves a small scar. In the lungs the primary focus of parenchymal infection is usually found immediately subjacent to the pleura in the lower part of the upper lobes or the upper part of the lower lobes of one lung and in this position the lesion produced is known as the Ghon focus. The healing of such a focus of infection characteristically produces subpleural fibrous scars with puckering of the pleural surface.

Reinfection tuberculosis (post-primary or secondary tuberculosis)

This results from the reactivation of a primary focus of infection or infection of an individual who has been previously immunized by BCG. It is not certain, in the first case, whether reinfection occurs or dormant bacilli commence to proliferate. The difference between primary and reinfection tuberculosis appears to depend on the presence in the latter of delayed hypersensitivity and, whilst in the primary complex, involvement of the draining lymph nodes is a prominent pathological feature of the disease, this is not so in reinfection tuberculosis.

Delayed hypersensitivity arises because primary infection by this organism produces a high degree of cell-mediated immunity to the protein fraction of the bacterium, the tuberculoprotein. This results in the development of specifically primed T-lymphocytes which react to its presence when they are once again exposed to it. Once reactivated the primed lymphocytes synthesize DNA and are transformed into immunoblasts. The medium in which they are dividing contains a variety of soluble factors known as the lymphokines and it is these substances which are responsible for the predominantly polymorphonuclear response which occurs in the secondary infection. Another factor released by the primed T-lymphocytes is cytotoxic and is, therefore, responsible for the necrosis characteristic of this type of reaction.

Although the early cellular response to the second infection is predominantly by polymorphonuclear leucocytes, these are rapidly replaced by cells of the mononuclear phagocyte system which phagocytose the offending organisms. These are then destroyed, the lipid is distributed throughout the cell and transformation occurs into the epithelioid cell type. This cell is large and pale, possesses a large vesicular nucleus, abundant cytoplasm and indistinct cellular margins. Around this lesion small lymphocytes rapidly aggregate so that the typical 'tubercle' is formed. This consists of a central zone of necrosis, peripheral to which is a mass of epithelioid cells between which are to be found the Langhans' giant cells formed by the fusion of epithelioid cells and, peripheral to this again, a zone of lymphocytes (Fig 1.2). In all, from the moment of infection to the development of the recognizable tubercle an interval of about 3 weeks occurs. Many tubercles may coalesce and the central caseous area which is first formed by coagulative necrosis softens and liquefies.

The future course of this pathological lesion varies:

1 It may completely resolve.

2 It may be surrounded by fibrous tissue and dystrophic calcification may occur within the central caseous tissue.