Chapter 46

Intensive Care for Patients with Malignant Disease

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"Malignant tumours vary very much, both in their rate of local growth and dissemination, but they are always ultimately fatal, the average duration of life being from three to six months in the case of sarcoma, and from two to three years in the case of carcinoma, whether the condition be treated or not . . . " [141].

"Few diseases are more tragic than acute leukaemia, as it is invariably fatal and it so often affects lives which seemed full of promise . . . Blood transfusion may bring the patient into a suitable condition for X-ray treatment, which is otherwise contra-indicated by the low number of normal polymorphonuclear cells, but any improvement is usually evanescent and it rarely does more than protract a painful situation" [136].

These two quotations from a "surgical" and "medical" textbook respectively, both published in 1937, serve to emphasize the enormous advances that have been made during the last half-century in the treatment of patients with malignant disease. Although there have been important developments in the management of some solid tumours, the most dramatic improvements in long-term prognosis have been seen in patients with haematological and lymphoreticular malignancies, a significant proportion of whom can now be cured. Even in those with acute myelogenous leukaemia (AML), a condition which 30 years ago was invariably fatal, with a median survial of only a few months [160], the use of very myelosuppressive cytotoxic chemotherapy can produce complete remission in the majority of patients and a cure can be anticipated in as many as 25% [140]. There have also been important improvements in supportive care; in particular the administration of platelet concentrates has reduced the incidence of fatal thrombocytopenic haemorrhage and the development of specialist nursing techniques, combined with the more effective use of antimicrobial agents, has greatly reduced the mortality from intercurrent infection.

Nevertheless, patients with malignant disease are prone to a wide variety of acute life-threatening disturbances related either to the effects of the tumour itself or to complications of its treatment. The majority of these disorders are potentially reversible and in view of the improved long-term prognosis it is appropriate to admit selected cases to the intensive care unit, provided that the prospects for cure or worthwhile palliation of the underlying malignancy are considered to be reasonable.

Dangerous complications directly caused by the tumour include pleural or pericardial effusions [180], renal failure induced by ureteric compression [54], pancytopenia due to marrow invasion, airway obstruction [159], metabolic disturbances, such as uraemia [54], hypercalcaemia [117] or hyperosmolar coma [69], various neurological syndromes [25] and massive haemorrhage from an ulcerated lesion.

Life-threatening complications of treatment are most often a result of immunosuppression caused by chemotherapy, radiotherapy or steroids. Such patients are very susceptible to overwhelming infection, particularly during the period of profound leucopenia induced by aggressive chemotherapy. In the majority of those with haematological malignancy admission to the intensive care unit is precipitated by pneumonia and/or septicaemia, often complicated by acute respiratory failure [2,7,69,101,159]. Sometimes bleeding, which is usually a result of thrombocytopenia caused by bone marrow suppression, is of sufficient severity to warrant admission [7,101,159].

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Other dangerous, less frequent, complications of anti-cancer treatment include cardiomyopathy induced by irradiation or cytotoxic agents [183], pulmonary fibrosis related to chemotherapy [55] or radiotherapy [63,69,159], graft-versus-host (GVH) reactions [40,147] and tumour lysis syndrome [172]. Recently a case of multiple organ failure has been described following the administration of interleukin-2 and lymphokine-activated killer cells for the treatment of metastatic hypernephroma [161]. Although these complications occur most frequently in patients with haematological malignancy, they are occasionally encountered in those with solid tumours.

Patients with malignant disease may also benefit from elective admission to the intensive care unit following extensive surgical procedures, particularly if they are high-risk cases by virtue of coexistent medical disorders. Intensive care may also be required for postoperative complications. In one centre, just over 70% of admissions to the intensive care unit were from the surgical services [185,186] and gastrointestinal, thoracic and urological surgery patients accounted for 56% of all admissions [185]. Overall, in a general intensive care unit only a small proportion of those admitted will have malignant disease. For example, in one series there were a total of 1593 admissions over two years, of which only 88 were patients with haematological malignancy [159].

Life-Threatening Medical Complications of Malignant Disease

Infection

Infection is a frequent complication and an important cause of death in patients with cancer [33], particularly those with haematological malignancy [21,119], in whom it is the commonest factor precipitating admission to the intensive care unit [7,101,159].

Impaired Resistance to Infection in Patients with Malignant Diseases

The increased susceptibility of patients with malignancy to infection may be related to reduced or abnormal granulocytes, decreased antibody production, impaired cellular immunity or a combination of these factors. Moreover mucocutaneous barriers may be disrupted by treatment, drainage tracts may become obstructed by tumour and the patient is often subjected to a variety of invasive procedures. In general immune competence is relatively intact prior to treatment and the majority of those with impaired cellular and humoral immunity are receiving chemotherapy, radiotherapy or corticosteroids.

The patient with acute leukaemia, for example, is predisposed to infectious complications by a variety of abnormalities including profound neutropenia, abnormalities of neutrophil function [21,119], a deficiency in the maturation of macrophages [90] and defects in humoral immunity [119]. Granulocyte function undergoes the earliest and most profound changes, whilst humoral factors are affected later during induction chemotherapy and in those who relapse [119]. Neutropenia is by far the most important cause of the increased susceptibility to infection and there is an inverse correlation between the granulocyte count and both the incidence and the severity of infection [22]. Although the incidence of infectious complications increases as the granulocyte count falls below 1×10^9 per litre it is not until the count is less than 0.5×10^9 per litre that the risk rises dramatically. The mortality rate from infection is related both to the duration of the neutropenia and to whether the neutrophil count rises or falls [21,28], a factor which also seems to have an important influence on outcome in those receiving intensive care [101]. Neutropenia is most profound and prolonged in those receiving intensive remission induction chemotherapy, which can also damage the mucosa of the alimentary canal and tracheobronchial tree. The most pronounced immune suppression is seen in patients in relapse, probably largely as a result of previous courses of chemotherapy [119].

Bone marrow transplantation is now established as a useful form of treatment for some patients with acute leukaemia but is a technique associated with an extremely high risk of infectious complications. Although some marrow recipients are in complete remission at the time of transplantation, others have failed to respond to chemotherapy, are already neutropenic and may be infected. All patients then receive intensive chemotherapy, irradiation or both, sufficient to cause marrow aplasia with a virtual absence of circulating granulocytes until the transplanted marrow starts to function. This is

combined with severe mucosal damage induced by the aggressive chemotherapy. There is also a prolonged period of cellular immune dysfunction and impaired humoral immunity [200].

Patients with chronic leukaemia have defects in both cellular and humoral immune function [21,70,156] which become more severe as the disease progresses. Later they may develop neutropenia as a result of either the disease or its treatment. In patients with lymphoproliferative disorders cell-mediated immunity is markedly impaired, particularly in those with Hodgkin's disease [96], and in some cases humoral immunity is also defective [70].

Carcinomas and sarcomas are also associated with immunosuppression, the degree of which depends on the extent of metastatic spread [1]. In general, cell-mediated immunity is more readily compromised than is the humoral response. Moreover, the increased use of chemotherapy to treat solid tumours means that an increasing number of these patients are being rendered granulocytopenic, although this is usually less profound and of shorter duration than in those with haematological malignancy.

Organisms Causing Infection

Patients with cancer are, therefore, particularly susceptible to serious infections caused not only by bacteria but also fungi, viruses, protozoa and helminths.

Bacteria still account for the majority of infections, particularly Gram-negative organisms, *Escherichia coli*, *Klebsiella* spp., or *Pseudomonas* spp. [23,42] and, less commonly, *Proteus or Enterobacter* spp. Although for a time the use of the semi-synthetic anti-staphylococcal penicillins had virtually eliminated *Staphylococcus aureus* as an important cause of infection in leukaemia patients, there has since been a resurgence in infections due to Gram-positive cocci, including *S. epidermidis* [21].

Less frequently infection may be due to unusual bacteria, *Legioniella pneumophila* and related organisms, JK bacteria and *Corynebacterium* species or *Listeria monocytogenes* [21]. Infections with multiple organisms are relatively common and *Clostridium difficile* is recognized as a cause of severe diarrhoea and pseudomembranous colitis [21]. In general anaerobic infections are unusual in leukaemic patients [23] but are common in those with gastrointestinal and genitourinary malignancies.

Infection is nearly always endogenous [156, 158] originating from organisms colonizing the patients alimentary canal, upper airways and skin, although in patients with leukaemia about half, or possibly more, are caused by organisms acquired after the initial diagnosis and hospitalization [158]. Sources of these acquired organisms include the hands of staff, food, water and, to a lesser extent, ambient air. Hands are a common source of *S. aureus* and many Gram-negative organisms whilst hospital food, especially salads, is frequently heavily contaminated by Gram-negative bacilli [138]. Water-loving organisms such as *Pseudomonas aeruginosa*, *Flavobacterium* spp. and *Serratia marescens* can contaminate water supplies. Transmission of *Legionella pneumophila* appears to be by aerosol and direct airborne spread is responsible for infection with some of the organisms encountered less commonly in cancer patients such as *Aspergillus*, *Mycobacterium tuberculosis* and respiratory viruses.

Colonization of the alimentary tract by Gram-negative organisms and fungi is encouraged by the alterations in its microbial flora which may occur in response to treatment with antibiotics, in particular the suppression of anaerobic organisms and a consequent reduction in "colonization resistance" [21]. Moreover, there may be alterations in specific bacterial receptor sites which allow new organisms to adhere to mucosal and epithelial surfaces [13] and chemotherapy is often complicated by areas of mucosal ulceration in the alimentary tract which can act as a focus for colonization. This may be followed by local infection, cellulitis, involvement of deep tissues and subsequent septicaemia. Cytotoxic agents may also damage the mucosa of the tracheobroncheal tree, as well as impairing mucociliary function, thereby encouraging spread of organisms from the oropharynx into the lungs.

Invasive procedures such as endotracheal intubation, central venous or arterial cannulation and insertion of urinary catheters disrupt natural barriers, facilitating colonization and infection, whilst parenteral nutrition is a well-recognized source of bloodstream invasion [14]. Skin infections occur most commonly at sites of damage due to venepuncture, insertion of intravenous cannulae and bone marrow aspirations or in warm, moist areas such as the groin or axilla. The current aggressive approach to the management of patients with haematological malignancy requires frequent vascular access for blood sampling as well as the administration of drugs, blood products and fluids. The use of large-bore, soft, non-irritant central venous catheters (Hickman) tunnelled subcutaneously greatly facilitates venous access and minimizes

the risk of infection. A dacron cuff placed approximately 2 cm distal to the skin exit site becomes epithelialized and inhibits the spread of organisms along the tunnel from the skin puncture site. Although tunnel infections are uncommon they can be devastating if they do occur. They are most often caused by *S. epidermidis, S. aureus* or Gram-negative bacilli, while infections of the catheter lumen or tip are usually due to *S. epidermidis*, and less frequently, Gram-negative rods or yeasts such as *Candida albicans*.

The incidence of fungal infections in patients with leukaemia has increased [21,81] and is usually related to a prolonged period of neutropenia combined with suppression of the normal bacterial flora by broad-spectrum antibiotics. Fungi are also an important cause of septicaemia and pneumonia in bone marrow transplant recipients. The majority of fungal infections in cancer patients are caused by organisms such as *Candida* and *Aspergillus* spp. which seldom cause infection except in those with compromised host defence mechanisms. Infection with fungi capable of infecting normal hosts, such as *Cryptococcus neoformans* and *Histoplasma capsulatum*, is probably no more frequent in those with malignant disease than in the general population. When it occurs, however, infection is more likely to be severe and widely disseminated [21].

Impaired cellular immunity, as occurs in lymophoproliferative disorders, chronic leukaemia and after marrow transplantation, is classically associated with infection by unusual bacteria such as *Listeria monocytogenes*, some species of *Salmonella, Mycobacterium tuberculosis, Legionella pneumophila* and *Nocardia asteroides*. There is also an increased risk of infection with fungi (*Cryptococcus neoformans, Histoplasma capsulatum* and *Coccidioides immitis*), viruses (cytomegalovirus (CMV), herpes simplex and varicella zoster), Protozoa (*Pneumocystis carinii* and *Toxoplasma gondii*), and the helminth *Strongyloides stercoralis*. Of these by far the most common are *Pneumocystis carinii* and varicella zoster.

Humoral immune dysfunction, also seen in chronic leukaemia and marrow transplant recipients, renders the patient susceptible to infection with encapsulated bacteria (*Pneumococcus, Haemophilus influenzae* and *Neisseria meningitidis*) as well as enteric Gram-negative bacilli and *Pseudomonas* spp.

Sites of Infection

The commonest sites of infection are the lung, mucosal surfaces (including oral and perirectal mucosal lesions) and disseminated infections [23] with bacterial or fungal septicaemia [13,33, 119,158]. Infections of the central nervous system are unusual except in those with impaired cell-mediated immunity, who may develop cryptococcal meningitis, but they may occur secondary to a generalized bacteraemia (especialy due to *S. aureus*) or fungaemia. Genitourinary infections are also infrequent except in the elderly, those with urinary catheters in place or patients with pelvic tumours.

Prevention of Infection

The high risk of infection in neutropenic patients with leukaemia has prompted the development of a variety of techniques designed to reduce the patient's endogenous microbial flora, minimize the acquisition of new pathogenic organisms, and decrease the incidence of infection. The most comprehensive approach is the "total protected environment (TPE)" in which the patient's gastrointestinal tract is decontaminated with oral non-absorbable antibiotics, as well as skin antiseptics, and antibiotic sprays/ointments are applied to all body orifices. The patient is isolated in a laminar air-flow room (LAFR), foods are sterile or semi-sterile and all who enter the LAFR wear sterile garments. Although the use of a TPE can significantly reduce the incidence of infection [157] virtually all patients will still require antibiotics at some stage during their period of neutropenia [129] and its long-term benefits remain to be determined. Moreover, this technique is costly, cumbersome to maintain and service, and patient compliance, particularly with the unpalatable oral non-absorbable antibiotics, is poor. Finally antibiotic-resistant organisms have emerged and present regimes afford no protection against latent organisms such as CMV [129]. Less vigorous protective isolation using a single room, mask, gown and gloves offers no significant benefit over careful handwashing in preventing the acquisition of new organisms and does not reduce the incidence of infection or improve survival [118].

The administration of oral non-absorbable antibiotics (e.g. gentamicin, vancomycin and nystatin) to decontaminate the gastrointestinal tract has been suggested as a means of reducing the patient's endogenous flora and preventing

infection. Unfortunately, when used alone this technique is of limited efficacy and has been associated with the emergence of aminoglycoside-resistant organisms [118]. Selective decontamination of the alimentary canal involves the use of antibiotics such as polymyxin B, nalidixic acid, amphotericin and trimethoprim–sulphamethoxazole to eradicate aerobes while preserving the anaerobic organisms which confer "colonization resistance" [189]. The results achieved with this method are more encouraging [64], although not all potential pathogens are suppressed and infections are not entirely eliminated; moreover, it is both labour intensive and expensive [129]. Reports of the efficacy of antimicrobial prophylaxis with systemically absorbed agents such as trimethoprim–sulphamethoxazole have been conflicting [65,129]. Antifungal prophylaxis with agents such as 5-fluorocytosine or ketoconazole is used in some centres, whilst acyclovir has been used successfully as prophylaxis against herpes simplex infections in bone marrow transplant recipients [149,199].

Prophylactic granulocyte transfusions may be an effective means of reducing the incidence and severity of infection in neutropenic patients [38,143], although in some studies the results have been inconclusive [196]. This approach is, however, limited by a number of logistic and medical problems and is therefore no longer recommended [86]. In particular there appears to be a higher risk of CMV infections and an increased incidence of alloimmunization in recipients of prophylactic as opposed to therapeutic granulocyte transfusions [195]. Alternative techniques for enhancing host defence mechanisms have included active immunotherapy using vaccination with *Pseudomonas* aeruginosa, pneumococcal polysaccharide, CMV, hepatitis and influenza. In general this approach has proved ineffective [202] probably because many chemotherapeutic agents suppress the antibody response to primary antigens [21,129]. Passive immunotherapy has therefore been attempted using *Pseudomonas* antiserum, hyperimmune globulins and antiserum to core glycolipid of Gram-negative bacteria (J-5.antiserum). There is some evidence that prophylactic administration of J-5.antiserum can reduce the incidence of infection in neutropenic patients with leukaemia and lymphoma [21]; intravenous immune globulin may help prevent CMV infection and interstitial pneumonia after bone marrow transplantation [198]. In two recent studies, prophylactic administration of immune globulin has been shown to have a protective effect against bacterial infections when used in high-risk groups [35,148].

Once the patient has been admitted to the intensive care unit measures to prevent infection which have been instituted on the ward, for example selective microbial suppression, should in general be continued. Simple protective isolation is of no value and TPE is usually impractical but careful attention to handwashing and good housekeeping is essential. Invasive procedures should be used only when clearly indicated. We have not hesitated to use invasive monitoring when indicated but would stress that strict attention to an aseptic technique and meticulous care of all intravascular cannulae, skin puncture sites and infusion lines is essential. Similarly in many of those requiring intensive care endotracheal intubation and mechanical ventilation is unavoidable and it has to be accepted that this further increases the risk of nosocomial pneumonia.

Approach to the Diagnosis of Infection

The diagnosis of infection in neutropenic patients can be extraordinarily difficult. Characteristically the classical signs and symptoms (except fever which is almost invariably present and is the best early sign) are absent because the patient is unable to mount an adequate inflammatory response. For example, the majority of those with pneumonia and a neutrophil count of $>1 \times 10^9$/litre will produce purulent sputum, whereas in the presence of severe neutropenia ($<100/mm^3$) less than 10% of patients will do so [166]. Moreover, cough is usually minimal or absent, the appearance of physical signs is delayed and the chest X-ray often initially appears normal [187]. The demonstration of arterial hypoxaemia in a toxic patient is often the first clue that the origin of infection is the lungs. Urinary tract infection may not be accompanied by pyuria and meningitis may be clinically silent. Finally it is important to appreciate that in these patients an apparently minor infection, for example, perianal cellulitis with minimal erythema and tenderness, may produce bacteriaemia with fever and chills.

In the neutropenic patient, therefore, a presumptive diagnosis of infection is made on the basis of a fever of more than 101 °F (38 °C) for more than 4 h, clinical signs of infection, or both. Temperatures above 104 °F (40 °C) are almost invariably due to infection. Occasionally

infection may be present in an afebrile patient, particularly in those receiving corticosteroids.

Immediately infection is suspected particular attention should be directed to the common sites of infection, such as the lungs, oropharynx, anorectal region and skin. Examination of the optic fundi may rarely reveal *Candida* endophthalmitis in patients with candidaemia [52]. Investigations should include three blood cultures for aerobic, anaerobic and fungal organisms, and a chest X-ray. Some recommend routine culture of sputum at this stage, obtained if necessary by transtracheal aspiration, and this should certainly be performed in patients with symptoms, signs or chest X-ray appearances of pulmonary involvement. In some cases, bronchoscopy and bronchoalveolar lavage is indicated. Culture of urine and pharyngeal swabs should be performed when symptoms are suggestive of infection in these sites. Aspiration or biopsy specimens should be taken from suspicious mucosal or skin lesions and lumbar puncture should be performed if there is a possibility of central nervous system involvement. Indwelling cannulae should be removed and their tips sent for culture. An exception can be made for Hickman cannulae which rarely become infected and are often the sole means of reliable intravascular access; removal of these can be deferred until the results of cultures of blood obtained both from a peripheral vein and through the cannula are available. Arterial blood gas analysis should be performed in those with tachypnoea.

Sporadic cases of Legionnaire's disease have been reported in immunocompromised hosts and such patients are at increased risk of acquiring the infection during specific hospital-associated epidemics [150]. The diagnosis can be established by direct fluorescent antibody staining of lung tissue, bronchial washings or transtracheal aspirates or by culturing the organism from lung tissue, blood or pleural fluid.

The diagnosis of *Clostridium difficile* enterocolitis is suggested if the organism is isolated from faecal specimens, although a definitive diagnosis requires demonstration of the toxin, and its neutralization by appropriate antitoxin, in a cell culture assay or by counter immunoelectrophoresis.

Although the majority of infections in patients with malignant disease are bacterial, other causative organisms must be excluded. When fungal infection is considered a possibility the difficulty is to differentiate colonization from invasive disease. Only 25%–30% of patients with disseminated fungal infection have positive blood cultures for yeasts [20] and alternative diagnostic techniques are being evaluated. The diagnosis of visceral candidiasis can in some cases be made ante-mortem by demonstrating a rise in anti-*Candida* antibody titres [134]. Unfortunately false-positive results are quite common and in about half of those with documented visceral candidiasis there may be no detectable antibody response [134]. Moreover, 70% of patients with acute leukaemia have been found to have agglutinating antibodies in their serum [134], which is similar to the percentage of normal subjects found to have anti-*Candida* agglutinins in their serum. Lastly the need for serial determinations of *Candida* antibody introduces a significant delay in initiating treatment. Attempts have therefore been made to detect *Candida* antigens or metabolites by a variety of methods. In a prospective study of the use of a latex agglutination technique for the early diagnosis of systemic candidiasis, Matthews and Burnie [105] were able to demonstrate the presence of *Candida* antigen in 75% of neutropenic patients with systemic infection; in 50% blood cultures were positive and in 25% both were negative. The clinical relevance of these findings remains to be determined.

Invasive aspergillosis nearly always involves the lungs, but less than 10% of patients in whom *Aspergillus* species is isolated from the sputum have invasive disease [51]. The diagnosis of invasive infection can be made on the basis of seroconversion using an immunodiffusion antibody test but this takes three days and again false negatives occur due to failure of an antibody response [51]. A rise in antibody titres may also occur with local infections and in colonized patients. A test for *Aspergillus* antigen is not yet available.

Viral infections may be diagnosed from the clinical presentation, for example the appearance of characteristic skin lesions in varicella zoster, and can be confirmed serologically or by demonstrating the virus in tissue specimens or body fluids. Hepatitis continues to be a serious problem in leukaemic patients and when transmitted by transfusion is associated with a higher mortality in patients with cancer [21,59]. Serological tests are available for type A and type B hepatitis, but "non-A non-B" viral hepatitis also occurs. Herpes simplex virus infections can be diagnosed by culturing the virus from the vesicles, by detecting multinucleated giant cells in scrapings from the skin lesions or by

serological methods. Similarly, in varicella zoster infections scrapings of biopsies of suspected lesions will show classic multinucleated giant cells indicating herpetic infection. The virus can also be isolated and the diagnosis can be confirmed serologically, although only retrospectively. CMV can easily be recovered from urine or saliva and its presence in stool specimens may indicate disseminated disease [21]. Serological diagnosis is also possible.

Until recently the definitive diagnosis of infection with *Pneumocystis carinii* could only be made by demonstrating the organism in lung tissue, since, although it is possible to demonstate antibodies to *P. carinii* in serum, these methods are unreliable in immunocompromised patients. It is now possible to detect the parasites in sputum or bronchoalveolar lavage fluid using monoclonal antibodies and immunofluorescence, a technique which seems to be highly sensitive and more specific than standard methods [45,89].

Principles of Treatment

Unless appropriate antimicrobial therapy is instituted promptly, death may occur within 24 h [21]. Empirical broad-spectrum antibiotic therapy must be initiated whenever a neutropenic patient develops a fever, unless there is an obvious non-infectious cause. This approach dramatically reduces the morbidity and mortality [103,131]. A combination of two or three agents is usually required to cover the range of potential pathogens and the combination should be both bactericidal and synergistic [6,21,92,129], with a low risk of organ toxicity. The chosen antibiotic combination should be administered intravenously and in full dosage, unless modification of the dose is indicated.

The choice of antibiotic regime depends on the organisms known to be prevalent at a particular institution and their sensitivity patterns, but will usually consist of an aminoglycoside plus either an antipseudomonal penicillin or a cephalosporin [87]. The commonly used aminoglycosides (gentamicin, tobramycin, amikacin, netilmicin) are of equal efficacy, but gentamicin is the least expensive. There is, however, some evidence that tobramycin is less nephrotoxic than gentamicin [132,174] and since neutropenic patients may require prolonged and repeated courses of aminoglycosides some clinicians prefer this agent. Amikacin is indicated when there is concern about resistance to the other aminoglycosides. The initial dose of aminoglycoside should be calculated using a nomogram, taking particular account of renal function, and should then be monitored by measuring blood levels. At the authors' institution initial empirical therapy consists of gentamicin and ceftazidime. If the patient remains pyrexial and unwell, further daily blood cultures and chest radiographs are performed, and if there is no microbiological confirmation of infection the antibiotic regime is re-evaluated after 48 h.

Subsequently the antibiotic presciption may be modified according to the results of cultures and sensitivities to a more specific, less toxic and less expensive combination. Many clinicians, however, would be reluctant to alter a combination which has produced resolution of fever and clinical improvement, regardless of the culture results. Duration of antimicrobial therapy is influenced by a number of factors. In those with an infection which has been documented clinically and/or microbiologically, and whose fever has remitted in response to treatment, antibiotics should be continued until the infection has clearly resolved, the patient has been afebrile for at least 48 h and treatment has been given for a total of five days or more. For those patients with only equivocal evidence of infection, but who have apparently responded to empirical treatment, antibiotics should be continued for four to five days after the patient has become afebrile. Some authorities recommend continuing antibiotics until the granulocyte count has recovered to greater than 1×10^9/litre [130], although others suggest that antibiotics can be stopped in selected cases, provided they are reinstituted immediately if fever recurs or the patient deteriorates [83].

A particularly difficult problem is the patient in whom it proves impossible to identify an infection and who fails to improve despite an apparently optimal antibiotic regime. In such cases some authorities suggest instituting empirical antifungal therapy with amphotericin B after a seven-day trial of antibiotics [132]. They suggest that amphotericin B should be administered together with antibiotics until the granulocyte count has increased to greater than 5×10^9/litre. If there is no evidence of fungal infection both antibiotics and amphotericin B can then be discontinued. However, the incidence of fungal infection varies considerably between different institutions, and from time to time in individual hospitals, and because treatment with amphotericin can be associated

with serious toxicity this recommendation is controversial.

White Cell Transfusions

Opinions still vary as to the role of granulocyte transfusions in the management of established infection in the neutropenic patient. Some recommend that they should be considered in patients with an absolute neutrophil count of less than or equal to 500 cells/mm^3 who have failed to respond within three days to antibiotics [21,26,108], while others no longer routinely use this form of treatment [129]. Although a number of early studies concluded that granulocyte transfusions were beneficial in patients with Gram-negative bacteraemia if the duration of their granulocytopenia exceeded one week [3, 72] only small numbers of patients were enrolled and varying definitions of bacteraemia and infection were used. A more recent prospective, randomized, controlled study in neutropenic patients with documented infection found no differences in either the successful treatment of infection or survival [53,197]. There are a number of possible explanations for these conflicting results. First, improvements in the use of antibiotics and supportive care have reduced the incidence of infection-related mortality, making it more difficult to demonstrate significant benefits from granulocyte transfusion [129]. Second, the potential advantages of granulocyte transfusions are diminished by technological difficulties such as the relatively small number of cells which can be collected, the reduction in their survival time which can result from alloimmunization and the adverse effects of filtration leukophoresis and radiation (given to prevent graft versus host disease) on granulocyte function [129]. Administration of granulocytes can also be associated with complications. These include alloimmunization to leucocytes and to other blood products and patients may, for example, become refractory to platelet transfusions [154]. Granulocyte transfusions can also cause pulmonary damage and, as well as the risk of leucoagglutinin reactions, patients receiving prophylactic granulocytes have a higher incidence of unexplained pneumonitis [53,178]. Moreover the combination of amphotericin B and leucocyte transfusion has been implicated as a cause of a lethal pulmonary reaction, characterized by hypoxaemia and new pulmonary infiltrates [201]. Finally there is a danger that leucocyte transfusions will transmit infection, for example *Toxoplasma gondii* and CMV [71]. We do not use granulocyte transfusions either prophylactically or for the treatment of documented infection.

Stimulation of Marrow Recovery

The characterization and production of human haemopoietic growth factors by recombinant DNA technology has led to numerous studies assessing their potential importance in haematopoiesis, particularly where leucopenia is a problem [8a,27,41a,53a,62a,108a,186a].

Granulocyte macrophage colony-stimulating factor (GM-CSF) was one of the first colony-stimulating factors to be tested in clinical trials in a variety of disease states and has been demonstrated to be active in leucopenic patients, causing dose-dependent increases in circulating neutrophils as well as monocytes and eosinophils [8a,186a]. Yet despite this leucocytosis, not all studies have demonstrated clinical efficacy in reducing infective complications [8a,41a]. On the other hand, Brandt et al. [24] and Nemunatis et al. [120a] reported a significant reduction in infections in groups treated with GM-CSF following intensive chemotherapy or radiotherapy and autologous bone marrow transplantation, compared with historical controls. The efficacy of the GM-CSF was dose dependent [120a]. A reduction in neutrophil migration by GM-CSF has been reported in vitro [54a] and in vivo [1a], with speculation that this may hamper activated neutrophils from getting to the site of infection.

Granulocyte colony-stimulating factor (G-CSF) has also been demonstrated to ameliorate neutropenic infections in patients being treated with aggressive chemotherapy for small cell carcinoma of the lung [27].

Further trials evaluating the role of G-CSF, GM-CSF and interleukin 3 (IL3) in cancer chemotherapy are currently in progress.

Passive Immunization. Attempts have been made to control those infections which respond poorly, if at all, to conventional agents by passive immunization. In immunosuppressed patients CMV frequently causes a severe illness with pneumonitis, which is fatal in some 85% of cases [110]. It has been observed that patients who seroconvert and develop a rising antibody titre to CMV following bone marrow transplantation have an increased duration of survival and lower mortality [62,137]. CMV immune globulin has, therefore, been administered to patients with documented CMV infections [66] but with

conflicting results. Although Blacklock et al. [18] reported an increased survival rate of 50% when CMV pneumonia was treated in this way, Reed et al. [137] were unable to repeat these observations in 14 marrow transplant recipients.

Passive immunization against other organisms, such as *Haemophilus influenzae* and *Pseudomonas*, is currently under investigation [46,126].

Septic Shock

Hypotension is second only to respiratory failure as a cause of admission of cancer patients to the intensive care unit. Although in a few cases the fall in blood pressure is precipitated by non-infectious complications such as gastrointestinal haemorrhage or cardiac failure, by far the most frequent diagnosis is septic shock [7,100,159, 186]. In our series of 60 patients with haematological malignancy, a total of 39 had septic shock, most often in association with respiratory failure [101], and in a group of adult patients dying with acute leukaemia the overall incidence of fatal bacterial septicaemia was 47% [33]. The commonest source of infection is the lungs [33]. In some cases the site of infection cannot be identified.

The principles governing the management of septic shock complicating malignant disease are the same as those for patients without cancer and appropriate treatment is similarly dependent on the percutaneous insertion of a number of intravascular cannulae.

The risks of invasive techniques, particularly infection and haemorrhage, are especially high in patients with malignant disease. The incidence of complications can be reduced if the procedures are performed only by experienced personnel using strictly aseptic techniques. The danger of serious haemorrhage can be minimized by prior administration of fresh frozen plasma and/or platelet concentrates as indicated and by puncturing the smaller peripheral arteries and veins where bleeding is most easily controlled. It is often possible to insert central venous and pulmonary artery catheters via a vein in the antecubital fossa. Failing this the internal jugular vein should be used for central venous access since direct pressure can be applied if there is venous bleeding or if the carotid artery is accidentally punctured. In the author's opinion the subclavian approach should be avoided since pressure cannot be applied effectively in the event of haemorrhage. Traditionally cannulation of the femoral vessels is thought to be associated with an increased risk of infection, although this may not in fact be the case [181] and we have occasionally used this route as a last resort. In practice serious complications related to percutaneous vascular cannulation are unusual [100] and one institution reported only two in a series of 150 leukaemic patients with respiratory failure who had complications related to invasive procedures [30]. In our view the benefits far outweigh the risks.

New Pulmonary Infiltrates

Infectious Causes

The lung appears to be particularly susceptible to infection during periods of immunosuppressive chemotherapy [50,124]. In one autopsy series of patients with leukaemia or lymphoma 79% died of infection, 43% of deaths resulted from pneumonia, and the lungs were the most common source of infection in the 53% who died with disseminated sepsis [95]. Moreover, mortality rates are high when these patients develop lung infiltrates. Pennington and Feldman [124] reported that the development of new pulmonary infiltrates and fever in neutropenic patients with haematological malignancy was associated with a mortality of 62%, whereas in a matched group of patients with fever and neutropenia alone mortality was only 9%. Similarly pneumonia is a common complication of bone marrow transplantation, occurring both early and late after engraftment, and is also associated with a high mortality [50,91]. The more widespread use of aggressive chemotherapy for the treatment of solid tumours has led to an increased incidence of pulmonary complications in these patients.

Bacterial Pneumonia

The development of pulmonary infiltrates in a febrile patient is usually due to bacterial infection [124,167,187]. Most frequently Gram-negative organisms such as *Klebsiella* spp., *Pseudomonas*, *E. coli*, *Proteus* and *Serratia* are responsible, whilst of the Gram-positive organisms staphylococci are most commonly isolated. Pneumococcal pneumonia is unusual in this population but does occur with increased frequency in asplenic and hypogammaglobulinaemic patients. Occasionally pulmonary infiltrates may be caused

by infection with *Legionella pneumophila* or, in those with depressed cellular immunity, the opportunistic bacterium *Nocardia asteroides*. Another unusual cause is tuberculosis, which occurs most frequently in those with lymphoproliferative disorders, neoplasms of the lung or tumours of the head and neck. Administration of steroids and other immunosuppressive agents not only predisposes to tuberculous infection but can also delay diagnosis by suppressing symptoms.

The clinical manifestations of pneumonia, such as cough and sputum production, are often unimpressive or absent. The chest X-ray is frequently normal initially [187], and when present radiographic changes consist of patchy, multilobar, alveolar-type infiltrates rather than consolidation or lobar pneumonia; cavitation is unusual. Pleural effusions, seen in one-third of patients, are typically small and empyema is rare [187].

In immunocompromised hosts antibiotic therapy may achieve a cure in approximately two-thirds of cases of Gram-negative pneumonia [187]. In patients with Legionnaire's disease who fail to respond to oral erythromycin, a change to intravenous administration, sometimes with the addition of rifampicin, may produce a response [150].

Fungal Pneumonia

Classically fungal pneumonia develops during, or immediately after, a course of broad-spectrum antibiotics. In immunocompromised patients it is associated with a greater than 90% mortality [50]. *Aspergillus* is the commonest cause of fungal pneumonia in these cases [81] and produces a fulminant necrotizing pneumonia with haemorrhagic pulmonary infarction [50]. Chest X-ray appearances are those of bronchopneumonia or consist of scattered patchy infiltrates. Sometimes nodular densities, lobar consolidation or occasionally the diffuse reticular pattern of interstitial infiltration may be seen. Areas of consolidation usually cavitate and crescentic radiolucencies may develop within or around parenchymal densities [50,173]. Invasion of the lungs by *Mucor* produces an identical clinical picture to that caused by *Aspergillus* infection. Primary *Candida* pneumonia is rare in immunocompromised patients [95,124] and a positive sputum culture most often reflects colonization of the oropharynx rather than pulmonary infection, although the lung may be involved along with other tissues in those with disseminated candidaemia. Cryptococcal pneumonia usually occurs in those with defective cell-mediated immunity and is a much less common cause of pulmonary infection than *Aspergillus*. The chest X-ray most often shows single or multiple nodules, with or without cavitation, although well-defined consolidation or diffuse interstitial or miliary infiltrates may also occur.

Pneumocystis carinii Pneumonia

Infection with this protozoan appears to be limited to the lungs, and is the commonest parasitic infection in immunocompromised hosts [50]; in one series of such patients *Pneumocystis* pneumonia was the single most frequent cause of diffuse pulmonary infiltrates [170]. In other centres, *Pneumocystis* pneumonia is less common [124]. It has been shown in children with acute leukaemia that the incidence increases in relation to the intensity of the chemotherapy [80].

The clinical presentation is a diffuse pneumonia producing severe hypoxaemia. The chest X-ray shows bilateral patchy reticular shadowing which progresses over three to five days to more homogeneous alveolar consolidations, often with air bronchograms. Typically, infiltrates are perihilar and radiate into both lung fields, an appearance which, in conjunction with extreme respiratory distress, may be mistaken for pulmonary oedema [79].

There is some evidence that subclinical pulmonary infestation with *Pneumocystis* may occur, even in normal hosts [50], and it has been suggested that infection with *Pneumocystis* is virtually universal in children by the age of 2 years [109]. It is possible, therefore, that some may be carriers of *Pneumocystis* and that invasive disease occurs when immune responses are impaired. Although airborne transmission of *Pneumocystis* has never been demonstrated in man, it can occur in laboratory animals and in view of reports of clusters of cases in hospitalized patients [169] some recommend that those with *Pneumocystis* pneumonia should be isolated from other immunosuppressed patients.

Viral Pneumonia

Viral infections are an uncommon cause of pneumonia in patients with malignant disease, with the exception or recipients of bone marrow transplants [120]. The commonest cause is CMV and in one series accounted for about half of the interstitial pneumonias occurring during the

first three months following bone marrow transplantation [120,137]. Typically CMV pneumonia is interstitial, bilateral and symmetrical, although in the early stages it may involve only the periphery of the lower lobes and subsequently extend upwards and centrally. Hypoxaemia is common. Mortality in bone marrow transplant recipients who develop CMV pneumonia can be as high as 50% [120].

Non-infectious Causes

Radiation Pneumonitis

This develops approximately eight weeks following completion of a course of radiotherapy and may be difficult to distinguish from an infectious cause of pulmonary infiltrates [63]. The patient is often febrile, with a non-productive cough, and the chest X-ray appearances are non-specific, although the lung shadowing may have relatively sharp margins which do not correspond to anatomical boundaries. Unilateral radiotherapy is almost never responsible for bilateral pulmonary infiltrates, although it has been described [15].

Cytotoxic Drug-Induced Lung Disease

Diffuse, bilateral interstitial inflammation of the lungs may be caused by a variety of cytotoxic agents, bleomycin, methotrexate, busulfan, carmustine, lomustine and procarbarzine [193]. There is some evidence that the lung injury from radiation or high alveolar O_2 tensions may predispose to pneumonitis caused by cytotoxic agents [57], and, in the case of bleomycin, may be in part dose related [55]. In most cases, however, cytotoxic-induced lung damage is idiosyncratic and unpredictable. Fever is common and the chest X-ray shows diffuse linear or reticulonodular infiltrates, often mixed with areas of alveolar filling.

Malignant Lung Disease

Lymphangitic spread of the malignant process will produce diffuse, bilateral, basal interstitial infiltrates which may be difficult to distinguish from CMV or *Pneumocystis* pneumonia. Metastatic spread of lymphoma or carcinoma to the lungs produces single or multiple nodules, with or without cavitation, the appearances of which may be similar to cryptococcal or nocardial abscesses.

Pulmonary Leukostasis

Pulmonary leukostasis may occur in patients with uncontrolled leukaemia and white blood cell counts in excess of 100×10^9/litre. It produces diffuse bilateral pulmonary infiltrates.

Pulmonary Haemorrhage

Pulmonary haemorrhage may occur in the absence of frank haemoptysis and should be suspected only in those with marked thrombocytopenia (platelet count $<20\,000/mm^3$) usually accompanied by a clinically obvious bleeding tendency.

Pulmonary Oedema

The radiographic appearances of pulmonary oedema can be difficult to distinguish from those of an infectious process, although the diagnosis can usually be made on the basis of the clinical features and the response to diuretics.

Non-specific Interstitial Pneumonitis

This is a histological diagnosis made when all special stains and cultures of biopsy material are negative and the pulmonary abnormality cannot be attributed to any of the causes described.

Invasive Diagnostic Procedures

Standard diagnostic procedures, including transtracheal aspiration, often fail to establish the aetiology of lung disease in immunosuppressed patients [124], particularly in those with diffuse bilateral involvement. In one series the diagnosis was established by cultures of sputum and blood in only 33% [170]. Thus if the patient fails to respond to empirical antimicrobial therapy more invasive diagnostic measures are often undertaken. These may involve percutaneous needle aspiration, needle biopsy, trephine drill biopsy, transbronchial lung biopsy or open lung biopsy. The choice depends on the patient's general condition, the location and type of the infiltrate, the nature of the underlying disease, the expected diagnostic yield, the complication rate and local expertise. The hazards of such procedures are increased in many patients with malignant disease because of associated prob-

lems such as thrombocytopenia, coagulopathy, poor lung function and impaired tissue healing [61]. The risks can, however, be minimized by the prior administration of platelets and the use of supplemental O_2 [124].

Percutaneous needle aspiration using a thin-walled 18G needle can provide uncontaminated lung tissue for microbiological and cytological examination. A specific diagnostic yield of 35% has been reported for needle aspiration [61], although others have claimed that, when performed with fluoroscopic guidance in patients with focal or localized pulmonary lesions suspected to be infectious, a positive diagnosis can be made in as many as 70% of cases [11,32]. The patient must be sufficiently alert and co-operative to be able to stop breathing for 5-s periods while the needle is advanced into the lesion. A 26% incidence of pneumothorax has been reported [32], although significant haemoptysis is unusual.

Percutaneous biopsy, either with a cutting needle or a trephine, provides a core of tissue and the diagnostic yield is higher. Unfortunately, the use of a cutting needle has been associated with an unacceptably high incidence of serious haemoptysis, especially in those with thrombocytopenia [11], and the complication rate with trephine air drills, in particular pneumothorax, is significantly higher than with other techniques [39].

Transbronchial biopsy is relatively safe and effective for establishing the aetiology of lung infiltrates and avoids the need for open thoracotomy [5,104,124]. Adequate tissue can be obtained in over 90% of cases and diagnostic information is provided in 70%–80% of both localized and diffuse infiltrates [50]. Nevertheless, sampling errors and false negatives may occur. In particular the biopsy may show only "non-specific interstitial pneumonitis" in nearly half the cases and this may be falsely negative for specific aetiologies such as infection in 20%–50% of instances [50]. The diagnostic yield may be increased by combining transbronchial forceps biopsy with bronchial brushings [50, 104]. Cunningham et al. [39] reported a yield of 74% with forceps biopsy but only 28% with brush biopsy. Mattay et al. [104] found similar yields of 63% and 68% for the two techniques individually, and 84% when the procedures were combined. Previously contamination of the lumen of the bronchoscope during its passage through the upper airways complicated interpretation of the results of culture but this can now be avoided by protecting sampling catheters and brushes with telescopic catheters with distal plugs [194].

The incidence of haemorrhage following fibreoptic bronchoscopy with transbronchial lung biopsy is low, provided thrombocytopaenic patients receive a platelet transfusion before the procedure [104,124]; uraemic patients are more likely to bleed [39]. The risk of pneumothorax is acceptably low [104,124] and can be further minimized by using fluoroscopy [104]. A pneumothorax may, however, precipitate respiratory failure and admission to the intensive care unit [101]. There is a danger of hypoxaemia during the procedure and supplemental O_2 must be administered [104,124].

Open lung biopsy via a limited thoracotomy is recommended when transbronchial biopsy fails to produce a diagnosis or is contraindicated (uncorrectable hypoxaemia, bleeding disorders) and when a definitive diagnosis must be established with the first procedure [36,177]. A specific diagnosis such as *Pneumocystis* pneumonia or leukaemic infiltration can be established in about 70% of immunosuppressed patients with pulmonary infiltrates [61,93], while a non-specific interstitial pneumonitis is found in the remainder [93]. Morbidity and mortality attributable to the procedure is low [93,106,152]. In one series [93] pneumothorax was seen in 7%, but there were no cases of persistent air leak; wound dehiscence and haemoptysis each occurred in only one patient (2%). Prolonged mechanical ventilation was required for respiratory failure, which was present preoperatively in 14 of 42 patients. Although the deaths of two patients might have been hastened, none could be directly attributed to the procedure. Other reported complications include bronchopleural fistula [152], pneumonia developing in association with recurrent pneumothoraces [152] and wound haematoma [106].

Once a patient with acute respiratory failure has been admitted to the intensive care unit it usually proves extremely difficult to establish the diagnosis [48]. In one series of such patients the diagnostic yield of both serology and transbronchial biopsy was negligible, although the diagnosis was made in three of the four patients in whom open lung biopsy was performed [48]. In mechanically ventilated patients with respiratory failure open lung biopsy is not only the most reliable means of establishing the diagnosis with minimal delay, but is also the safest technique. Although there is a significant risk of pneumothorax, haemostasis can be secured under direct vision, and with the use of auto-

matic stapling devices the likelihood of postoperative intrapleural haemorrhage is negligible [93].

In many cases the results of biopsy will have an important influence on patient management. For example, failed treatment of the underlying disease or the presence of pulmonary fibrosis related to drug treatment may be established [152] and specific diseases may be excluded, avoiding the use of toxic agents [93]. In some patients a specific diagnosis leads to the institution of life-saving therapy [50]. Overall when the diagnosis is determined by open lung biopsy therapy may be altered in as many as one half of the patients [145]. Nevertheless, clinicians are often reluctant to alter drug regimens when open lung biopsy fails to provide a definitive diagnosis, in some cases the results of biopsy may be misleading, the reliability of a nonspecific diagnosis is uncertain and it cannot be assumed that when an organism is detected it is the only infective agent present [106]. Moreover, identifying the aetiology of lung infiltrates does not guarantee improved survival [145] and there is some doubt whether open lung biopsy improves either the quality or quantity of life for this specific population [106]. An empirical approach to the treatment of pulmonary infiltrates may therefore be preferred in those patients in whom the risks of invasive diagnostic procedures is considered too high [192].

More recently bronchoalveolar lavage, a technique in which sterile saline is introduced into the lungs via a fibreoptic bronchoscope in order to obtain secretions, cells and protein from the lower respiratory tract, has been used successfully to diagnose opportunistic pulmonary infections [114]. Milburn et al. [111] used this technique to evaluate interstitial pneumonitis in recipients of bone marrow transplants and found it to be safe and effective in establishing a rapid diagnosis of *Pneumocystis carinii*, fungal and CMV infections. The advent of monoclonal antibody detection of *Pneumocystis carinii* infections has further improved the diagnostic efficiency of bronchoalveolar lavage [45,89].

Respiratory Failure

In one series of patients dying with neoplastic disease respiratory failure was the primary cause of death in 19% and respiratory insufficiency (including aspiration) was a contributory factor in a further 3% [4]; respiratory failure is the commonest indication for the admission of patients with malignant disease to an intensive care unit [7,69,82,101,159]. Although respiratory failure does occur in patients with solid tumours, particularly carcinomas of the lung and, less frequently, the breast, it is seen most often in those with haematological malignancies [37,58,175] and is the commonest acute complication of bone marrow transplantation requiring intensive therapy [184].

Causes

By far the commonest cause of respiratory failure in cancer patients is pneumonia [48,101, 159,175]. Non-infectious causes include chemotherapy-induced lung damage [55,193], radiation pneumonitis [63], infiltration of the lungs with tumour cells, intrapulmonary haemorrhage and pulmonary embolus. Tracheobronchial compression by tumour can produce life-threatening airway obstruction requiring mechanical ventilation and this is often precipitated by diagnostic surgical procedures, such as mediastinotomy, performed under general anaesthesia. Very occasionally transtracheal aspiration in a patient with a coagulopathy can precipitate uncontrollable haemorrhage with haematoma formation and tracheal compression of sufficient severity to require emergency endotracheal intubation or tracheostomy. In some patients pleural effusions, fluid overload, cardiac failure [159] or the development of a pneumothorax may contribute to the onset of respiratory failure, while others require mechanical ventilation for postoperative respiratory insufficiency.

In many cases patients are admitted to the intensive care Unit with a diagnosis of adult respiratory distress syndrome (ARDS) [69,100, 175] based on the established criteria. The development of this clinical syndrome in cancer patients is most often related to pulmonary infection, systemic sepsis and/or disseminated intravascular coagulation; occasionally pulmonary aspiration is implicated. Some would include radiation pneumonitis, chemotherapy-induced lung damage, diffuse pulmonary infiltration with tumour and extensive intraparenchymal haemorrhage as causes of ARDS. Acute respiratory distress has also been described as a complication of hyperleucocytic granulocytic leukaemias [191]. Many of these patients were somnolent and confused, all had a marked leucocytosis with a high percentage of circulat-

ing blast cells and in every case the onset of respiratory distress was associated with a rapid rise in leucocyte count. Moreover, in those who survived, the regression of symptoms paralleled the reduction in white count. It is postulated that the very high and rapidly increasing white blood count leads to mechanical obstruction of the capillaries by large and rigid leucocytes. This precipitates local tissue hypoxia and an increase in capillary permeability, predominantly in the lungs and nervous system.

ARDS may also follow aggressive chemotherapy and is probably related to the release of a variety of mediators from necrotic tumour cells, sometimes combined with the development of disseminated intravascular coagulation [73]. Often this situation is accompanied by other manifestations of the "tumour lysis syndrome".

Treatment of leukaemia with cytosine arabinoside has been implicated in the development of a frequently fatal non-cardiogenic pulmonary oedema [68]. The mechanism of the increased capillary permeability in such cases is unclear but may be related to tumour lysis and the release of cytoplasmic proteolytic enzymes, or to a direct cytotoxic effect. A significant relationship between the dose used and the development of the syndrome was not apparent [68].

In view of the crucial role attributed to activated granulocytes in the pathogenesis of ARDS it might be anticipated that markedly neutropenic patients would be protected from the development of this syndrome. Ognibene et al. [122] have, however, described 11 patients who fulfilled clinical criteria for the diagnosis of ARDS, despite severe neutropenia preceding the onset of respiratory symptoms. In none of these did pulmonary histology reveal a neutrophil infiltrate and in five there was diffuse alveolar damage without evidence of infectious pneumonitis. Although diffuse lung injury resembling ARDS can occur in leucopenic patients recovery of the white blood cell count may be associated with worsening oxygenation and an increase in pulmonary microvascular permeability [139], a finding consistent with the hypothesis that circulating white blood cells are an important cause of increased capillary permeability in ARDS.

Clinical Presentation and Management

The development of acute respiratory failure (ARF) is usally heralded by unexplained tachypnoea; initially blood gas analysis may show only moderate hypocapnoea but hypoxaemia rapidly ensues. (It is worth noting that in leukaemic patients with an extremely high white cell count the arterial O_2 tension may be falsely lowered by continuing metabolism of white cells after the sample has been obtained. This pseudohypoxaemia can be minimized by immediately placing the sample in ice and by performing blood gas analysis as soon as possible thereafter [34].) Other clinical features may include fever, breathlessness, dry cough, haemoptysis and tachycardia. Chest X-ray abnormalities, usually consisting of interstitial or alveolar infiltrates which rapidly become bilateral, are often delayed for several hours and can precede the onset of ARF by between one and seven days [30,48]. Further deterioration is accompanied by falling lung compliance and worsening hypoxaemia, often resistant to administration of supplemental O_2 via a face mask, as well as increasing respiratory distress. Such patients will require some form of mechanical respiratory support and most will initially respond well to the application of a positive end-expiratory pressure (PEEP) combined with the administration of a high inspired O_2 concentration [30,48]. In a few cases continuous positive airways pressure (CPAP) administered via a face mask or an endotracheal tube may be sufficient, while in others intermittent mandatory ventilation (IMV) proves satisfactory [30]. Those with severe hypoxaemia and very stiff lungs will, however, require controlled mechanical ventilation, often facilitated by heavy sedation and the administration of muscle relaxants. In a few selected cases with reversible unilateral lung disease, selective ventilation may prove life saving [31].

Stringent measures to reduce the risk of superadded pulmonary infection must be adopted. Patients with malignant disease who develop acute respiratory failure are more susceptible to sepsis than those without cancer [37] and pneumonia is commonly associated with septicaemia. In our series 50 of 60 patients with haematological malignancy admitted to the intensive care unit were in respiratory failure; nine had pneumonia alone, three pneumonia complicated by pneumothoraces which had occurred after endoscopic transbronchial biopsy and 34 had both pneumonia and septicaemic shock. Although the patient may be admitted with respiratory failure death is usually associated with progressive and intractable hypotension [159], often accompanied by coagulation disorders, acidosis and multiple organ failure

[48]. Indeed in as many as 50% of cases sustained sepsis leads to haemodynamic deterioration within 24–48 h of the onset of respiratory failure and the response to supportive measures is then often disappointing [30]. Leukaemic blast cells can produce large amounts of lactic acid and this may exacerbate the acidosis which often accompanies shock and hypoxia.

When patients with airway obstruction due to tumour compression require mechanical ventilation a long expiratory phase is often necessary to avoid overinflation of the lungs. This may necessitate a slow respiratory rate and a reduced minute volume. Hypercarbia may, therefore, be unavoidable and in such cases heavy sedation and the administration of muscle relaxants is often necessary. Aggressive treatment to reduce the tumour bulk should be initiated as soon as possible. In some cases it may be possible to pass an endotracheal tube beyond a laryngeal or upper tracheal narrowing, thereby relieving the obstruction, and the patient can then continue to breathe spontaneously. An emergency tracheostomy is rarely indicated and is attended by a considerable risk of haemorrhage and infection.

Haemorrhage

Haemorrhage is one of the commonest causes of sudden deterioration particularly in acute leukaemia, where haemorrhage precipitates 16% of admissions to the intensive care unit [47] and at one time contributed to 23% of deaths [33]. In one series of patients with all types of cancer, bleeding was the cause of death in 11% and a contributory factor in a further 25% [4]. The causes of the increased susceptibility to bleeding are summarized in Table 46.1.

Table 46.1. Causes of increased haemorrhagic tendency

Thrombocytopenia
Leukaemia
Bone marrow infiltration
Treatment related
Autoimmune
Platelet sequestration
Platelet function abnormalities
Coagulation factor abnormalities
Disseminated intravascular coagulation (DIC)
Vitamin K deficiency
Liver disease
Drug-induced
Increased fibrinolysis

Platelets

In one series of patients with malignancy, thrombocytopenia with a platelet count of less than 50×10^9/litre was the cause of haemorrhage in 61% of patients and of these 80% had a platelet count less than 20×10^9/litre [33]. Qualitative platelet abnormalities such as decreased platelet aggregation, reduced platelet factor 3 activity and impaired clot retraction may also be present [60], especially in patients with leukaemia. Sequestration of platelets in the spleen may cause severe thrombocytopenia in patients with chronic lymphatic leukaemia and in such cases splenectomy often leads to recovery of platelet counts. Immune thrombocytopenia may occasionally occur, again often in those with chronic lymphatic leukaemia. Treatment with glucocorticosteroids may limit platelet destruction.

Most recommend that platelet transfusions should be given prophylactically if the platelet count is below 20×10^9/litre. Severe haemorrhage can often then be prevented. If invasive procedures are planned when the platelet count is less than 50×10^9/litre, platelets should be given immediately prior to the procedure [92a].

Repeated platelet transfusions may cause immune sensitization, particularly if random, multiple donor platelets are used. In order to reduce sensitization and obtain a better yield, fresh, single-donor platelets may be used. In the event of sensitization, HLA-matched donor platelets may be necessary.

Disseminated Intravascular Coagulation (DIC)

DIC is the second commonest cause of severe, generalized haemorrhage and in one series was responsible for 12% of deaths due to bleeding in leukaemics [33]. DIC may develop either due to the effects of the malignancy itself, especially in those with leukaemia, or as a complication of septicaemia. It is particularly common in patients with acute promyelocytic leukaemia, possibly because the malignant cells produce procoagulant substances. Elevated levels of clotting factors may also be found in these patients and this may exacerbate the situation.

Symptomatic DIC is manifest by bleeding from a variety of sites. Renal failure may develop [60]. Consumption of coagulation factors causes prolonged prothrombin and thrombin times, with a variable effect on the partial thromboplastin time. The fibrinogen level and platelet counts are reduced and fibrin degradation products are increased.

Treatment involves replacing platelets and clotting factors as indicated and controlling the underlying condition. Paradoxically, however, DIC may initially worsen when leukaemia is treated since cell lysis can cause further release of pro-coagulants. Platelet transfusions are given to maintain the platelet count above 50×10^9/litre. Fresh frozen plasma and cryoprecipitate should be infused as indicated to replace consumed clotting factors. In patients in whom haemorrhage is not severe, heparin therapy (5–10 units/(kg/h)) may be instituted in an attempt to control the underlying haemostatic abnormality. In patients with acute promyelocytic leukaemia, heparin therapy has been found to significantly reduce the incidence of fatal haemorrhage [43].

Coagulation Factor Abnormalities

Clotting factor abnormalities are common in patients with acute leukaemia, reduced levels of factors V, VII and X being found in 18%–45% of patients [60,98]. In patients with acute promyelocytic leukaemia, hyperfibrinogenaemia is found in as many as 85% [60]. Conversely, in other types of leukaemias, levels of fibrinogen, as well as other clotting factors, are often elevated. This may induce a hypercoagulable state, predisposing to DIC [98].

Vitamin K Deficiency

Vitamin K deficiency may occur in patients receiving antibiotics which partially or totally sterilize the gastrointestinal tract. There is a reduction in the vitamin K-dependent factors VII, IX, X and prothrombin. The deficiency can be easily corrected by parenteral administration of vitamin K.

Liver Disease

Hepatic production of clotting factors can be impaired in patients with extensive liver metastases or in leukaemics, who often have hepatic dysfunction because of liver infiltration, haemorrhage into the liver substance, cholestasis or following administration of hepatotoxic drugs such as methotrexate [127].

Drugs

Almost all cytotoxic agents can produce bone marrow suppression with significant thrombocytopenia. Moreover, L-asparaginase and vincristine can also produce clotting factor abnormalities, although with the latter they are seldom significant. L-Asparaginase causes a reduction in the synthesis of many clotting factors, especially IX, X, XI and fibrinogen [75], largely due to a generalized decrease in protein synthesis. Other mechanisms may also be involved, however, since the reduction in clotting factors occurs more rapidly than would be anticipated if it were the only cause [60]. If coagulation abnormalities are detected, or haemorrhage occurs, they can be temporarily corrected using fresh frozen plasma or cryoprecipitate. Further deterioration is prevented by discontinuing therapy with L-asparaginase. Vincristine can very occasionally cause hypofibrinogenaemia, by an ill-defined mechanism. Specific therapy is rarely necessary as other clotting factors are not affected [60].

Fibrinolysis

Leucocytes from patients with acute leukaemia release enzymes with fibrinolytic activity, occasionally leading to a haemorrhagic diathesis [60]. Epsilon-aminocaproicacid is an antifibrinolytic enzyme which can curtail this. Great care is needed, however, since with indiscriminate use it can cause a thrombotic tendency.

Metabolic Disturbances

Ectopic Hormone Production

Non-endocrine tumours occasionally produce hormones in large quantities and severe metabolic derangement may result. Many such ectopic hormones have been identified, including adrenocorticotrophic hormone, antidiuretic hormone, parathyroid hormone, insulin and

glucagon [67]. Treatment depends on the hormone being produced and the nature of the underlying tumour.

Tumour Lysis Syndrome

Treatment of sensitive tumours with cytotoxic agents can produce rapid lysis of malignant cells, resulting in severe hyperuricaemia, hyperphosphataemia, hyperkalaemia and acute renal failure [203]. The syndrome is most frequently seen in those with lymphoid malignancies and acute lymphoblastic leukaemia, especially of the Burkitt type [94]. Patients who have very chemosensitive malignancies should be well hydrated and commenced on allopurinol prior to therapy [172], but despite these measures severe metabolic derangements sometimes occur. If vigorous hydration fails to control the abnormalities, haemodialysis may be required, especially if there is progressive hyperkalaemia or if renal failure supervenes.

Hypercalcaemia

Hypercalcaemia is a common complication occuring in up to 10% of patients with malignant disease [115,163]. It is common in those with squamous cell carcinoma of the bronchus, breast cancer and haematological malignancies (multiple myeloma and lymphomas) [117]. Although potentially life threatening it is easily diagnosed and normally reversible.

Hypercalcaemia of malignancy can be subdivided into three groups.

Bone Metastases

In this situation there is widespread osteolytic bony destruction. This group accounts for 70% of cases of malignant hypercalcaemia [117]. Bone destruction may be due to a combination of direct invasion by tumour cells and stimulation of osteoclastic activity, possibly mediated by prostaglandins or cytokines such as interleukin 1 [153].

Humoral Hypercalcaemia

When not attributed to direct body invasion it has been postulated that humoral mechanisms may be responsible for increased bone resorption. A variety of mediators of increased osteoclastic activity have been suggested, including parathyroid hormone analogues, prostaglandins [117] and tumour necrosis factor [17].

Haematological Malignancies

Hypercalcaemia is a common complication of haematological malignancy, particularly in those with multiple myeloma, and is probably due to a combination of direct bony involvement and the production of humoral factors such as interleukin 1 [84]. Some patients with lymphoma have high circulating levels of 1, 25-dihydroxy vitamin D_3, which stimulates bone resorption and increases calcium absorption from the gastrointestinal tract [144].

The clinical manifestations of hypercalcaemia are summarized in Table 46.2.

The diagnosis is readily established by measuring the plasma calcium, corrected for serum albumin [67]. X-rays and bone scan may identify metastatic lesions.

Treatment of Hypercalcaemia

Treatment can be specific, i.e. directed at the malignancy, non-specific, i.e. aimed primarily at lowering the plasma calcium level, or both (Table 46.3).

Hydration

Hydration can produce rapid biochemical improvement. Initial fluid replacment should be with intravenous normal saline, combined with an increase in oral fluid intake if appropriate. Potassium and magnesium levels should be maintained with supplements as necessary. Six

Table 46.2. Effects of hypercalcaemia

System	Effect
Neurological	Mood change Psychosis Obtundation and seizures Coma
Musculoskeletal	Pain Myopathy
Renal/fluid balance	Polyuria/polydipsia Volume depletion Renal tubular damage Acute renal failure
Gastrointestinal	Anorexia Nausea/vomiting Abdominal pain Constipation

Table 46.3. Management of hypercalcaemia of malignancy

Specific
Surgery
Chemotherapy
Radiation
Non-specific
Hydration
Induce calciuresis
Fluids
Frusemide
Inhibit bone resorption
Steroids
Calcitonin
Mithramycin
Prostaglandin synthetase inhibitors (non-steroidal anti-inflammatory agents)
Diphosphonates
Reduce calcium absorption
Diet
Steroids
Dialysis
Oral/intravenous phosphorus
Mobilization

to ten litres of fluids should be infused over a 24-h period.

Frusemide

Frusemide blocks calcium reabsorption in the ascending loop of Henle and increases sodium excretion, helping to prevent hypernatraemia with saline hydration. The usual starting dose is 40–80 mg 8-hourly.

Steroids

Steroids may exert a useful hypocalcaemic effect, although the reduction in calcium levels may be delayed by up to one week. The mechanism of action is ill defined [171]. The usual starting dose is 40–60 mg of prednisolone orally daily.

Calcitonin

Calcitonin inhibits osteoclastic bone resorption and has a transient calciureic effect. There is evidence that when used in conjunction with steroids its hypocalcaemic action is potentiated and may be more sustained [171].

Mithramycin

This cytotoxic antibiotic inhibits RNA synthesis and thereby reduces bone resorption. The drug is infused intravenously and causes maximum reduction of serum calcium within two to three days. Hypercalcaemia recurs, in about a week unless other measures are instituted.

Diphosphonates

These pyrophosphate analogues are resistant to the effects of endogenous phosphatases and therefore inhibit mobilization of bone mineral. 3-Aminohydroxypropylidene-1,1-biophosphonate is the most potent and has been shown to effectively maintain normocalcaemia if infused once every two to three weeks [115].

Phosphorus

Intravenous phosphates have not been widely used because of the risk of extraskeletal calcification. When used intravenously a precipitous fall in the serum calcium may occur, sometimes resulting in death [117].

Oral therapy is safer and can be effective, provided it is initiated after hydration; 1–3 g daily of elemental phosphorus is administered in divided doses.

Dialysis

Dialysis may be necessary in patients who do not respond to other therapy and for those in renal failure.

There is no single, universally safe or effective treatment for hypercalcaemia and a variety of different agents may have to be used, either in combination or successively. With this approach, hypercalcaemia can usually be controlled, although mortality still remains high (22% in one series [162]).

Cardiovascular Disturbances

Cardiovascular disturbances are responsible for the death of about 7% of cancer patients [4]. A variety of complications of malignancy, or its treatment, can precipitate acute disorders of cardiovascular function, many of which can be life threatening (Table 46.4).

Superior Vena Cava Obstruction (SVCO)

SVCO is caused by mediastinal tumour extension, 75% of cases being due to bronchogenic

Table 46.4. Cardiovascular complications

Superior vena cava obstruction
Cardiac tamponade
Pericardial constriction
Drug-induced
Immediate – dysrhythmias
Delayed – cardiomyopathy

carcinoma and 15% related to malignant lymphoma [25].

Clinical features often develop insidiously. The patient may present with headaches, nausea, dizziness and visual changes. This may progress to stridor, respiratory distress, stupor and syncope; convulsions may develop because of cerebral oedema and reduced cardiac output. On examination there is distension of thoracic and neck veins, facial swelling and plethora; the upper limbs and trunk may be oedematous. Papilloedema may be present in extreme cases [25,121]. The clinical diagnosis can usually be confirmed by chest radiography. When there is difficulty in establishing the diagnosis, a superior vena cavagram or radionuclide studies may be indicated [44]; computed axial tomography scans may help to further delineate the extent of the mass.

Energetic treatment may be life saving. Dexamethasone 4 mg IV/IM q.d.s. may produce rapid resolution of symptoms. Specific therapy should be initiated as soon as possible. Radiotherapy is the treatment of choice in most cases [9]. In patients with venous thrombosis, further deterioration may be prevented by anticoagulation. Surgical intervention is occasionally necessary and the use of expanding wire stents at the site of obstruction is being explored [142].

With aggressive management, 25% of patients who present with SVCO survive at least one year [9].

Cardiac Tamponade

Cardiac tamponade is a rare complication of malignancy, usually due to direct involvement of the pericardium by metastatic tumour. The commonest causes are bronchogenic carcinoma and breast cancer [151], although, rarely, a primary tumour of the pericardium may be responsible. Radiation of the chest may also occasionally be complicated by formation of a pericardial effusion.

Once the diagnosis has been established, pericardiocentesis should be performed urgently. Treatment to control the effusion should then be initiated and this may be directed at the underlying malignancy or at preventing local reaccumulation of fluid [135]. The latter is achieved by surgical pericardiectomy [151], local instillation of cytotoxic drugs such as bleomycin [188] or radiotherapy.

Constrictive Pericarditis

Constrictive pericarditis may be caused by local tumour extension around the heart or may follow radiotherapy. Symptoms and signs are similar to those of cardiac tamponade. Treatment is surgical.

Drug-Induced Cardiovascular Disturbances

Some cytotoxic agents can precipitate acute dysrhythmias, especially in patients with pre-existing cardiac disorders. Adriamycin and amsacrine are most often implicated [183]. A variety of dysrhythmias have been reported with adriamycin but these are usually reversible and do not normally warrant discontinuation of therapy [183].

A more serous complication of treatment with adriamycin is the development of a cardiomyopathy. This is dependent on the cumulative dose; the incidence following a dose of less than 550 mg/m^2 being 0.1%–1.2%, whereas with doses above this level the incidence rises to 13.3%. Adriamycin cardiomyopathy has a high mortality – up to 61% in one series [16]. Patients may present with symptoms and signs of congestive cardiac failure weeks or even months after the last dose of adriamycin [183]. Further therapy with adriamycin is contraindicated if the patient survives. Newer, less cardiotoxic drugs, such as epirubicin, are currently being investigated.

Cyclophosphamide is a commonly used alkylator, which is not cardiotoxic in standard doses. With the larger doses now being used in patients undergoing bone marrow transplantation, however, delayed cardiotoxicity has been reported. Patients present with acute congestive cardiac failure, days or weeks following administration of the drug; and usually die within weeks [183]. The cause is thought to be direct toxic endothelial damage; secondary extravasation of blood containing high concentrations of cyclophosphamide may then cause further

damage. Extensive haemorrhagic myocardial necrosis with pericarditis is found at autopsy [29].

Gastrointestinal Disorders

Acute gastroenterological problems are common. Intra-abdominal tumours may cause bowel obstruction, perforation or haemorrhage, and the management of these is usually surgical. Treatment with chemotherapy or radiotherapy may also precipitate perforation or haemorrhage, especially if the bowel wall was previously infiltrated with tumour [102].

Chemotherapy-induced toxicity may also manifest as severe diarrhoea or a paralytic ileus, the latter being well described following vincristine. Treatment is conservative, with replacement of fluids and electrolytes, as appropriate [112].

Pseudomembranous enterocolitis may occur following antibiotic treatment. The syndrome ranges in severity from mild diarrhoea to severe enterocolitis with toxic megacolon, and may result in bowel perforation. It is caused by infection with *Clostridium difficile*, which also produces a variety of enterotoxins, responsible in part for the clinical manifestations [190]. Treatment is with fluid replacement and oral vancomycin or metronidazole, but in severe cases with bowel perforation surgical intervention may be necessary.

Neutropenic enterocolitis is a recently recognized complication in patients undergoing aggressive chemotherapy for neoplastic diseases, especially haematological malignancies. Inflammation and damage of the bowel wall seem to be caused by a variety of factors, including cytotoxic agents, leukaemic infiltration or bacterial invasion [12]. In one autopsy series 10%–12% of leukaemic patients were found to have histological evidence of neutropenic enterocolitis [12]. Management involves resting the bowel and maintaining adequate fluid balance. Surgical intervention may be necessary if perforation occurs; mortality is high.

Renal Disorders

Acute renal disorders can occur in patients with neoplastic diseases, ranging in severity from mild impairment to life-threatening acute renal failure [97]. There are many causes (Table 46.5) [54,155]. Ethical dilemmas may arise if renal replacement therapy is necessary.

Table 46.5. Causes of renal failure in patients with malignancy

Pre-renal
Hypovolaemia
Haemorrhage
Dehydration
Circulatory collapse
Renal vascular obstruction
Renal
Tumour infiltration
Complications of tumours
Paraproteinaemia: myeloma
Hypercalcaemia
Immune complex disease
Disseminated intravascular Coagulation
Hyperuricaemia
Treatment-related
Cisplatin
Methotrexate
Antibiotics, especially aminoglycosides
Tumour lysis syndrome
Radiation nephritis
Septicaemia
Post-renal
Obstructive
Bladder outlet
Urethral
Ureteric
Retroperitoneal fibrosis

Neurological Disorders

A variety of acute neurological disturbances may arise in patients with malignant disease (Table 46.6) but these are a relatively unusual cause of admission to intensive care.

Intracranial tumour, either primary or metastatic, can cause raised intracranial pressure and focal neurological deficit, depending upon the area infiltrated. There may be an associated endocrinopathy, particularly if the hypothalmic/pituitary area is involved [67].

Treatment is directed at the underlying condition, but rapid clinical improvement may follow corticosteroid therapy. In extreme cases, mannitol may bring about a more rapid but temporary reduction in raised intracranial pressure.

Table 46.6. Causes of neurological disorders in patients with malignancy

Direct effect
Intracranial tumours
Spinal tumours
Leptomeningeal infiltration
Remote
Paraneoplastic syndromes
Infective
Abscess
Meningoencephalitis
Vascular
Haemorrhage
Thrombosis
Treatment-related
Radiotherapy
Chemotherapy
Systemic: peripheral neuropathy
Intrathecal: convulsions, arachnoiditis, encephalopathy

Decompressive shunting may be required when there is evidence of severe obstructive hydrocephalus.

Epidural, intradural or intramedullary tumours may cause spinal cord compression. Treatment depends upon the histology and level of cord compression, and should be instituted as an emergency to prevent irreversible neurological damage [168].

Leptomeningeal infiltration is most common in those with acute leukaemias (usually lymphoblastic), high-grade non-Hodgkin's lymphomas and disseminated breast or lung cancer. The incidence in patients with leukaemia has decreased significantly since the introduction of prophylactic intrathecal chemotherapy and cranial/craniospinal radiotherapy. Nevertheless, this remains a significant cause of morbidity and mortality. Patients present with multiple cranial and peripheral nerve palsies or obstructive hydrocephalus. Treatment is with intrathecal cytotoxic agents and radiotherapy.

Treatment related morbidity following radiotherapy to the neuraxis is not uncommon, but is usually minor and self-limiting, occurring weeks to months after the radiotherapy. On the other hand, intrathecal chemotherapy, usually with methotrexate, can produce severe neurological disturbance, ranging from mild chemical arachnoiditis to severe encephalopathy, pontine myelinolysis, stroke-like syndrome or severe necrotizing leukoencephalopathy, which is often fatal [85,146]. Systemic chemotherapy, especially with the *Vinca* alkaloids and cisplatin, is frequently associated with peripheral neuropathies. Rare complications such as seizures and encephalopathy have been reported with vincristine therapy [85].

Paraneoplastic Syndromes

Paraneoplastic syndromes may present in many different ways, ranging from peripheral neuropathy to myasthenic syndromes. Diagnosis is by exclusion of other causes. Treatment is directed at the underlying neoplasm [25].

Hyperviscosity Syndrome

Increased blood viscosity may occur in patients with Waldenstrom's macroglobulinaemia and myeloma, and can cause mucosal bleeding, neurological disturbances, retinopathy and cardiac failure. Fundoscopy may reveal papilloedema, haemorrhages or retinal vein thrombosis. In extreme cases, progressive loss of consciousness and coma may occur. Treatment with plasma exchange may be life saving.

Graft-Versus-Host Disease

More intensive treatment with higher doses of chemotherapy and radiotherapy, often in association with bone marrow transplantation (autologous or allogeneic), has been increasingly used in the past decade in an attempt to increase tumour cell kill. This has been accompanied by an increased incidence of complications, due to the higher doses of toxic chemotherapeutic agents, more prolonged immunosuppression and the development of GVH disease in those who have recieved allogeneic transplants. The incidence of GVH disease varies, but may be as high as 45%–75%, and the mortality is significant [147]. GVH disease may present acutely or as a more chronic disease. Clinically the patient suffers from severe skin rashes (which may become bullous, with ulceration and epidermal necrosis), florid diarrhoea and hepatic abnormalities [19,40].

Postoperative Intensive Care

The potential benefits of admitting cancer patients to an intensive care unit following major surgery include the ability to use continuous haemodynamic monitoring to assist optimal volume replacement and preserve renal function, the early identification of cardiovascular and respiratory disturbances and the availability of facilities for respiratory support, including mechanical ventilation. Moreover, the patient will receive constant skilled nursing care and effective analgesia can be assured.

The extensive surgical procedures now sometimes undertaken as part of the radical treatment of cancer are inevitably associated with considerable postoperative morbidity and mortality. Pelvic exenteration, for example, is a prolonged and traumatic procedure, frequently accompanied by considerable blood loss; many therefore recommend routine postoperative intensive care for such cases [10,56,74,123] and it has been suggested that such a policy can contribute to significant reductions in mortality [10, 56]. These patients are generally hypovolaemic on admission since the average blood loss is in excess of 2 litres, and this may be exacerbated by a preoperative reduction in plasma and red cell volume [77]. Furthermore, intraoperative volume replacement is often inadequate and postoperative losses from traumatized tissue may amount to as much as 22% of the total red cell volume. Significant acute decreases in serum albumin have also been described following pelvic exenteration [123], lowering the threshold for the development of pulmonary oedema and emphasizing the need for accurate replacement of the circulating volume.

For such patients, therefore, central venous pressure monitoring and continuous intra-arterial pressure recording are essential. Although some also recommend the routine use of a balloon flotation pulmonary artery catheter [123], this is probably only necessary in selected high-risk cases, in particular those with pre-existing cardiac disease. In the majority of patients central venous pressure monitoring, assessed in conjunction with other indices of cardiovascular performance such as heart rate, blood pressure, urine output and peripheral temperature, will allow optimal replacement of volume losses. It has, however, been shown that survival of critically ill postoperative patients is associated with supranormal values for cardiac index, left ventricular stroke work index, O_2 delivery and O_2 consumption [164]. Subsequent prospective studies have suggested that overall mortality can be reduced by instituting aggressive supportive treatment to achieve the median values for oxygen delivery and consumption seen in survivors [165,165a]. In the most seriously ill patients, therefore, and in those who fail to respond to simple measures, a thermodilution pulmonary artery catheter should be inserted to allow determination of relevant cardiorespiratory variables and some would advocate further treatment in order to attain these "therapeutic goals" (in particular a cardiac index >4.5 litres/(min/m^2), oxygen delivery >600 ml min^{-1}m^{-2} and an O_2 consumption index >167 ml/(min/m^2).

Respiratory abnormalities are also common after extensive surgical procedures in those with malignant disease. Surgery and anaesthesia produce alveolar collapse, with reductions in vital capacity and compliance associated with premature airway closure, impaired ability to cough and muscle splinting. There is also depression of macrophage function and ciliary activity, whilst the lower respiratory tract may become colonized with bacteria. It is not surprising, therefore, that in susceptible patients these changes can be associated with retention of secretions, atelectasis and superimposed infection, or that in some cases they precipitate respiratory failure. These abnormalities of lung function are particularly severe following upper abdominal surgery and thoracotomy, when vital capacity may be reduced by as much as 30% [30]. Moreover, pulmonary complications are much more common in patients with pre-existing respiratory disease. Many of those requiring thoracotomy for pulmonary, oesophageal or mediastinal tumours, or upper abdominal surgery such as gastrectomy, are elderly, smoke heavily and are therefore very susceptible to postoperative pulmonary complications. Respiratory difficulties are particularly common following gastro-oesophageal resection but are relatively unusual after pulmonary resection for primary malignancy. Nevertheless sputum retention, pneumonia and pulmonary oedema may all precipitate respiratory failure following lobectomy or pneumonectomy. The development of a bronchopleural fistula is a particularly ominous complication. In some cases postoperative respiratory failure is related to the development of ARDS precipitated, for example, by severe haemorrhage, sepsis or pulmonary aspiration.

Some patients, for example those with bronchiectasis or chronic airflow limitation, may benefit from a period of intensive physiotherapy, with bronchodilators when indicated and antibiotics for active infection, prior to surgery. In the postoperative period simple but effective measures include chest physiotherapy with deep breathing and coughing, as well as exercises designed to improve respiratory muscle function. The application of CPAP by face mask can be useful as a means of achieving re-expansion of collapsed alveoli and increasing functional residual capacity, particularly following upper abdominal surgery. In those with sputum retention insertion of a minitracheostomy may enable secretions to be cleared and avoid the need for mechanical ventilation.

Elective postoperative ventilation is now a well-established practice in high-risk patients in whom some degree of respiratory failure might otherwise be anticipated. Girtanner et al. [56], for example, recommend elective ventilation for at least 12 h following pelvic exenteration. In the author's opinion, however, this is usually unnecessary and it is perhaps more reasonable to ventilate such patients only for a few hours until they are judged to be able to sustain adequate spontaneous ventilation. Orr and his colleagues [123] use predetermined extubation criteria (arterial O_2 tension >100 mmHg, arterial CO_2 tension <45 mmHg, with fraction of inspired O_2 <0.4, negative inspiratory force >35 mmHg, forced vital capacity >15 ml/kg) and have found the mean time to extubation to be less than 6 h, although this was significantly longer in the elderly. No patient developed respiratory failure or required reintubation. A few patients will require longer periods of mechanical ventilation for established post-operative respiratory failure.

The provision of adequate analgesia is an essential component of postoperative care, not least because pain seriously limits the patient's ability to cough and expand their lungs. Moreover mobilization may be delayed and the risk of complications may thereby be increased. Pelvic exenteration, thoracotomy, cystectomy and upper abdominal surgery are all examples of procedures performed for malignant disease which are associated with considerable pain in the postoperative period.

As required, intramuscular administration of narcotics is inadequate in such patients because of wide variations in blood levels and fluctuations in the quality of analgesia. Continuous intravenous or subcutaneous infusions of narcotic, titrated to achieve satisfactory pain relief, are much more satisfactory and patient controlled analgesia systems may provide superior analgesia with reduced dosage requirements. In many cases optimal pain relief is best achieved with regional blockade via the extradural or, less often, the intrathecal route, using either local anaesthetic agents or opiates.

Although many adult patients hospitalized with cancer are malnourished [107], the value of perioperative parenteral nutrition as a means of reducing morbidity and mortality in those undergoing major surgery remains unclear. The incidence of malnutrition is highest in patients with gastrointestinal malignancy, but even in this group of patients the benefits of perioperative parenteral nutrition are unproven. Thus although Muller et al. [116] found that preoperative parenteral nutrition reduced both the incidence of major complications and mortality, others have failed to demonstrate any reduction in either morbidity or mortality [76,182]. Malnutrition is also common in patients with other forms of cancer requiring surgery [176]; for example, in one series approximately 40% of those undergoing radical cystectomy for carcinoma of the bladder were malnourished. These patients spent more days in the intensive care unit and their operative morbidity and mortality rates were higher, although there was no difference in survival between the well-nourished and poorly nourished patients beyond 36 months [113]. In this retrospective study the provision of perioperative nutritional support to the malnourished patients did not appear to alter operative complications [113].

Prognosis

As might be anticipated, mortality rates are high when patients with malignant disease develop an acute illness severe enough to warrant admission to an intensive care unit [7,37,48,49, 57,69,82,100,101,128,159,162,175,184–186], particularly in those with respiratory failure [7, 37,48,57,69,82,100,101,128,159,184]. An overall hospital mortality rate of about 70%–80% can be expected in patients admitted to intensive care with acute complications of haematological malignancies [7,82,100,101,159] or bone marrow transplantation [7,184], rising to 80%–96% when they develop respiratory failure [7,37,48, 57,69,82,100,101,128,159,184] although lower

mortality rates (23%–55%) have been reported when patients with all types of malignancy, including solid tumours [69,162,185,186], as well as surgical patients [185,186] are included. Mortality will also be lower when significant numbers of patients with metabolic abnormalities are admitted, since most of these survive [69]. In a recent publication Sculier et al. [162] reported that 77% of cancer patients admitted to an intensive care unit with medical emergencies survived. Their patient population was, however, unusual since the commonest causes of admission, in descending order of frequency, were hypercalcaemia, thromboembolic disease, cardiac arrhythmias, encephalopathies and "diffuse pneumopathies".

The long-term prognosis for those who do survive to leave the hospital is also often poor [49,128,175]. In one series of cancer patients with respiratory failure 26% survived to be extubated but only 7% lived for six months or more [175] and in a group of patients with haematological malignancy the median duration of survival of the 18% who were discharged from hospital was 12 months, with a range of one month to seven years [128].

When patients with lung cancer require mechanical ventilation for respiratory failure the chances of long-term survival are remote; Ewer et al. [49] reported that of 46 such patients seven were weaned from ventilatory support and survived for at least 24 hours, but only four were discharged from hospital and of these three died within four months.

In the ten-year period between January 1980 and December 1989, we admitted 92 patients with life-threatening medical complications of haematological malignancy of whom 21 (23%) survived to leave hospital. Their median duration of survival was 23 months (range six weeks to eight years) with eight patients currently alive at 8, 7, 7, 5, 4, 3, 3 years and 4 months after leaving hospital. The long-term survival rate was 86% at six months, 62% after one year, and 43% after three years, higher than reported in the series of Brunet et al. (64% at six months, 44% after one year) [28a].

Not only are mortality rates high in critically ill cancer patients, but it must be recognized that in most cases transfer of a patient to the intensive care unit involves a quantum increase in the commitment of resources, rather than simply a continuation of supportive care [185, 186]. Moreover, the decision to institute intensive care crystallizes fears of impending death, and the prospect of removal to a strange environment with unfamiliar staff can engender considerable anxiety. Subsequently, the delivery of intensive care inevitably involves mental and physical distress for the patients and their relatives, especially when treatment is unsuccessful. Both for a humane approach to the management of malignant disease, and to ensure that limited resources are used appropriately, it is therefore important to avoid admitting patients who cannot benefit from intensive care and to limit further extraordinary measures when the outlook is clearly hopeless. These decisions can be extraordinarily difficult, but must be based on the best possible understanding of the factors which determine both the immediate and long-term outcome in critically ill patients with malignant disease.

It is also important to consider the quality of life of survivors when evaluating the benefits of intensive care. We have assessed the quality of life of the seven patients in our series who are alive more than one year after hospital discharge using three validated measures: the Nottingham Health Profile [80a], the Hospital Anxiety and Depression Scale [202a], and the Perceived Quality of Life Scale (PQOL) [123a], each of which assesses different aspects of quality of life. The results indicate that six of the seven patients have a good quality of life, broadly similar to that of the same age and sex norms in the general population, whilst that of the other is acceptable. None of the patients reported any increased physical limitations to their daily activity following intensive care. The majority returned to full-time employment without any difficulties and reported a moderate-to-high level of satisfaction with most aspects of their daily lives as assessed by the PQOL assessment. They all expressed great satisfaction regarding their family life and the support that they received from family and friends. Only one patient could be considered to be suffering from anxiety and none were depressed. Most encouragingly, all seven patients stated that under similar circumstances they would be willing to undergo intensive care treatment again. These findings emphasize the importance of being able to identify those patients who might benefit from intensive care because the few who do survive long term may enjoy an excellent quality of life.

A number of authors have therefore attempted to identify features associated with a fatal outcome. For example, Poe et al. [133] found that in immunocompromised patients with pulmonary infiltrates the need for mechanical ventila-

tion within 72 h, an initial room air arterial O_2 tension <50 mmHg and corticosteroid therapy were the dominant independent variables, in that order, to significantly predict mortality. Indeed no patient survived who simultaneously had a room air arterial O_2 tension <50 mmHg, was receiving corticosteroids and was mechanically ventilated. In patients with haematological disorders admitted to an intensive care unit, pneumonia, the necessity for respirator therapy, residual malignancy, sepsis and shock all had a significantly adverse effect on outcome [7] and following bone marrow transplantation septic shock was invariably rapidly fatal [184]. We also found that septic shock occurring in patients with haematological malignancy was associated with a poor prognosis; the mortality of the 39 patients requiring inotropes was high (35 deaths), only three of 30 who received inotropic doses of dopamine, dobutamine or adrenaline were discharged from hospital alive [101]. The combination of pneumonia and septic shock had a particularly poor prognosis (32 of 34 patients died) and no such patient who received inotropes survived [101].

It is well recognized that patients who survive a critical illness usually show an early improvement in response to treatment and this also appears to be the case for those with malignant disease. It has been suggested, for example, that recovery is unlikely when patients with respiratory failure complicating haematological malignancy require mechanical ventilation for more than a few days [159] and in one series of patients with lung cancer no patient ventilated for more than six days could be weaned from respiratory support [49]. Moreover, the duration of artificial ventilation correlated strongly with a poor prognosis [49]. Others have remarked that if there are no signs of recovery within 72 h the chances of meaningful recovery are low [37] and following bone marrow transplantations mortality was 100% in patients requiring mechanical ventilation for more than seven days [184]. Some authors, however, have found no significant difference between the duration of mechanical ventilation in survivors and non-survivors [128,175] and in the series of Brunet et al. there were four long-term survivors who required ventilatory support for more than 25 days [28a].

The importance of the number of organ systems involved in determining outcome has been demonstrated by a number of investigators. Snow et al. [175], for example, reported a mortality rate of 91% in cancer patients when respiratory failure was complicated by renal failure and commented that "the most striking predictor of mortality was dysfunction of increasing numbers of critical organ systems". In another series mortality was 100% when patients with malignant disease developed respiratory failure complicated by just one other organ system failure [37] and in patients admitted with acute complications of bone marrow transplantation those with less than three-system failure always survived, while multi-organ failure was significantly associated with death in the intensive care unit [184]. In our own series we found that in the 14 patients who had respiratory failure requiring mechanical ventilation, but in whom three or fewer systems were affected, the mortality was 57%. Conversely when four or more systems were involved none of the patients who required IPPV survived. When patients without respiratory failure were included we found that those who died in hospital had significantly more systems affected (median 5, range 2–7) than those who were discharged (median 3, range 1–4) [101].

The outcome of a critical illness is related not only to the number of organ systems which fail, but also to the severity of the acute physiological disturbance and the patient's previous health status. These factors can be quantified by calculating an "acute physiology score" from the most abnormal values of selected physiological variables and combining this with points awarded for age and chronic health status to derive the APACHE II score. This scoring system has now been extensively validated and correlates closely with outcome for large groups of critically ill patients [88]. This close relationship between APACHE II score and outcome was clearly apparent in our patients with haematological malignancy but within each of six score bands hospital mortality was consistently higher than previously reported in a mixed population of critically ill patients [88], rising to a mortality of 100% in score bands above 30 [101]. Moreover, no patient with an APACHE II score greater than 26 survived to leave hospital, similar to Johnson's observation that all those granulocytopenic patients with scores greater than 23 on admission to the ward or the intensive care unit died [82]. It is recognized, however, that the relationship between the APACHE score and outcome depends on the nature of the patient's acute illness and most of our patients were suffering from respiratory failure, septic shock or both, conditions known

to be associated with a higher than average mortality, even in those without cancer [88]. Knaus et al., therefore, recommend calculating a predicted risk of death for each individual patient by weighting the APACHE II score according to their diagnostic category. The predicted risk of death for the group can then be estimated by summing the individual risks and dividing by the total number of patients. In our patients with haematological malignancy the mean predicted risk of death in survivors was 34.8% (range 6.6%–56.7%) and in non-survivors 66.6% (range 16.6%–97.1%) ($P < 0.05$ – comparison of two proportions); no patient with a predicted risk of death greater than 60% survived. For the whole group of 60 patients the mean predicted risk of death was 59.7% (range 6.6%–97.1%) compared with an actual mortality of 78% ($P = 0.004$ – comparison of two proportions), suggesting that hospital mortality rates for patients with haematological malignancy are significantly higher than those in a general population of critically ill patients. This conclusion is supported by observing that our mortality rates are remarkably similar to those reported by other authors in patients with haematological malignancy (see above). Moreover, a number of other studies [37,69,82] have also indicated that mortality rates for those with malignant disease are higher than for other medical ICU patients with an acute illness of equivalent severity.

The nature and progress of the underlying malignancy would be expected to be of considerable importance in determining outcome. It is recognized that a significant number of critically ill cancer patients (10%–21%) die on the general ward shortly after discharge from the ICU [59,101,184,185] in most instances when it has become clear that the underlying malignancy has not been controlled and the decision has been made to limit further aggressive treatment. In our series of patients with haematological malignancy the APACHE II scores and number of systems affected in patients who died on the ward were no different from those of the patients who left hospital alive, confirming the importance of the progress of underlying malignancy rather than the severity of the acute illness as a determinant of long-term survival [101]. Similarly, Dragsted et al. [42a] found that, although the in-unit mortality was not influenced by the presence of malignancy, the mortality during the ensuing hospital stay was significantly greater in those with cancer.

More specifically, in patients with haematological malignancy and respiratory failure the chances of survival may be greater in those with chronic lymphatic leukaemia than in those with acute myelogenous leukaemia, and those with Hodgkin's disease may be more likely to survive than those with non-Hodgkin's lymphoma [128]. We also noted a tendency for a worse prognosis in patients with acute myeloid leukaemia and non-Hodgkin's lymphoma than in those with acute lymphoblastic leukaemia, although this was not statistically significant [101]. Snow et al. [175] had no six-month survivors amongst those with acute lymphoblastic leukaemia, acute myeloid leukaemia, or adenocarcinoma of the lung, and all their patients with respiratory failure following bone marrow transplantation died while receiving mechanical ventilation. In contrast, our eight patients who are still alive include 3 with AML, 2 with ALL, as well as 1 CML, 1 NHL, and 1 HL.

In those who have relapsed or who have failed to achieve complete remission after an induction course of chemotherapy, cure is unlikely [99]. In our experience the mortality of patients who had relapsed (21 of 22) was significantly higher than those on first presentation (26 of 35), and all three patients in remission survived. Others, however, have not found any differences in survival between those undergoing primary treatment and those with relapsed malignancy [128].

In most patients a successful outcome depends on recovery of bone marrow function following effective chemotherapy, while persistent neutropenia appears to adversely affect survival. In our series all long-term survivors either had adequate neutrophil counts throughout or showed an appreciable recovery of bone marrow function whilst in the intensive care unit. Conversely 36 of the 47 patients who died in hospital were leucopenic at the time of death. Similarly Torrecilla et al. [184] reported that only one of eight neutropenic patients admitted to intensive care following bone marrow transplantation survived, and his white count returned to normal whilst on the intensive care unit. Others [7] have also suggested that reversal of granulocytopenia during intensive care increases the likelihood of survival. On the other hand Peters et al. [128] could not demonstrate any difference in total leucocyte or neutrophil counts between survivors and non-survivors in patients with haematological malignancy complicated by respiratory failure.

Moreover Johnson et al. [82] could find no correlation between the duration of leucopenia and mortality in a group of granulocytopenic patients with haematological malignancy receiving intensive care or ward-based care.

The long term prognosis of those patients who survive to leave hospital seems to depend solely on the nature and the progress of the underlying malignancy. In our experience, neither the aetiology of the acute illness precipitating intensive care admission, nor its severity (as assessed by APACHE II score and the number of failed organs), appeared to influence the duration of long-term survival. Indeed, three of our four longest survivors received mechanical ventilation, had APACHE II scores of 24–26 and failure of three organs. Uncontrolled malignancy was responsible for all the deaths in those patients who were discharged from hospital. Similarly, Crawford et al. [38a] found that some of the inpatients who developed complications after marrow transplantation with failure of three or four organs requiring mechanical ventilation survived long term. Review of the clinical records of these patients revealed no distinguishing characteristics in terms of the duration or mode of ventilation, types of complication or rapidity of recovery.

A number of studies have identified various factors associated with a poor short-term outcome [82,101,159] and these can be used as guidelines when assessing the prognosis of individual patients. We suggest that in those with medical complications of haematological malignancy an APACHE II score of greater than 30, the dysfunction of an increasing number of organ systems, failure to recover from neutropenia after chemotherapy, and unresponsive malignant disease, particularly in patients who have relapsed, are all indicative of a poor prognosis. In such cases clinicians, in consultation with other members of staff and the patients' relatives, should consider discontinuing aggressive supportive treatment.

Neither ourselves nor others [38a] have been able to distinguish any features of the acute illness which influence the likelihood of long-term survival; this seems to depend solely on the progress of the underlying malignancy – something which is often difficult to predict before or during intensive care. Despite the high mortality rate, intensive care is therefore justified for patients with acute life-threatening complications of malignancy unless or until it is clear that there is no prospect of recovery from the acute illness or that the underlying malignancy cannot be controlled.

References

1. Adler A, Stein JA, Ben-Efraim S (1980) Immunocompetence, immunosuppression and human breast cancer II. Further evidence of initial immune impairment by integrated assessment effect of nodal involvement (N) and of primary tumour size (T). Cancer 45:2061–2073; 2074–2083

1a. Addison IE, Johnson B, Devereux S et al. (1989) Granulocyte-macrophage colony stimulating factor may inhibit migration in vivo. Clin Exp Immunol 76:149–153

2. Adonis C (1983) Problems encountered in an intensive care medical oncology unit in Paris. Proceedings 130th International Cancer Congress: Cancer Management. Liss, New York, pp 423–426

3. Alavi JB, Root RK, Djerassi I et al. (1977) A randomized clinical trial of granulocyte transfusion for infection in acute leukaemia. N Engl J Med 296:706–711

4. Ambrus JL, Ambrus CM, Mink IB, Pickern JW (1975) Causes of death in cancer patients. J Med 6:61–64

5. Anderson HA, Fontana RS (1972) Transbronchoscopic lung biopsy for diffuse pulmonary diseases: technique and results in 450 cases. Chest 62:125–128

6. Anderson ET, Young LS, Hewitt WL (1978) Antimicrobial synergism in the therapy of gram-negative rod bacteremia. Chemotherapy 24:45–54

7. Anger B, Schmeiser T, Sigel H, Heimpel H (1987) Intensive care therapy for patients with hematological diseases. Haematol Bluttransfus 30:519–523

8. Antman KS, Griffin JD, Elias A et al. (1988) Effect of recombinant human granulocyte macrophage colony-stimulating factor on chemotherapy-induced myelosuppression. N Engl J Med 319:593–598

8a. Antman K, Griffin J, Elias A et al. (1987) Use of recombinant human granulocyte-macrophage colony stimulating factor to ameliorate chemotherapy myelosuppression in sarcoma patients. Blood Suppl 70:373

9. Armstrong BA, Perez CA, Simpson JR, Hederman MA (1987) Role of irradiation in the management of superior vena cava syndrome. Int J Radiat Oncol Biol Phys 13:531–539

10. Averette HE, Lichtinger M, Sevin BU, Girtanner RE (1984) Pelvic exenteration: a 15 year experience in a general metropolitan hospital. Am J Obstet Gynecol 150:179–184

11. Bandt PD, Blank N, Castellino RA (1972) Needle diagnosis of pneumonitis: Value in high risk patients. JAMA 220:1578–1580

12. Baniel J, Lombrozo R, Ziv Y, Wolloch Y (1988) Neutropenic enterocolitis. Acta Chir Scand 154:71–73

13. Beachey EH (1981) Bacterial adherence: adhesin–receptor interactions mediating the attachment of bacteria to mucosal surfaces. J Infect Dis 143:325–345

14. Benezra D, Gold JWM, Armstrong D (1986) Indwelling central venous catheter infections. In: Proceedings of 4th international symposium on infections in the immunocompromised host. Ronneby Brunn, Sweden

15. Bennett OE, Million RR, Acekerman LV (1969) Bilateral radiation pneumonitis: a complication of the radiotherapy of bronchogenic carcinoma. Cancer 23:1001–1018
16. Beretta E, Villani F (1980) Cardiomyopathy in adults after combination adriamycin and DTIC. Cancer Treatment Rep 64:353
17. Bertolini DR, Nedwin GE, Bringman TS, Smith DD, Mundy GR (1986) Stimulation of bone resorption and inhibition of bone formation in vitro by human tumour necrosis factors. Nature 319:516–518
18. Blacklock HA, Griffiths P, Stirk P, Prentice HG (1986) Cytotect treatment of cytomegalovirus pneumonitis after matched allogeneic bone marrow transplantation. In: Proceedings of 4th international symposium on infections in the immunocompromised host. Ronneby Brunn, Sweden, p 33
19. Blume KG, Petz LD (eds) (1983) Clinical bone marrow transplantation. Churchill Livingstone, Edinburgh
20. Bodey GP (1966) Fungal infectious complicating acute leukaemia. J Chronic Dis 19:667
21. Bodey GP, Bolivar R, Fainstein AV (1982) Infectious complications in leukemic patients. Semin Hematol 19:193–226
22. Bodey GP, Buckley M, Sathe YS et al. (1966) Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med 64:328–340
23. Bodey GP, Rodriguez V, Chang H-Y, Narboni G (1978) Fever and infection in leukaemic patients: a study of 494 consecutive patients. Cancer 41:1610–1622
24. Brandt SJ, Peters WP, Atwater SK et al. (1988) Effect of recombinant human granulocyte–macrophage colony stimulating factor on haematopoietic reconstitution after high dose chemotherapy and autologous bone marrow transplantation. N Eng J Med 318:869–876
25. Brennan JT (1987) Oncologic emergencies and paraneoplastic syndromes. Primary Care 14:365–379
26. Brettler DB (1985) Granulocytopenia. In: Rippe JM, Irwin RS, Alpert JS, Dalen JE (eds) Intensive care medicine. Little, Brown & Co, Boston, pp 846–853
27. Bronchud MH, Scarffe JH, Thatcher N et al. (1987) Phase I/II study of recombinant human granulocyte colony-stimulating factor in patients receiving intensive chemotherapy for small cell lung cancer. Br J Cancer 56:809–813
28. Brown AE (1984) Neutropenia, fever and infection. Am J Med 76:421–428
28a. Brunet F, Lanore JJ, Dhainaut JF et al. (1990) Is intensive care justified for patients with haematological malignancies? Intensive Care Med 16:291–297
29. Buja LM, Ferrans VH (1975) Myocardial injury produced by antineoplastic drugs. Recent Adv Stud Cardiac Struct Metab 6:487
30. Carlon GC (1978) Respiratory failure in cancer patients. Curr Probl Cancer 4:47–57
31. Carlon GC, Ray C Jr, Klein R et al. (1978) Criteria for selective positive end expiratory pressure and independent synchronised ventilation for each lung. Chest 74:501–507
32. Castellino RA, Blank N (1979) Etiological diagnosis of focal pulmonary infection in immunocompromised patients by fluoroscopically guided percutaneous needle aspiration. Radiology 132:563–567
33. Chang HY, Rodriguez V, Narboni G et al. (1976) Causes of death in adults with acute leukaemia. Medicine 55:259–268
34. Chillar RK, Belman MJ, Farbstein M et al. (1980) Explanation for apparent hypoxaemia associated with extreme leukocytosis: leucocytic oxygen consumption. Blood 55:922–924
35. Co-operative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukaemia (1988) Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukaemia. N Eng J Med 319:902–907
36. Cockerill FR, Wilson WR, Carpenter HA, Smith TF, Rosendow EC (1985) Open lung biopsy in immunocompromised patients. Arch Intern Med 145:1398–1404
37. Cox SC, Norwood SM, Duncan CA (1985) Acute respiratory failure: mortality associated with underlying disease. Crit Care Med 13:1005–1008
38. Clift RA, Sanders JE, Thomas ED, Williams B, Buckner CD (1978) Granulocyte transfusions for the prevention of infection in patients receiving bone-marrow transplants. N Engl J Med 298:1052–1057
38a. Crawford SW, Schwartz DA, Peterson F et al. (1988) Risk factors in mechanical ventilation after marrow transplantation. Am Rev Respir Dis 137:682–687
39. Cunningham JH, Zavala DC, Corry RJ et al. (1977) Trephine air drill, bronchial brush and fibreoptic transbronchial lung biopsies in immunosuppressed patients. Am Rev Resp Dis 115:213–220
40. Deeg HJ (1988) Acute graft vs host disease. In: Deeg HJ, Klingemann HG, Phillips GL (eds) Bone marrow transplantation. Springer-Verlag, Berlin, pp 86–98
41. Delamore IW (1986) Multiple myeloma and other paraproteinaemias. Churchill Livingstone, Edinburgh, 324–325
41a. Devereux S, Linch DC, Patterson KP et al. (1989) Granulocyte-macrophage colony stimulating factor accelerates neutrophil recovery after autologous bone marrow transplantation in Hodgkin's disease: bone marrow transplantation. 4:49–54
42. Dick JD, Shull V, Karp JE, Valentine J (1988) Bacterial and host factors affecting *Pseudomonas aeruginosa* colonization versus bacteremia in granuloctyopenic patients. Eur J Cancer Clin Oncol 24(suppl 1):S47–S54
42a. Dragsted L, Quist J, Madsen M (1989) Outcome from intensive care II. A 5 year study of 1308 patients: short term outcome. Eur J Anaesth 6:131–144
43. Drapkin RL, Gee TS, Dowling MD et al. (1978) Prophylactic heparin therapy in acute promyelocytic leukemia. Cancer 41:2484–2490
44. Eisenberg RL (1985) Diagnostic imaging in internal medicine. McGraw-Hill, New York
45. Elvin KM, Bjorkman A, Linder E, Heurlin N, Hjerpe A (1988) *Pneumocystis carinii* pneumonia: detection of parasites in sputum and bronchoalveolar lavage fluid by monoclonal antibodies. Br Med J 297:381–384
46. Engelhard D, Aker M, Lugassy G et al. (1986) Combined therapy with intravenous immune globulin and granulocyte transfusions in uncontrolled overwhelming *Pseudomonas aeruginosa* septicaemia in neutropenic cancer patients. In: Proceedings of the 4th international symposium on infections in the immunocompromised host. Ronneby Brunn, Sweden, p 89
47. Ersek MT (1984) Clinical reviews in critical care: the adult leukemia patient in the intensive care unit. Heart Lung 13:183–193
48. Estopa R, Marti AT, Kastanos N et al. (1984) Acute respiratory failure in severe hematological disorders. Crit Care Med 12:26–29
49. Ewer MS, Ali MK, Atta MS et al. (1986) Outcome of lung cancer patients requiring mechanical ventilation for pulmonary failure. JAMA 256:3364–3366

50. Fanta CH, Pennington JE (1981) Fever and new lung infiltrates in the immunocompromised host. Clin Chest Med 2:19–39
51. Fisher DD, Armstrong D, Yu B, Gold JWM (1981) Invasive aspergillosis: prognosis in early diagnosis and treatment. Am J Med 71:571–577
52. Fishman LS, Griffin JR, Sapico FL et al. (1972) Hematogenous candida endophthalmitis: a complication of candidemia. N Engl J Med 286:675–681
53. Ford JM, Brown LM, Cullen MH, Oliver RTD, Lister TA (1982) Prophylactic granulocyte transfusions: results of a randomised clinical trial in patients with acute myelogenous leukaemia. Transfusion 22:498–501

53a. Gabrilove JL, Jakubowski A (1990) Haemopoietic growth factors: biology and clinical application. J Nat Cancer Inst Monogr 10:73–77

54. Garnick MB, Mayer RJ (1978) Acute renal failure associated with neoplatic disease and its treatment. Sem in Oncol 5:155–166

54a. Gasson JC, Weisbart RH, Kaufman SE et al. (1984) Purified human granulocyte-macrophage colony stimulating factor: direct action on neutrophils. Science 226:1339–1342

55. Ginsberg SJ, Comis RL (1984) The pulmonary toxicity of antineoplastic agents. In: Perry MC, Yarbro JW (eds) Toxicity of chemotherapy. Grune & Stratton, New York
56. Girtanner RE, DeCampo T, Alleyn JN, Averette HE (1981) Routine intensive care for pelvic exenterative operations. Surg Gynaecol Obstet 153:657–659
57. Goldiner PL, Carlon GC, Cvitkovic E et al. (1978) Factors influencing post operative morbidity and mortality in patients treated with bleomycin. Br Med J 1:1664–1667
58. Goldiner PL, Pinilla J, Turnbull A (1976) Acute respiratory failure in patients with advanced lymphoma. In: Lecker MJ (ed) Hodgkin's disease. Wiley, New York, pp 371–376
59. Grady GF, Bennett AJE (1972) Risk of post-transfusion hepatitis in the United States: a prospective cooperative study. JAMA 220:692–701
60. Gralnick HR (1990) Hemostasis and thrombosis in acute and chronic leukaemia. In: Henderson E, Lister TA, (eds) William Dameshek and Frederick Gunz's Leukemia, 5th edn. Saunders, Philadelphia, pp 711–731
61. Greenman RL, Goodall PT, King D (1975) Lung biopsy in immunocompromised hosts. Am J Med 59:488–496
62. Grob JP, Grundy JE, Prentice HE et al. (1987) Immune donors can protect marrow transplant recipients from severe cytomegalovirus infections. Lancet i:774–776

62a. Groopman JE, Mitsuyasu RT, DeLeo MJ et al. (1987) Effect of recombinant human granulocyte-macrophage colony stimulating factor on myelopoiesis in the acquired immunodeficiency syndrome. N Eng J Med 317:593–598

63. Gross NJ (1977) Pulmonary effects of radiation therapy. Ann Int Med 86:81–92
64. Guiot HFL, Van den Broek PJ, Van der Meer JWM, van Furth R (1983) Selective antimicrobial modulation of the intestinal flora of patients with acute nonlymphocytic leukaemia: a double blind placebo-controlled study. J Infect Dis 147:615–623
65. Gunther I, Kaben U, Dunker H, Brijmohan-Gunther R, Konrad H (1988) Selective decontamination of the digestive tract and fungal infection in acute leukaemia patients. Recent Results Cancer Res 108:82–88
66. Hagenbeek A, Brummelhuis HGJ, Donkers A et al. (1986) Rapid clearance of cytomegalovirus-specific IgG after repeated intravenous infusions of human immunoglobulin into allogeneic bone marrow transplant recipients. J Infect Dis 155:897–902
67. Hall R, Anderson J, Smart GA, Besser GM (1981) Fundamentals of clinical endocrinology. Pitman Medical, London
68. Haupt MH, Hutchins GM, Moore GW (1981) Ara-C lung: noncardiogenic pulmonary oedema complicating cytosine arabinoside therapy of leukaemia. Am J Med 70:256–261
69. Hauser MJ, Tabak J, Baier H (1982) Survival of patients with cancer in a medical critical care unit. Arch Intern Med 142:527–529
70. Heron EM, Gutterman JU, Mavlighit GM (1976) Effect of haematological malignancies and their treatment on host defence factors. Clin Haematol 5:425
71. Hersmain J, Meyers JD, Thomas ED et al. (1982) The effect of granulocyte transfusion as the incidence of cytomegalovirus infection after allogenic marrow transplantation. Ann Intern Med 96:149–152
72. Herzig RH, Herzig GP, Graw R et al. (1977) Successful granulocyte transfusion therapy for gram-negative septicemia. N Engl J Med 296:701–705
73. Hewlett RI, Archie F, Wilson AF (1977) Adult respiratory distress syndrome (ARDS) following aggressive management of extensive acute lymphoblastic leukaemia. Cancer 39:2422–2425
74. Hinds CJ, Watson JD (1985) Intensive Care. In: Shepherd JH, Monaghan JH (eds) Clinical gynaecological oncology. Blackwell, Oxford, pp 351–368
75. Hoagland CH (1984) Haematologic complications of cancer chemotherapy. In: Perry MC, Yarbro JW (eds) Toxicity of chemotherapy. Grune & Stratton, New York, pp 433–448
76. Holter AR, Fischer JE (1977) The effects of perioperative hyperalimentation on complications in patients with carcinoma and weight loss. J Surg Res 23:31–34
77. Hoye RG, Bennett SH, Geelhoed GW, Gorschboth C (1972) Fluid volume and albumin kinetics occurring with major surgery. JAMA 10:1255–1259
78. Hughes WT (1977) *Pneumocystis carinii* pneumonia. N Engl J Med 297:1381–1383
79. Hughes WT (1987) *Pneumocystis carinii* pneumonitis. N Engl J Med 317:1021–1023
80. Hughes WT, Feldman S, Aur RJA et al. (1975) Intensity of immunosuppressive therapy and the incidence of *Pneumocystis carinii* pneumonitis. Cancer 36:2004–2009

80a. Hurt SM, McEwen J, McKenna SP (1986) Measuring health status. Croom Helm, London, pp 163–202

81. Jehn U (1988) Managing fungal and viral infection in the immunocompromised host. Recent Results Cancer Res 108:61–70
82. Johnson MH, Gordon PW, Fitzgerald FT (1986) Stratification of prognosis in granulocytopenic patients with haematologic malignancies using the APACHE-II severity of illness score. Crit Care Med 14:693–697
83. Joshi JH, Schimpff SC, Tenney JH et al. (1984) Can antibacterial therapy be discontinued in persistantly febrile granulocytopenic cancer patients? Am J Med 76:450–457
84. Kanis JA, Yates AJP, Russel RGG (1986) Hypercalcaemia and skeletal complications of myeloma. In: Delaware W (ed) Multiple myeloma and other paraproteinemias. Churchill Livingstone, Edinburgh
85. Kaplan RS, Wiernk PH (1984) Neurotoxicity of antitumour agents. In: Perry MC, Yarbro JW (eds) Toxicity of chemotherapy. Grune & Stratton, New York pp 365–431

86. Klastersky J (1979) Granulocyte transfusions as a therapy and a prophylaxis of infections in neutropenic patients. Eur J Cancer 15:15–22
87. Klastersky J, Zinner SH, Calandra T et al. (1988) Empiric antimicrobial therapy for febrile granulocytopenic cancer patients: lessons from four EORTC trials. Eur J Clin Oncol 24:35–45
88. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. Crit Care Med 13:818–829
89. Kovacs JA, Ng VL, Masur H et al. (1988) The diagnosis of *pneumocystis carinii* pneumonia: improved detection in sputum with use of monoclonal antibodies. N Engl J Med 318:589–593
90. Krishnan EC, Menon CD, Krishnan L, Jewell WR (1980) Deficiency in maturation process of macrophages in human cancer. J Nat Cancer Inst 65:273–276
91. Krowka MJ, Rosenow EC, Hoagland HC (1985) Pulmonary complications of bone marrow transplantation. Chest 87:237–246
92. Lau WK, Young LS, Black RE et al. (1977) Comparative efficacy and toxicity of amikacin/carbenicillin versus gentamicin/carbenicillin in leukopenic patients: a randomised prospective trial. Am J Med 62:959–966
92a. Lee EJ, Schiffer CA (1987) Serial measurement of lymphocytotoxic antibody and response to nonmatched platelet transfusions in alloimmunized patients. Blood 70:1727–1729
93. Leight GS, Michaelis LL (1978) Open lung biopsy for the diagnosis of acute, diffuse pulmonary infiltrates in the immunosuppressed patient. Chest 73:477–482
94. Leonov Y, Golik A, Kaufman S, Gilboa Y (1987) Acute tumour lysis syndrome with extreme metabolic abnormalities. Clin Lab Haematol 9:85–89
95. Levine AS, Schimpff SC, Graw RG Jr et al. (1974) Hematological malignancies and other marrow failure states: progress in the management of complicating infections. Semin Hematol 11:141–203
96. Levy R, Kaplan HS (1974) Impaired lymphocyte function in untreated Hodgkin's disease. N Engl J Med 290:181–186
97. Lishner M, Pomeranz A, Rozenbajm E, Korets Z, Srenkman L (1987) Hypercalcaemia induced acute renal failure as presenting feature of T cell leukaemia. Eur J Paediatr 146:68–69
98. Lisiewicz J (1978) Mechanism of haemorrhage in leukaemias. Semin Thromb Hemost 4:241–267
99. Lister TA, Rohatiner AZS (1982) The treatment of acute myelogenous leukaemia in adults. Semin hematol 19:172–191
100. Lloyd-Thomas AR, Dhaliwal HS, Lister TA, Hinds CJ (1986) Intensive therapy for life-threatening medical complications of haematological malignancy. Intensive Care Med 12:317–324
101. Lloyd-Thomas AR, Wright I, Lister TA, Hinds CJ (1988) Prognosis of patients receiving intensive care for life threatening medical complications of haematological malignancy. Br Med J 296:1025–1029
102. Lundy J, Sherlock P, Kurtz R, Fortner JG, Turnbull AD (1975) Spontaneous perforation of the gastrointestinal tract in patients with cancer. Am J Gastroenterol 63:447–450
103. Markman M, Abeloff MD (1983) Management of hematologic and infectious complications of intensive induction therapy for small cell carcinoma of the lung. Am J Med 74:741–746
104. Mattay RA, Farmer WC, Odero D (1977) Diagnostic fibreoptic bronchoscopy in the immunocompromised host with pulmonary infiltrates. Thorax 32:539–545
105. Matthews RC, Burnie JP (1988) A prospective assessment of a reverse passive latex agglutination test in the serodiagnosis of systemic candidosis. Serodiagn Immunother Infect Dis 2:95–101
106. McCabe RE, Brooks RG, Mark JBD, Remington JS (1985) Open lung biopsy in patients with acute leukaemia. Am J Med 78:609–616
107. Meguid MM, Meguid V (1985) Preoperative identification of the surgical cancer patient in need of postoperative supportive total parenteral nutrition. Cancer 55:258–262
108. Merritt JA, Entracher MS (1985) The acute leukemias. In: Rippe JM, Irwin RS, Alpert JS, Dalen JE (eds) Intensive care medicine. Little, Brown & Co, Boston, pp 853–858
108a. Metcalf D, Begley CG, Johnson GR et al. (1986) Biological properties in vitro of a recombinant human granulocyte-macrophage colony stimulating factor. Blood 67:37–45
109. Meuwissen JH, Tauber I, Leeuwenberg ADEM et al. (1977) Parasitologic and serological observations of infection with pneumocystis in humans. J Infect Dis 136:43–49
110. Meyers JD, Flournoy N, Thomas ED (1986) Risk factors for cytomegalovirus infection after human marrow transplantation. J Infect Dis 153:478–488
111. Milburn HL, Prentice HG, Du Bois RM (1987) Role of bronchoalveolar lavage in the evaluation on interstitial pneumonitis in recipients of bone marrow transplants. Thorax 42:766–772
112. Mitchell EP, Schein PS (1984) Gastrointestinal toxicity of chemotherapeutic agents. In: Perry MC, Yarbro JW (eds) Toxicity of chemotherapy. Grune & Stratton, New York pp 269–295
113. Mohler JL, Flanigan RC (1987) The effect of nutritional status and support on morbidity and mortality of bladder cancer patients treated by radical cystectomy. J Urol 137:404–407
114. Morrison HM, Stockley RA (1988) The many uses of bronchoalveolar lavage. Br Med J 296:1758
115. Morton AR, Cantrill JA, Craig AE et al. (1988) Single dose versus daily intravenous amino-hydroxypropylidene biphosphonate (APD) for the hypercalcaemia of malignancy. Br Med J 296:811–814
116. Muller JM, Brenner U, Dienst C, Pichlmaier H (1982) Preoperative parenteral feeding in patients with gastrointestinal carcinoma. Lancet i:68
117. Mundy GR, Martin TJ (1982) The hypercalaemia of malignancy: pathogenesis and management. Metabolism 31:1247–1277
118. Nauseff WM, Maki DG (1983) A study of the value of simple protective isolation in patients with granulocytopenia. N Engl J Med 304:448–453
119. Nedelkova M, Bacalova S, Georgieva B (1981) Infectious complications and host immune defence in acute leukaemia. Eur J Cancer 17:617–622
120. Neiman PR, Reeves W, Ray G et al. (1977) A prospective analysis of interstitial pneumonia and opportunistic viral infection among recipients of allogenic bone marrow grafts. J Infect Dis 136:754–767
120a. Nemunaitis J, Singer JW, Buckner CD et al. (1988) Use of recombinant human granulocyte-macrophage colony stimulating factor in autologous bone marrow transplantation for lymphoid malignancies. Blood 72:834–836
121. Nieto AF, Dofy DB (1986) Superior vena cava obstruction: clinical syndrome, aetiology and history. Curr Probl Cancer 10:441–484

122. Ognibene FP, Martin SE, Parker MM et al (1986) Adult respiratory distress syndrome in patients with severe neutropenia. N Engl J Med 315:547–551
123. Orr JW, Shingleton HM, Soong SJ et al. (1983) Hemodynamic parameters following pelvic exenteration. Am J Obstet Gynecol 146:822–892
123a. Patrick DL, Davis M, Southerland LI et al. (1988) Quality of life following intensive care. J Gen Int Med 3:218–223
124. Pennington JE, Feldman NT (1977) Pulmonary infiltrates and fever in patients with hematologic malignancy: assessment of transbronchial biopsy. Am J Med 62:581–587
125. Pennington JE, Reynolds HY, Carbone PP (1973) *Pseudomonas* pneumonia: a restrospective study of 36 cases. Am J Med 55:155–160
126. Pennington JE, Small GJ (1987) Passive immune therapy for experimental *Pseudomonas aeruginosa* pneumonia in the neutropenic host. J Infect Dis 155:973–978
127. Perry MC (1984) Hepatotoxicity of chemotherapeutic agents. In: Perry MC, Yarbro JW (eds) Toxicity of chemotherapy. Grune & Stratton, New York, pp 297–315
128. Peters SG, Meadows JA, Gracey DR (1988) Outcome of respiratory failure in haematologic malignancy. Chest 94:99–102
129. Pizzo PA (1984) Granulocytopenia and cancer therapy: past problems, current solutions, future challenges. Cancer 54:2649–2661
130. Pizzo PA, Robinchaud KJ, Gill FA et al. (1979) Duration of empiric antibiotic therapy in granulocytopenic cancer patients. Am J Med 67:194–200
131. Pizzo PA, Robinchaud KJ, Gill FA et al. (1982) Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. Am J Med 72:101–111
132. Pizzo PA, Robinchaud KJ, Wesley R et al. (1982) Fever in the paediatric and young adult patient with cancer. Medicine 61:153–165
133. Poe RH, Wahl GW, Qazi R et al. (1986) Predictors of mortality in the immunocompromised patient with pulmonary infiltrates. Arch Intern Med 146:1304–1308
134. Preisler HD, Hasenclever HF, Henderson ES (1971) Anti-Candida antibodies in patients with acute leukaemia: a prospective study. Am J Med 51:352–361
135. Press OW, Livingston R (1987) Management of malignant pericardial effusion and tamponade. JAMA 257: 1088–1092
136. Price FW (ed) (1937) A textbook of the practice of medicine. Oxford University Press, Oxford
137. Reed EC, Bowden RA, Dandliker PS et al. (1987) Efficacy of cytomegalovirus immunoglobulin in marrow transplant recipients with cytomegalovirus pneumonia. J Infect Dis 156:641–645
138. Remington JS, Schimpff SC (1981) Please do not eat the salads. N Eng J Med 304:433–435
139. Rinaldo JE, Borovetz H (1985) Deterioration of oxygenation and abnormal lung microvascular permeability during resolution of leukopenia in patients with diffuse lung injury. Am Rev Respir Dis 131:579–583
140. Rohatiner AZS, Gregory WM, Barnett MJ et al. (1988) Short term therapy for acute myelogenous leukaemia. J Clin Oncol 6:218–226
141. Romainis WHC, Mitchiner PH (1937) The science and practice of surgery volume 1. Churchill, London
142. Rosch J, Bedell JE, Putnam J et al. (1987) Gianturco expandable wire stents in the treatment of superior vena cava syndrome recurring after maximum-tolerance radiotherapy. Cancer 60:1243–1246
143. Rosenheim MS, Farewell VT, Price TH et al. (1980) The cost effectiveness of therapeutic and prophylactic leukocyte transfusion. N Eng J Med 302:1058–1062
144. Rosenthal N, Insogna KL, Godsall JW et al. (1985) Elevations in circulating 1,25-dihydroxy vitamin D in three patients with lymphoma-associated hypercalcaemia. J Clin Endocrinol Metab 60:29–33
145. Rossiter SJ, Mille DC, Churg AM et al. (1979) Open lung biopsy in the immunosuppressed patient: is it really beneficial? J Thorac Cardiovasc Surg 77:338–343
146. Rubinstein LJ, Herman MM, Long TF, Wilbur JR (1975) Disseminated necrotizing leukoencephalopathy: a complication of treated central nervous system leukaemia and lymphoma. Cancer 35:291–305
147. Sallerfors B, Gale RP (1987) A critical analysis of acute graft-versus-host disease in twins. In: Gale RP, Champlin R (eds) Prognosis in bone marrow transplantation. Liss, New York pp 281–293
148. Santosham M, Reid R, Ambrosino DM et al. (1987) Prevention of *Haemophilus* influenzae type B infections in high risk infants treated with bacterial polysaccharide immune globulin. N Engl J Med 317:923–929
149. Saral R, Burns W, Laskin OL, Santos GW, Lietman PS (1981) Acyclovir prophylaxis of herpes-simplex-virus infections. N Engl J Med 305:63–67
150. Saravolatz LD, Burch KH, Fisher E et al. (1979) The compromised host and Legionnaires disease. Ann Intern Med 90:533–537
151. Satler LF, Rackley CE (1986) The medical emergency of cardiac tamponade: recognition and management. Cardiovasc Clin 16:181–189
152. Satterfield JR, McLaughlin JS (1979) Open lung biopsy in diagnosing infiltrates in immunosuppressed patients. Ann Thorac Surg 28:359–362
153. Scher HI, Yagoda A (1987) Bone metastases: pathogenesis, treatment and rationale for use of resorption inhibitors. Am J Med 82:6–28
154. Schiffer CA, Aisner J, Daly PA et al. (1979) Alloimmunization following prophylactic granulocyte transfusion. Blood 54:766–774
155. Schilsky RL (1984) Renal and metabolic toxicities of cancer treatment. In: Perry MC, Yarbro JW (eds) Toxicity of chemotherapy. Grune & Stratton, New York pp 317–342
156. Schimpff SC (1989) Infection in the leukaemia patient: diagnosis, therapy and prevention. In: Henderson E, Lister TA (eds) William Dameshek and Frederick Gunz's Leukemia, 5th edn. Saunders, Philadelphia, pp 687–709
157. Schimpff SC, Greene WH, Young VM et al. (1975) Infection prevention in acute nonlymphocytic leukaemia: laminar air flow room reverse isolation with oral, non-absorbable antibiotic prophylaxis. Ann Intern Med 82:351–358
158. Schimpff SC, Young VM, Greene WH et al. (1972) Origin of infection in acute nonlymphocytic leukemia: significance of hospital acquisition of potential pathogens. Ann Intern Med 77:707–711
159. Schuster DP, Marion JM (1983) Precedents for meaningful recovery during treatment in a medical intensive care unit: outcome in patients with hematological malignancy. Am J Med 75:402–408
160. Scott RB (1957) Leukaemia. Lancet i:1053–1058
161. Sculier JP, Bron D, Verboven M, Klastersky J (1988) Multiple organ failure during interleukin-2 administra-

tion and LAK cells infusion. Intensive Care Med 14:666–667
162. Sculier JP, Ries F, Verboven N, Coune E, Klatersky J (1988) Role of intensive care unit in a medical oncology department. Eur J Cancer Clin Oncol 24:513–517
163. Sherwood LM (1980) The multiple causes of hypercalcaemia in malignant disease. N Eng J Med 303:1412–1413
164. Shoemaker WC, Appel PL, Bland R, Hopkins JA, Change P (1982) Clinical trial of an algorithm for outcome prediction in acute circulatory failure. Crit Care Med 10:390–397
165. Shoemaker WC, Appel PL, Waxman K et al. (1982) Clinical trial of survivors' cardiorespiratory patterns as therapeutic goals in critically ill postoperative patients. Crit Care Med 10:398–403
165a. Shoemaker WC, Appel P, Kram H et al. (1988) Prospective trial of supranormal values of survivors as therapeutic goals in high risk surgical patients. Chest 94:1176–1186
166. Sickles EA, Greene WH, Wiernik PH (1975) Clinical presentation of infection in granulocytopenic patients. Arch Intern Med 135:715–719
167. Sickles EA, Young VM, Greene WH et al. (1973) Pneumonia in acute leukaemia. Ann Intern Med 79:528–534
168. Siegal T, Siegal T (1987) Treatment of metastatic epidural cord compression: state of the art. In: Lapis K, Eckhardt S (eds) UICC 14th international cancer congress, Budapest: Radiotherapy, Paediatric Oncology, Neuro-oncology, pp 329–336
169. Singer C, Armstrong D, Rosen PP et al. (1975) *Pneumocystis Carinii* pneumonia: a cluster of eleven cases. Ann Intern Med 82:722–777
170. Singer C, Armstrong D, Rosen PP, Walzer PD, Yu B (1979) Diffuse pulmonary infiltrates in immunosuppressed patients: Prospective study of 80 cases. Am J Med 6:110–120
171. Singer FR, Fernandez M (1987) Therapy of hypercalcaemia of malignancy. Am J Med 82:34–41
172. Slevin ML, Cotterill AM, Bell R, Lister TA (1981) The "tumour overkill syndrome": a potentially lethal complication of cancer chemotherapy. Postgrad Med J 57:727–729
173. Slevin ML, Knowles GK, Phillips HJ, Stansfeld AG, Lister TA (1982) The air crescent sign of invasive pulmonary aspergillosis in acute leukaemia. Thorax 37: 554–5
174. Smith CR, Lipsky JJ, Laskin OL et al. (1980) Double-blind comparison of the nephrotoxicity and auditory toxicity of gentamicin and tobramycin. N Engl J Med 302:1106–1109
175. Snow RM, Miller WC, Rice DL, Ali MK (1979) Respiratory failure in cancer patients. JAMA 241:2039–2042
176. Solomon MJ, Smith MF, Dowd JB, Bistrian BR, Blackburn GL (1978) Optimal nutritional support in surgery for bladder cancer: preservation of visceral protein by amino acid infusions. J Urol 119:350–354
177. Springmeyer SC, Silverstri RC, Sale GE et al. (1982) The role of transbronchial biopsy for the diagnosis of diffuse pneumonias in immunocompromised marrow transplant recipients. Am Rev Resp Dis 126:763–765
178. Strauss RG, Connett JE, Gale RP et al. (1981) A controlled trial of prophylactic granulocyte transfusions during initial induction chemotherapy for acute myelogenous leukaemia. N Engl J Med 305:597–603
179. Tenholder MF, Hooper RG (1980) Pulmonary infiltrates in leukaemia. Chest 78:468–473
180. Theologides A (1978) Neoplastic cardiac tamponade. Semin Oncol 5:181–192
181. Thomas F, Burke JP, Parker J et al. (1983) The risk of infection related to radial versus femoral sites for arterial catheterization. Crit Care Med 11:807–812
182. Thompson BR, Julian TB, Streple JF (1981) Perioperative total parenteral nutrition in patients with gastrointestinal cancer. J Surg Res 30:497–500
183. Tokaz LK, Von Hoff DD (1984) The cardiotoxicity of anticancer drugs. In: Perry MC, Yarbro JW (eds) Toxicity of chemotherapy. Grune & Stratton, New York
184. Torrecilla C, Cortes JL, Chamorro C, Rubio JJ, Galdos P, De Villota ED (1988) Prognostic assessment of the acute complications of bone marrow transplantation requiring intensive therapy. Intensive Care Med 14: 393–398
185. Turnbull AD, Goldiner P, Silverman D, Howland W (1976) The role of an intensive care unit in a cancer centre. Cancer 37:82–84
186. Turnbull AD, Carlon GC, Baron R, Sichel W, Young C, Howland W (1979) The inverse relationship between cost and survival in the critically ill cancer patient. Crit Care Med 7:20–23
186a. Vadhan-Raj S, Keating M, LeMaistre A et al. (1987) Effects of recombinant human granulocyte-macrophage colony stimulating factor in patients with myelodysplastic syndromes. N Eng J Med 317:1545–1552
187. Valdivieso M, Gil-Extremera B, Zornoza J et al. (1977) Gram-negative bacillary pneumonia in the compromised host. Medicine 56:241–254
188. Van Belle SJP, Volkaert A, Taeymans Y, Spapen H, Block P (1987) Treatment of malignant pericardial tamponade with sclerosis induced by instillation of bleomycin. Int J Cardiol 16:155–160
189. Van Der Waaij D (1988) Selective decontamination of the digestive tract: general principles. Eur J Clin Oncol 24 (Suppl 1):S1–S4
190. Van Ness MM, Cattau EL (1987) Fulminant colitis complicating antibiotic associated pseudoembraneous colitis. Am J Gastroenterol 82:374–377
191. Vernant JP, Brun B, Mannoni P, Dreyfus B (1979) Respiratory distress of hyperleukocytic granulocytic leukemias. Cancer 44:264–268
192. Wardman AG, Cooke NJ (1984) Pulmonary infiltrates in adult acute leukaemia: empirical treatment or lung biopsy? Thorax 34:647–650
193. Willson JKV (1978) Pulmonary toxicity of antineoplastic drugs. Cancer Treatment Rep 62:2003–2008
194. Wimberley N, Faling LJ, Bartlett JG (1979) A fibreoptic bronchoscopy technique to obtain uncontaminated lower airway secretions for bacterial culture. Am Rev Resp Dis 119:337–343
195. Winston DJ, Ho WG, Howell CL et al. (1980) Cytomegaloviruses associated with leukocyte transfusions. Ann Intern Med 93:671–675
196. Winston DJ, Ho WG, Gale RP (1981) Prophylactic granulocyte transfusions during chemotherapy of acute non lymphocytic leukaemia. Ann Intern Med 94:616–622
197. Winston DJ, Ho WG, Gale RP (1982) Therapeutic granulocyte transfusions for documented infections. Ann Intern Med 97:509–515
198. Winston DJ, Ho WG, Lin CH et al. (1987) Intravenous immune globulin for prevention of cytomegalovirus

infection and interstitial pneumonia after bone marrow transplantation. Ann Intern Med 106:12–18
199. Winston DJ, Ho WG, Gale RP, Champlin RE (1988) Prophylaxis on infections in bone marrow transplants. Eur J Clin Oncol 24:15–23
200. Witherspoon RP, Sterb R, Ochs HD et al. (1981) Recovery of antibody production in human allogenic marrow graft recipients, influence of time post transplantation: the presence or absence of chronic graft-versus-host disease and antithymocyte globulin treatment. Blood 58:360–368
201. Wright DG, Robinchaud KJ, Pizzo PA, Deisseroth AB (1981) Lethal pulmonary reactions associated with the combined use of amphotericin B and leukocyte transfusions. N Engl J Med 304:1185–1189
202. Young LS, Meyer RD, Armstrong D (1973) *Pseudomonas aeruginosa* vaccine in cancer patients. Ann Intern Med 79:518–522
202a. Zigmond AS, Smith RP (1983) The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 67:361–370
203. Zusman J, Brown DM, Nesbit ME (1973) Hyperphosphatemia, hyperphosphaturia and hypocalcaemia in acute lymphoblastic leukaemia. N Eng J Med 289:1335–1340