

## Editorial

*Pneumocystis carinii* pneumonia

The first description of pneumocysts is credited to Chagas<sup>1</sup> in 1909, who mistook them for trypanosomes in guinea pig lungs. Carini reported similar structures in rat lungs infected with *Trypanosoma cruzi*. Subsequently Dr and Madame Delanoe in Paris found pneumocysts in sewer rats without trypanosomiasis and proposed the name *Pneumocystis carinii* in honour of the Brazilian Carini.<sup>1</sup> Although Chagas probably reported the first human case of pneumocystosis, its importance was not recognised until the second world war, when outbreaks of pneumonia occurred throughout Europe in malnourished children in overcrowded orphanages.<sup>2,3</sup> Histologically, the lungs of such patients showed considerable mononuclear cell interstitial infiltration and foamy vacuolated alveolar exudates. The condition was named interstitial plasma cell pneumonia. A definite association with *P carinii* infection was made in 1952.<sup>4</sup> Subsequently, pneumocystis pneumonia was diagnosed in infants with congenital immunodeficiency states. Epidemic pneumocystis pneumonia has virtually disappeared from Europe, but is still recognised in parts of the world where malnutrition and poverty prevail.<sup>1,2,5</sup>

Until recently pneumocystis pneumonia largely affected patients receiving immunosuppressive treatment and corticosteroids for cancer, organ transplantation, and other conditions. Reports from 1981 onwards, however, detailed the association between pneumocystis pneumonia, other opportunistic infections, and Kaposi's sarcoma in previously well homosexual men and drug abusers.<sup>6</sup> The acquired immune deficiency syndrome (AIDS) has caused intense interest in the medical and lay press. Recently, 169 cases of AIDS have been recorded in the United Kingdom, 762 in Europe, and 8495 in the United States (Communicable Disease Surveillance Center, 1985, unpublished). As pneumocystis pneumonia is by far the commonest opportunistic infection (85%) in AIDS, clinicians and micro-

biologists will need to become familiar with the diagnosis and treatment of pneumocystosis.

**The organism**

The taxonomy of *P carinii* continues to cause debate. At times it has been considered both as a trypanosome and as a fungus, largely owing to its ability to take up silver stains. It is now generally held to be a sporozoan with a life cycle similar to that of *Toxoplasma gondii*. This conclusion is supported by its susceptibility to antiparasitic agents. Although there are minor antigenic differences between strains isolated from various animal sources, they would all appear to belong to a single species since the similarities are greater than the differences.

The life cycle remains incompletely understood. Nevertheless detailed morphological studies of infected human and animal lungs by light and electron microscopy have increased our knowledge in recent years.<sup>7,8</sup> The parasite exists in both trophozoite and cystic forms within the lung. The trophozoites are pleomorphic and 1-4  $\mu\text{m}$  in diameter, staining well with Giemsa. In contrast, the cysts are 5-7  $\mu\text{m}$  in diameter, possess a thick wall, and stain best with methenamine silver stain, which makes them readily identifiable in tissues, although they are often outnumbered by the trophozoite forms at certain stages of the infection. The thick walled cysts contain up to eight smaller bodies or sporozoites. These are thought to emerge and develop into trophozoites, which may or may not undergo binary fission before maturing and developing into cysts to repeat the life cycle. Electron microscopic studies have shown the cyst to undergo maturation with the liberation of trophozoites before collapse.<sup>9</sup> The trophozoite possesses a nucleus but few cytoplasmic organelles, although tubular extensions of the surface cytoplasm, or filopodia, can be visualised.

Koch's postulates have yet to be fulfilled in relation to pneumocystis pneumonia. Isolation of the parasite from the human lung, first reported by Pifer and her colleagues,<sup>10</sup> is not routinely possible. Vari-ous cell lines permit isolation of the parasite in tissue

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(Reprints will not be available.)

culture. These include Vero, CEL, WI-38, MRC 5, and Chang liver cells.<sup>10-12</sup> The most successful so far appears to be the use of the Vero cell line with minimal essential medium and 2% fetal bovine serum.<sup>13</sup> The ratio of organisms to cells appears to be critical, as do the conditions of incubation. An atmosphere of 5% oxygen and 10% carbon dioxide favours growth, which is often maximal within a few days.<sup>14</sup> There is a trend towards a greater predominance of cystic forms over the trophozoites with more prolonged incubation. More recently *P. carinii* has been cultivated in cell lines derived from lung.<sup>15</sup>

The ready isolation of the parasite from the human lung would undoubtedly facilitate diagnosis and allow cultivation of large numbers of cysts and trophozoites. This in turn would lead to a greater understanding of the parasite, its antigenic determinants, and factors governing its various stages of growth.

### Pathogenesis

*P. carinii* has been found to exist saprophytically in the lungs of a wide range of animal species, including man.<sup>16</sup> There is evidence to suggest that it is frequently acquired in early childhood, where it usually causes inapparent infections, coinciding with loss of maternally acquired antibody.<sup>17, 18</sup> Infection presumably occurs by inhalation, although in view of the reports of congenital infection transplacental infection cannot be excluded.<sup>19</sup> It probably remains in a latent state for many years and undergoes reactivation in response to immune suppression, although case clustering has raised the possibility of hospital acquired infection.<sup>20</sup> The main predisposing conditions include lymphatic leukaemia,<sup>21</sup> malignant lymphoma, and organ transplantation.<sup>22-24</sup> More recently pneumocystis pneumonia has proved the major infectious complication among those with AIDS.<sup>25</sup> Other, less frequent predisposing causes are collagen vascular disease,<sup>26</sup> solid tumours, other haematological conditions, and primary immunodeficiency states,<sup>27</sup> and it occasionally occurs in immunocompetent neonates.<sup>28</sup> In all these circumstances, except in starvation and AIDS, *P. carinii* infection is uncommon unless corticosteroids or cytotoxic agents have been used.<sup>26</sup> Of the two classes of agents, corticosteroids are the major predisposing factor and this is reflected in the various animal models of pneumocystis pneumonia.<sup>8</sup> Among the cytotoxic and immunosuppressive drugs azathioprine, methotrexate, and the vinca alkaloids are the most frequently identified.<sup>26</sup> There is little doubt that the frequency of pneumocystis pneumonia is proportional to the degree of immunosuppression.

### Models of infection

The principle animal model has been the rat treated with corticosteroids. This has allowed the study of changes in the lung and growth characteristics of *P. carinii*.<sup>8, 30</sup> Rats treated with cortisone for eight weeks show progressive increase in the intensity of the *P. carinii* infection. This is enhanced by a low protein diet. Control rats not treated with cortisone show only a low level of infection throughout. The pneumonia occurs by reactivation of latent infection and there is no experimental animal that can reliably be infected with exogenous *P. carinii*. Rats treated with cortisone for only four weeks show a gradual decrease in the intensity of infection after steroids are withdrawn, although organisms were still evident up to 21 weeks later.

Light microscopy shows that in mild infection organisms lie in small numbers along alveolar walls. As infection increases, more alveoli become filled with clumps of organisms, alveolar lining cells hypertrophy, and there is a mild mononuclear cell interstitial infiltration. Foamy eosinophilic material appears in the alveolar spaces, which eventually become completely filled. When the steroids are stopped at four weeks, however, there is a dramatic increase in the interstitial cellular infiltration and alveolar macrophages. Interstitial fibrosis may appear subsequently.<sup>8</sup>

Electron microscopy shows that the *P. carinii* trophozoites lie in tight apposition to type I pneumocytes and are covered by the liquid alveolar lining layer.<sup>8, 31</sup> Increased permeability of the alveolar capillary membrane (as shown by leakage of horse-radish peroxidase) is the first change seen in alveolar structure after infection.<sup>32</sup> Later the type I pneumocytes degenerate, denuding the alveolar wall, and the trophozoites come into direct contact with the basement membrane. Some are found below the epithelium or in the interstitium. Extrapulmonary spread has been seen rarely in man,<sup>33</sup> most commonly in lymph nodes and spleen. The foamy eosinophilic material in the alveoli probably represents degenerative membranes of the organism and alveolar cells, surfactant, and protein exudate. The evolution of these alveolar changes explains why dyspnoea is the earliest manifestation of pneumocystis pneumonia.

Healthy rats usually have no serum antibodies to *P. carinii* when young, but these appear with age. Corticosteroid treatment and protein malnutrition stimulate heavy infection but depress antibody production. When corticosteroids are stopped high antibody levels develop. Specific antibody can be detected in lavage fluid from infected rats and also coating the organism.<sup>34</sup> Alveolar macrophages will

not ingest trophozoites unless antipneumocystis serum is present, suggesting that both cellular and humoral forms of immunity are important.<sup>35</sup> Indirect fluorescent antibody staining, with specific rabbit antisera to rat *P. carinii*, has proved the most sensitive method of detecting organisms in tissue sections and alveolar fluid of cortisone treated rats.<sup>36</sup>

### Clinical features

The clinical features of pneumocystis pneumonia have been well described in infants with epidemic interstitial plasma cell pneumonia, children and adults having immunosuppressive treatment, and those with AIDS. Constant features include symptoms of a febrile illness with dyspnoea and dry cough from progressive alveolar filling. Those who develop pneumocystis pneumonia are, however, also at risk of various other pulmonary diseases that may modify the clinical presentation. Gadjusek<sup>3</sup> reported that epidemic pneumocystis pneumonia started insidiously over seven to 14 days with non-specific malaise and a gradually increasing respiratory rate. Coryza, fever, cough, and weight loss were unusual initially. At the height of the illness there was considerable dyspnoea, cyanosis, intercostal recession, flaring of the nasal alae, and sometimes mediastinal emphysema and pneumothorax. Characteristically, few signs were heard on chest examination. Treatment was with rest and oxygen and over a quarter of patients died. Survivors recovered slowly over four to six weeks. Children with congenital immunodeficiency diseases may present in a similar way.

Occasionally, apparently normal individuals develop pneumocystis pneumonia and may present with a non-specific pneumonia. In one study *P. carinii* infection was implicated in 18% of apparently normal children admitted to hospital because of pneumonia. The clinical features were similar to those in children with other types of pneumonia.<sup>28</sup>

By contrast, patients who are on immunosuppressive treatment usually present with an abrupt onset of illness with dyspnoea in over 90%, high fever in two thirds, and dry cough in half. Sputum production, haemoptysis, and chest pain occur in less than 8%. Lung crepitations are detected in only a third of cases; other chest signs are unusual. Symptoms may develop acutely<sup>37</sup> but the average duration of symptoms is about two weeks. Symptoms may coincide with a reduction or cessation of corticosteroid treatment.<sup>38</sup> This may reflect a loss of anti-inflammatory effect—as in cortisone treated rats, where the cessation of corticosteroids is associated with a considerable increase in the lung's inflammatory response.<sup>30</sup>

There appear to be several differences between

pneumocystis pneumonia in AIDS patients and the condition affecting other immunosuppressed adults.<sup>37 39–41</sup> One likely explanation for this may be that, unlike AIDS, immunosuppression in non-AIDS patient may often be modified both during and after pneumocystis pneumonia. The attack rate of 35–60% is high in AIDS. Symptoms appear to develop much more insidiously, over four weeks or so, although increased awareness of the condition may result in earlier presentation and diagnosis.<sup>39</sup> Fevers, dyspnoea, dry cough, weight loss, diarrhoea, and malaise are common. Chest signs are sparse or absent. Pneumocystis pneumonia has, however, been diagnosed in both symptom free patients with abnormal chest radiographs<sup>39</sup> and patients with mild symptoms who have normal radiographs.<sup>25 42 43</sup> Patients with AIDS and pneumocystis pneumonia improve more slowly than others and the mortality rate is higher.<sup>37</sup>

### Laboratory investigations

There are no haematological and biochemical tests that are helpful in diagnosing pneumocystis pneumonia. Abnormalities often result from the underlying disease or as a result of its treatment. Arterial blood gas estimations usually show severe hypoxia; arterial oxygen tensions ( $\text{PaO}_2$ ) of 8 kPa (60 mm Hg) or less are common.<sup>39 42</sup> Hypercapnia and respiratory acidosis occur at a late stage. Serial lung function testing in patients with AIDS and pneumocystis pneumonia shows progressive reduction in total lung capacity and vital capacity and a rise in the alveolar-arterial partial pressure gradient for oxygen. A reduction in diffusing capacity for carbon monoxide (TLCO) to less than 70% of the predicted value is reported in nearly all cases.<sup>25 42 44</sup>

### Radiographic findings

The typical radiographic finding is diffuse, bilateral alveolar and interstitial shadowing, beginning in the perihilar region and later coalescing and spreading into a butterfly pattern with relative sparing of lung apices and bases. Initially the shadowing is reticulonodular but progresses over three to five days into diffuse, fluffy shadows and finally dense homogeneous consolidation. Air bronchograms are present in over half the cases.<sup>38 45 46</sup> This pattern is not unique to pneumocystis pneumonia and a diagnosis cannot be made on radiographic appearance alone. Many atypical features have been described.<sup>46</sup> Nevertheless, the presence of focal lobar or segmental shadows, lung cavitation, large pleural effusions, and hilar lymphadenopathy are against the diagnosis of pneumocystis pneumonia, although

they may be associated with the underlying disease process or a concurrent infection. Radiographic shadowing may lag behind symptoms. Normal chest radiographs have been reported in 10–20% of patients with AIDS at the time of diagnosis of pneumocystis pneumonia.<sup>25 42 43</sup> Although the radiographs subsequently became abnormal, such patients have a good prognosis.<sup>47</sup>

Gallium 67 lung scans invariably have diffuse abnormalities in patients with pneumocystis pneumonia even in the presence of a normal chest radiograph.<sup>43</sup> In one series, gallium scans were positive in 96 of 98 cases of pneumocystis pneumonia, including 10 with normal chest radiographs.<sup>25</sup> Although there is a very high sensitivity for pneumocystis pneumonia, scans are positive in a wide variety of other active lung conditions. For instance, 47% of patients with AIDS who had acute diffuse lung shadowing not caused by pneumocystis pneumonia had a positive gallium scan.<sup>25</sup> The specificity of the scan for diagnosing pneumocystis pneumonia can be increased by using a graded scoring system.<sup>43</sup>

### Diagnosis

The clinical, laboratory, and radiographic patterns are not characteristic and the diagnosis can only be made with confidence by demonstrating the organism in the lung or bronchoalveolar fluid.

### DIAGNOSTIC PROCEDURES

There are several different ways of sampling lung tissue.<sup>48</sup> Most have been used successfully to diagnose pneumocystis pneumonia. Percutaneous needle aspiration is popular in some centres for children; a diagnostic rate of 60–95% for pneumocystis pneumonia is reported in experienced hands.<sup>49 50</sup> It is quick, well tolerated, and a relatively safe procedure in children, pneumothorax being the main risk. In one series 17% of patients required a chest drain for pneumothorax.<sup>49</sup>

For adults the initial procedure of choice is fiberoptic bronchoscopy.<sup>42 51–4</sup> This is widely available and safe. At bronchoscopy bronchial and transbronchial biopsy specimens, peripheral brush biopsy specimens, bronchial aspirates, and bronchoalveolar lavage fluid can be obtained. In a recent series of patients with AIDS who had lung shadowing pneumocystis pneumonia was diagnosed by bronchoscopy in 368 of 373 (95%) episodes.<sup>25</sup> The diagnosis was made after both touch preparation and fixation of transbronchial lung tissue in 95% of cases, lavage in 79%, bronchial washings in 55%<sup>42</sup> and brush biopsies in 39% of cases. No important complications were recorded but a repeat broncho-

scopy was sometimes necessary for a diagnosis. Other infections such as cytomegalovirus and *Mycobacterium avium intracellulare* can also be diagnosed by this technique. Kaposi's sarcoma, however, is not readily identified by bronchoscopy.<sup>25</sup> *P. carinii* infection has also been diagnosed by bronchoalveolar lavage in AIDS patients with symptoms who had normal chest radiographs.

If pneumocystis pneumonia is suspected in a patient with AIDS who has normal chest radiograph, it is recommended that invasive tests should be considered if any of the following are abnormal: gallium scan, TLCO, or alveolar–arterial oxygen gradient.<sup>25</sup> We do not yet know whether any of these tests will be a useful screening procedure for patients with AIDS. Precautions to be taken when a patient with AIDS is being investigated by bronchoscopy have been reviewed elsewhere.<sup>25 54</sup> The success rate for diagnosing pneumocystis pneumonia at bronchoscopy is probably marginally lower in those who do not have AIDS,<sup>38</sup> perhaps because of a lower pathogen burden in the lungs. Bronchoalveolar lavage, however, has been used successfully in immunosuppressed adults to diagnose pneumocystis pneumonia.<sup>40 55 56</sup>

The diagnostic problem is somewhat different in patients without AIDS because of the diversity of infective and non-infective pulmonary disease that may be present, and open lung biopsy is favoured by groups who have had extensive experience of diagnosing pneumocystis pneumonia. In patients without AIDS who have acute lung shadowing<sup>33 38 50</sup> *P. carinii* is the commonest pathogen identified at open biopsy. Open lung biopsy is successful in giving a specific diagnosis (usually of infection) in 50–80%,<sup>48</sup> and is also the best way of identifying the other causes of acute lung shadowing.<sup>57–60</sup> The operative mortality rate is up to 1% and minor complications occur in a proportion of cases.<sup>48</sup>

### LABORATORY DIAGNOSIS OF *P. carinii* INFECTION

At present laboratory diagnosis depends on the identification of the parasite within tissue or lavage material. Isolation of *P. carinii* in tissue culture remains a research procedure. Serological testing in most instances provides only supportive evidence, except in selective centres offering antigen detection.

Histologically the typical lung changes on haematoxylin and eosin staining include foamy intra-alveolar exudate; mild interstitial infiltrates of lymphocytes, plasma cells, and histiocytes; and an increase in alveolar macrophages, but an absence of neutrophils.<sup>3 61</sup> Various atypical features have been reported, including lack of alveolar exudate and the

presence of interstitial fibrosis and of granulomas.<sup>61</sup> The parasite can be found in both cystic and trophozoite forms. The cystic form is most readily visualised with silver stains such as the Gomori methenamine variety and the Gram-Weigert stain. Cysts have also been visualised by Gram staining.<sup>62</sup> The trophozoites frequently outnumber the cystic forms and may be easily overlooked. Staining of biopsy touch preparations, ground transbronchial biopsy specimens, and centrifuged lavage deposit can provide a rapid diagnosis of pneumocystis pneumonia.

The serodiagnosis of pneumocystis pneumonia has been widely explored owing to the difficulty in isolating the pathogen and the hazards of obtaining biopsy material. Various tests have been in use, although critical standardisation of the techniques has yet to be established. For example, the source of the antigen has varied widely: some centres have used naturally infected animal sources while others have relied on human tissue.<sup>10 63 64</sup> The complement fixation test has been useful in the diagnosis of epidemic pneumocystis pneumonia,<sup>65</sup> but of little help in the immunocompromised patient in whom antibody responses are considerably impaired. Immunofluorescence tests have gained popularity and have used antisera raised in immunised animals as well as convalescent serum from both infected patients and animals.<sup>66 67</sup> Using indirect immunofluorescent antibody (IFA) testing with a cyst suspension as antigen, Pifer found some 71% of children with pneumocystis pneumonia to be seropositive at the time of diagnosis, with a titre of 1/16 or more. More than 75% of normal children are, however, seropositive by 4 years of age.<sup>17 63</sup> An enzyme linked immunospecific assay (ELISA) has also been used and has shown varying titres among different groups.<sup>68</sup> This emphasises the fact that the mere presence of detectable antibody cannot be equated with the presence of active pneumocystis pneumonia. A fourfold rise in titre is, however, usually diagnostic while titres above 1:32 are certainly suspicious and appear to be associated with pneumocystis pneumonia. In the United Kingdom immunofluorescence testing is carried out only in reference centres, a human lung source being used as the antigen. The anticipated increase in patients with AIDS means that there will be considerable opportunities for the critical evaluation of serological tests in the diagnosis of pneumocystis pneumonia.

Another approach to the serodiagnosis of pneumocystis pneumonia is antigen detection. This had considerable appeal since a host response to infection is not required. Pifer *et al*<sup>17</sup> used counter-current immunoelectrophoresis (CIE) to detect *P*

*carinii* antigen, with rabbit antiserum against *P carinii* isolated in tissue culture from human and murine lung. They found that 95% of patients with cancer who had pneumocystis pneumonia were antigenaemic, compared with 15% of cancer patients without pneumonitis and none of the normal children tested. Thus positive tests for antigen do not always indicate active disease but may reflect antigen mobilisation for other reasons. Nevertheless, clearance of antigenaemia does correlate well with clinical improvement.<sup>68</sup> Fractionated *P carinii* antigens may improve specificity.<sup>69</sup> In the future more sensitive antigen detection systems, such as radioimmunoassay and ELISA,<sup>70</sup> are likely to make the diagnosis of pneumocystis pneumonia simple, rapid, and reliable through the examination of serum, lavage material, or possibly urine.

## Management

### GENERAL MEASURES

The commonest complication of pneumocystis pneumonia is respiratory failure. This may require oxygen treatment and in some instances assisted ventilation. The need for assisted ventilation is associated with a poor prognosis. Of 102 patients with AIDS who required assisted ventilation, only 14% survived.<sup>25</sup> In patients having immunosuppressive treatment the aim should be to improve the immunocompetence of the individual by reducing immunosuppressive treatment or control of the underlying disease. The fact that at present the immunocompetence of patients with AIDS cannot be improved may explain the higher mortality rate in this group. Some clinicians favour the introduction, or an increased dosage, of corticosteroids to reduce the inflammatory response to pneumocystis pneumonia; but the fact that the condition is frequently associated with other opportunistic infections is probably the biggest argument against re-introduction of corticosteroids in such patients. Anecdotal reports suggest that lung lavage may be beneficial in removing some of the alveolar exudate and improving oxygenation (analogous to the management of alveolar proteinosis).<sup>38</sup>

### SPECIFIC TREATMENT

The initial observation in 1958 that pentamidine was effective in the treatment of pneumocystis pneumonia in infants with the epidemic form of the disease was a major breakthrough.<sup>71</sup> Pentamidine is an aromatic diamidino compound synthesised some 50 years ago and used in the treatment of African trypanosomiasis and resistant forms of leishmaniasis. Its efficacy in pneumocystis pneumonia was shown in a series of some 212 patients, in whom

the mortality fell from 50% in the untreated group to 3.5% in those receiving pentamidine isethionate.<sup>72</sup> The mode of action is not clear. One suggestion is that it interferes with folate metabolism,<sup>73</sup> although folinic acid does not reduce its efficacy in experimental animal models.<sup>74</sup>

The standard dosage regimen of pentamidine isethionate is 4 mg/kg a day for 14 days by the intramuscular route.<sup>75</sup> Unfortunately toxicity is common, nephrotoxicity being recognised in almost a quarter of recipients,<sup>26</sup> probably as a result of drug concentration within the kidney.<sup>76</sup> The list of other reported adverse reactions is impressive and includes hepatotoxicity with hypoglycaemia and occasionally liver necrosis, weakness, seizures, hypocalcaemia, nausea, vomiting, sweating, tachycardia, thrombocytopenia, and sterile abscesses at the injection site. Occasional deaths have been recorded.<sup>75</sup>

Animal studies in 1966 indicated that antifolate agents such as pyrimethamine and sulphonamides were effective in pneumocystis pneumonia.<sup>74</sup> The subsequent availability of trimethoprim (TMP) led Hughes and his colleagues to conduct a successful study of the combination of trimethoprim and sulphamethoxazole (TMP-SMX) in the treatment of pneumocystis pneumonia in the rat model.<sup>77</sup> TMP is concentrated in lung tissue and is less toxic to the marrow than pyrimethamine. Subsequent carefully executed trials showed the effectiveness of TMP-SMX in human pneumocystis pneumonia.<sup>78</sup> Response rates are similar to those with pentamidine<sup>79</sup> but adverse reactions are largely avoided. TMP-SMX is known to inhibit nucleic acid synthesis through inhibition of the folic acid pathway. The sulphonamide inhibits the conversion of para-aminobenzoic acid to dihydrofolate, which in turn is blocked by TMP by its action on the enzyme dihydrofolate reductase. Neither pentamidine nor TMP-SMX is microbicidal—they are thought to act largely on the trophozoite form. The daily dose of TMP-SMX associated with optimal response rates consists of TMP 20 mg/kg plus SMX 100 mg/kg in three or four divided doses for a total of 14 days,<sup>79</sup> although in patients with AIDS complicated by pneumocystis pneumonia more prolonged treatment is often necessary.<sup>47</sup> Intravenous SMX-TMP is a useful alternative.<sup>80,81</sup> The dose of TMP is 10–20 mg/kg/day. The higher dose is often recommended initially, being reduced to 10–15 mg/kg a day when there is clinical improvement.

Although TMP-SMX is better tolerated than pentamidine it is not entirely without side effects. The most common complications are various rashes, which may occasionally be manifest as the Stevens-Johnson syndrome. Adverse reactions to high dose

TMP-SMX are much more frequent in patients with AIDS.<sup>82</sup> This is somewhat surprising owing to the overall anergy of this population and possibly argues against hypersensitivity as the basis for the reaction.

The use of TMP-SMX in renal failure may result in toxic blood levels. There is rather limited information available concerning dose modification.<sup>83,84</sup> Drug assay would appear desirable in these circumstances since it has been suggested that the therapeutic serum concentrations are 3–5 mg/l for TMP and 100–150 mg/l for SMX two hours after oral administration.<sup>79</sup>

#### RESPONSE TO TREATMENT

The best guide to successful treatment is clinical improvement of the patient. Resolution is indicated by a fall in fever within one to five days and clearing of the chest radiograph within four to 10 days. Patients with AIDS take longer to improve.<sup>39</sup> Repeat lung function measurements<sup>44</sup> and gallium scans<sup>43</sup> do not appear to be helpful in monitoring response. Similarly, repeat lung biopsy or bronchoalveolar lavage not infrequently shows persistence of *P. carinii*, even after two to three weeks of apparently effective treatment, particularly in patients with AIDS.<sup>25,41,43</sup> Clearance of *P. carinii* and the inflammatory response appears faster in those without AIDS.<sup>41</sup> In patients showing a poor response repeat bronchoscopy or lung biopsy may show a concurrent opportunistic infection. In survivors lung function abnormalities return to normal over a period of many weeks,<sup>44</sup> although fibrosis has been reported.<sup>38</sup>

In patients failing to respond to TMP-SMX by about the fifth day of treatment a change to pentamidine should be considered, particularly if there are signs of deterioration. Combined treatment with pentamidine and TMP-SMX has been considered in the hope of achieving either a synergistic effect or, by dose reduction, fewer side effects. In the cortisone treated rat model, however, this combination has not been shown to be more effective.<sup>85</sup>

#### CHEMOPROPHYLAXIS

Chemoprophylaxis was first used in the control of epidemic pneumocystis pneumonia<sup>86</sup> and subsequently in children with acute lymphoblastic leukaemia and other solid tumours undergoing chemotherapy.<sup>87,88</sup> Most experience has been gained at St Jude's Hospital, Memphis, where it has been shown that no cases of pneumocystis pneumonia have occurred since 1977 in patients with acute lymphoblastic leukaemia who have received adequate chemoprophylaxis with doses of TMP of 150 mg/m<sup>2</sup>/day and SMX of 750 mg/m<sup>2</sup>/day in two divided doses.<sup>89</sup>

Second attacks of pneumocystis pneumonia are well recognised and have occurred in up to 15% of leukaemic patients after treatment with pentamidine.<sup>90</sup> Prophylactic TMP-SMX is prescribed for at least one year after recovery from pneumocystis pneumonia unless there is improvement in the immunological state of the patient. Chemoprophylaxis of pneumocystis pneumonia in patients with AIDS may present problems owing to the high incidence of side effects with TMP-SMX. Alternative agents are needed and preliminary experience using pyrimethamine and sulfadoxine (Fansidar) has proved encouraging in those with AIDS<sup>91</sup> and in epidemic pneumocystis pneumonia.<sup>86</sup> Confirmation of efficacy and the optimal dosage have yet to be established.

#### MANAGEMENT OF THE IMMUNOSUPPRESSED PATIENT WITH LUNG SHADOWS

In practice the immunosuppressed patient presents not with obvious pneumocystis pneumonia but rather with an acute progressive lung infiltrate of unknown cause. Possible diagnoses include such diverse conditions as pulmonary oedema, pulmonary haemorrhage, the underlying disease (for example tumour or vasculitis) directly affecting the lung, reaction to the drug treatment or radiotherapy and various bacterial, fungal, viral and protozoal infections. In those with AIDS other infections are common and include in decreasing order of frequency: cytomegalovirus, *Mycobacterium avium intracellulare*, *M tuberculosis*, *Legionella pneumophila*, and cryptococcus, although Kaposi's sarcoma must also be considered.<sup>25</sup> This emphasises the importance of making a correct diagnosis of acute lung shadowing.

When the clinician is faced with an immunosuppressed patient with acute lung shadowing, the commoner respiratory pathogens should be sought immediately by routine methods. Most would then give broad spectrum antibiotics while awaiting the results. Failure to improve, or deterioration, makes urgent consideration of invasive techniques necessary. Fibreoptic bronchoscopy is the next procedure of choice, although transtracheal aspiration may be helpful.<sup>38</sup> Bronchoalveolar lavage may be performed without transbronchial biopsy in patients with uncorrectable and serious bleeding disorders. If the results are unhelpful and further information is needed, open lung biopsy should be considered as a matter of urgency. Useful clinical algorithms are given elsewhere.<sup>25 92</sup> Some studies show that open lung biopsy results in a change or confirmation of the preoperative treatment in half to two thirds of such cases.<sup>57 59 60</sup> Open biopsy offers a high chance of obtaining a definite diagnosis, which in turn allows a

more confident management plan and will prevent unnecessary and potentially toxic, multiple, empirical treatments. It can be argued, however, that the results of open lung biopsy do not alter the overall prognosis in such patients and empirical treatment is preferable and as safe.<sup>57 92 93</sup> The choice of diagnostic procedure will depend to a large extent on the expertise and facilities that are available locally, both in performing the various invasive techniques and also in handling the specimens in the laboratory. Close liaison is essential between the clinician, surgeon, microbiologist, and cytohistopathologist. An urgent "out of hours" invasive technique is of little use if the specimens are not dealt with immediately in the laboratory by an experienced operator.

#### The future

In Britain, most clinicians' experience of pneumocystis pneumonia is very limited. It seems likely, however, that doctors other than oncologists and transplantation specialists will need to be aware of the presentation, diagnosis, and treatment of this infection. Clinicians will hope that further research will establish reliable serological methods for diagnosis by antigen and antibody detection, find practical ways of culturing human *P carinii*, and clarify the best method of diagnosing pneumocystis pneumonia at the earliest stage in susceptible individuals.

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