Therapeutic Conferences

Pneumonia—Pre-existing Lung Disease

FROM THE DEPARTMENTS OF THERAPEUTICS AND PHARMACOLOGY, MEDICINE, AND GENERAL PRACTICE, UNIVERSITY OF ABERDEEN

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Case 3—Chronic obstructive lung disease.

HOUSE PHYSICIAN: This 70-year-old granite worker has long-standing chronic obstructive bronchitis. He recently developed an upper respiratory tract infection, and was admitted with bronchopneumonia. He was febrile, cyanosed, and coughing up purulent sputum.

DR. PALMER: Unlike our previous patients, this man has chronic obstructive lung disease—"C.O.L.D.". Therefore, it is to be expected that the bronchial tree below the larynx, which is normally sterile, will be populated with pneumococci, usually of low virulence, and more importantly with *Haemophilus influenzae*. If the infection develops in hospital a penicillinase-producing staphylococcus must be considered as a possible pathogenic organism. Of course, one must never forget the possibility of these patients having tuberculosis.

PROFESSOR MACGREGOR: I agree. If tubercle bacilli are not looked for the patient may not be diagnosed until he infects someone else.

HOUSE PHYSICIAN: Pneumococci and *H. influenzae* have been isolated. There are no acid-fast bacilli.

STUDENT: Because *H. influenzae* is not adequately sensitive to ordinary penicillins presumably you are going to use a broad-spectrum antibiotic.

DR. WOOD: Yes. The much wider range of activity of ampicillin compared with penicillin G, though it has a very similar structure, makes it a drug of first choice. As it is acid-stable, it is given by mouth in a dose of 250-500 mg, six hourly.

DR. HOWIE: In some hospitals the dose recommended is 1 g four times a day, which is at least double the highest normal dose that a general practitioner prescribes. In my experience even 500 mg four times a day causes a definite problem with diarrhoea—and rashes. The diarrhoea, perhaps, is not a problem to a hospital, where there are nurses, but may be the last straw in a household where an elderly couple are struggling along together, one ill and the other just able to cope.

DR. PETRIE: Even so, ampicillin is particularly useful because of its action against *H. influenzae*. It is, of course, slightly less active than penicillin G against most Gram-positive cocci.

Appointments of Speakers

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R. A WOOD, B.SC., M.R.C.P.ED., Lecturer in Therapeutics

TETRACYCLINE

STUDENT: There has been no mention of tetracycline in any of the cases.

DR. PALMER: I prefer bactericidal drugs, and tetracycline is bacteriostatic at low doses. Nevertheless, I agree with you that in this patient tetracycline could well be given.

PROFESSOR MACGREGOR: The different tetracyclines are very similar and can be discussed as a group. We have discussed their adverse effects on teeth (see B.M.J., 10 July, p. 101) especially if they are given to young children or to pregnant women. What other side effects are important?

DR. WOOD: Alimentary tract superinfections with *Candida albicans, Proteus, Pseudomonas,* and staphylococci occur. These usually follow prolonged high-dosage therapy.

STUDENT: Should nystatin not be given routinely with tetracycline?

DR. WOOD: This combination has not been proved to be superior. Tetracycline should be given alone and if any fungal superinfection should occur then it should be treated with nystatin or, if parenteral therapy is required, the drug of choice is amphotericin B.

DR. PETRIE: Various forms of renal damage have been reported, one of which was the development of a Fanconi syndrome associated with outdated tetracycline. It is thought that epianhydrotetracycline was responsible. This was formed in the presence of citric acid which was included in the tetracycline capsule to improve absorption. It has now been removed.

DR. WOOD: The tetracyclines may cause liver damage when high doses are given or when there is renal insufficiency. Doctors must remember to scale the dose down when using a tetracycline parenterally.

ABSORPTION OF TETRACYCLINE

DR. PETRIE: An interaction worth emphasizing is the reduction in the absorption of tetracycline if it is given along with divalent metals such as iron, calcium, magnesium, or aluminium; even milk and antacids may interfere with the absorption of tetracycline.

PROFESSOR MACGREGOR: Photosensitization may occur in patients taking demethychlortetracycline. These patients should avoid prolonged exposure to sunlight. This preparation is better absorbed than tetracycline and is more slowly excreted. Several other new tetracyclines have been introduced but they

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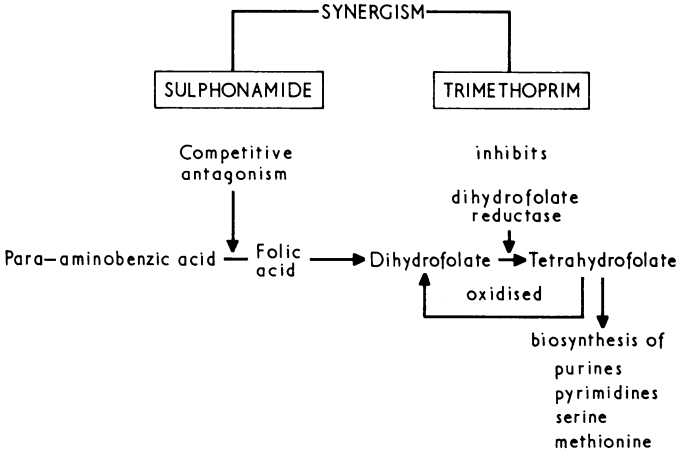
await fuller evaluation and are unlikely to prove much superior to existing drugs. How is the patient now?

HOUSE PHYSICIAN: In spite of receiving ampicillin now for several days the sputum is still purulent so I have changed to the combination of trimethoprim-sulphamethoxazole (Septrin or Bactrim), two tablets twice daily (see fig.).



Schematic "sequential blockade" – sulphamethoxazole + trimethoprim

DR. PALMER: This is useful in the management of cases such as this because it is highly effective against *H. influenzae* and the pneumococcus.

PROFESSOR MACGREGOR: The synergistic effect of trimethoprim and sulphamethoxazole is quite striking, with up to a tenfold increase in activity when the drugs are combined. The proprietary preparations contain five times as much sulphamethoxazole as trimethoprim. Once they are absorbed and distributed they achieve levels in the plasma at a ratio of 20:1. This is near the optimum synergistic ratio to inhibit many organisms.

Sulphamethoxazole was chosen as the sulphonamide because of very similar absorption and excretion characteristics to trimethoprim. Both drugs act on the same metabolic pathway at successive stages (see fig.)

STUDENT: Are side effects prominent?

DR. PETRIE: In clinical practice trimethoprim seems relatively non-toxic, though it may cause rashes and gastric upsets. Folic acid deficiency may theoretically be induced but at low doses of the drug used for short periods this may not be of much consequence. At high doses trimethoprim is teratogenic in the rat but it does not appear to be in the man. It is, of course, difficult to separate the adverse reactions due to trimethoprim from the recognized reactions to the sulphonamides as the drugs are used in a combined preparation.

OTHER DRUGS

PROFESSOR MACGREGOR: Another broad-spectrum combination group of antibiotics is the combination of penicillin with streptomycin, which is very satisfactory treatment in some cases. We have discussed the rotation of broad-spectrum antibiotics and the combination of antibiotics, and this combination allows the restriction of the use of newer antibiotics.

DR. WOOD: We know that this man does not have tubercle bacilli in his sputum. The use of streptomycin in combination with penicillin may be criticized if sputum cultures and sputum smears have not been obtained. The *Mycobacterium tuberculosis* likes nothing better than to meet a single antibiotic as it develops resistance rather rapidly.

HOUSE PHYSICIAN: I should have said that this patient's blood urea nitrogen is raised.

PROFESSOR MACGREGOR: Of course, one has to be very careful in patients over 40, but if there was any renal impairment I would avoid the aminoglycoside group of antibiotics, which includes both streptomycin and kanamycin. These drugs affect vestibular function and may also cause disturbances of hearing. They also cause hypersensitivity reactions including rashes and drug fever.

STUDENT: Don't they also cause slight neuromuscular blockade?

DR. PETRIE: Yes; this has some clinical relevance if the patient receives muscle relaxants or anaesthetics or if he has myasthenia gravis.

DR. PALMER: We use kanamycin only very occasionally. It has been associated with renal damage.

PROFESSOR MACGREGOR: We certainly restrict the use of kanamycin and use it only in extremely ill patients once vigorous therapy and other intensive measures have failed. I would emphasize that if a patient is improving on a simple antibiotic drug there is no need to change to more potent and dangerous drugs because new organisms, sensitive to more toxic drugs, have been cultured from the sputum. Sputum cultures can be misleading, particularly if the patient is already on antibiotics. Secondly, the organisms grown may not be the cause of the infection.

The results must be interpreted with caution and in consultation with bacteriological colleagues. Of course, if the patient's clinical condition is deteriorating the reports must be taken seriously indeed.

DR. PALMER: I agree—the important point in management is to assume that these infections are almost always due to the pneumococcus or *H. influenzae* and to treat accordingly. The sputum culture may lead to a change of treatment if the patient's clinical condition is deteriorating or the sputum remains persistently purulent.

MANAGEMENT IN GENERAL PRACTICE

DR. HOWIE: In general practice few sputum cultures are done, for a variety of reasons. I am sure that many potential pneumonias and lower respiratory tract infections are nipped in the bud by practitioners playing for safety and using antibiotics on perhaps minimal indications.

STUDENT: You have discussed the management of the infective aspects of this man's illness at length but what other measures are important in the general management?

DR. PALMER: This patient's obstructive lung disease is probably mild because on admission the arterial blood gas tensions showed only mild hypoxaemia—Pa_{O_2} 70 mm Hg (normal for age 85-90 mm Hg) without significant hypercapnia—Pa_{CO_2} 44 mm Hg (normal 35-44 mm Hg). Therefore, he did not have ventilatory failure because the Pa_{CO_2} is normal, and he did not require oxygen because the Pa_{O_2} is not much reduced. But he does have difficulty caughing up tenacious sputum. He is therefore having vigorous physiotherapy, postural drainage, frequent steam inhalations, and bromhexine 16 mg three times a day—twice the recommended dose.

STUDENT: Do you advocate prophylactic broad-spectrum antibiotics for patients who have chronic obstructive lung disease?

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DR. PALMER: It has not been clearly shown that continuous long-term prophylaxis reduces the number of infective episodes which are initiated by viruses, but there is some evidence that possibly the duration of the illness may be reduced. I much prefer to give these patients a supply of a broad-spectrum antibiotic. I tell them to begin treatment whenever the sputum becomes purulent, or whenever they develop upper respiratory tract infection. I ask such patients to continue the antibiotic until the sputum becomes mucoid again.

DR. HOWIE: I agree completely with this policy. Many patients in domiciliary practice may safely be given a supply of tetracycline (1 g daily) for use on their own initiative. Patients who have chronic obstructive lung disease become very reasonable judges of their own health and can be trusted to start treatment and then to tell their doctor that they have done so. I would go a little further than Dr. Palmer and suggest that treatment should be continued for the first week back at work.

PROFESSOR MACGREGOR: We have seen three patients where bacterial infection caused the patient to be ill. It is clear that there is no need to use the newer drugs if established drugs, such as penicillin G or V, are sufficient. There is no need to use broad-spectrum antibiotics in all patients, though they are of particular value in patients with pre-existing lung disease.

Close collaboration with bacteriologist colleagues is essential at all times, as sputum cultures may not reflect the organism causing the infection. If a patient is getting better on treatment with a non-toxic antibiotic, the isolation of a new organism, sensitive perhaps to more toxic drugs, should not influence the management.

DR. PALMER: I, too, would stress that close collaboration with bacteriologist colleagues is essential especially in the "difficult" case. I think that doctors should always persuade all patients, particularly those with respiratory illness, to give up cigarette smoking.

Any Questions?

We publish below a selection of questions and answers of general interest

Cervical Spondylosis

What is known of the aetiology of cervical spondylosis? And what is the prognosis with treatment?

Cervical spondylosis is generally defined as a chronic disc degeneration of the cervical spine accompanied by narrowing of disc space and osteophyte formation, particularly associated with the uncovertebral joints (joints of Luschka) and the apophysial joints. Anatomically these are closely related to the emergent nerve roots and the vertebral blood vessels. The spinal cord is also at its widest in this region; so that the signs and symptoms of cervical spondylosis tend to be those of associated nerve pressure, vascular impairment, or cord compression.

The aetiology of cervical spondylosis is unknown, but a number of factors are important. Cervical spondylosis is an osteoarthrosis, and the aetiological factors are to some extent the same. Over the age of 50, when three quarters of the population have definite *x*-ray changes. In fact, 40% of randomly selected hospital inpatients of 50 years or more may have signs of root involvement.

Apart from the general aetiological factors of osteoarthrosis, the important aetiological factors in cervical spondylosis are thought to be: (1) Postural defects, such as those associated with dorsal kyphosis and a poked forward head; (2) Injury, particularly the whiplash injury associated with road traffic accidents; (3) Occupational factors, such as the carrying of heavy weights on the head or hard physical work in cramped surroundings, as in coal mining. Treatment is on the whole unsatisfactory and has little, if any, effect on the ultimate outcome or prognosis. Acutely painful episodes tend to run a spantaneous course of 2-3 weeks, and simple measures such as analgesic drugs, heat, and soft felt collars are useful in improving patients' comfort.

The place of manipulation in treatment remains controversial, but some patients are undoubtedly immediately relieved by gentle mobilization of the neck, provided that this is accompanied by manually applied traction. Further studies of this type of treatment are awaited with interest. The more chronic neck and referred pain tends also to run a self-limiting course of 3-4 months every year or so, and in these patients treatment is also able to relieve symptoms only to a limited extent. The usual methods used are applied heat, sometimes traction is used, sometimes exercises, in particular postural and shoulder elevation exercises, also exercises to strengthen the posterior spinal muscles, and a collar is often prescribed.

However, trials of physical treatment in cervical spondylosis have never shown any great advantage of one form of treatment over another, and in these circumstances, the best thing to do seems to be the simplest. Probably, therefore, heat, home exercise, and a soft collar are as good a method management of cervical spondylosis as any other.

In those patients with neurological signs of cord involvement, the problems of treatment are considerably more difficult. Decompression of the cord has been carried out and occasionally this is of value, but on the whole surgical treatment of chronic cervical cord compression due to spondylosis is highly unsatisfactory.

Local Reaction to A.C.T.H. Injections

A patient with rheumatoid arthritis receiving A.C.T.H. injections of 0·5 to 0·75 ml at varying intervals has recently started getting small, indurated, slightly tender areas at the site of injection. These started when she was well into a course of gold injections which have certainly helped her as shown by the diminished need for A.C.T.H. Are the reactions significant and recognized?

Though details of the type of A.C.T.H. are not given, I presume from the milligram dosages quoted (as opposed to Units) that the synthetic A.C.T.H. is being used, depot-tetracosactrin (Synacthen-depot, Cortrosyn-depot). This compound is known to give rise to local reactions when given subcutaneously or into muscles of small bulk,[1-3] and it should be given by deep intramuscular injection into large muscles such as those of the buttock. It seems probable that the reactions are due principally to the contained zinc hydroxide on which the tetracosactrin is adsorbed to produce a repository preparation.

1 Besser G. M., Butler, P. W. P., and Plumpton, F. S., *British Medical Journal*, 1967, **4**, 391.
2 Nelson, J. K., *et al.*, *British Medical Journal*, 1968, **1**, 557.
3 Treadwell, B. L. J., and Dennis, P. M., *British Medical Journal*, 1969, **4**, 720.

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