Drug Treatment of Disease

DRUG TREATMENT OF CHRONIC BRONCHITIS

BY

J. G. SCADDING, M.D., F.R.C.P.*Physician, Brompton Hospital; Director of Studies, Institute of Diseases of the Chest; Physician, Postgraduate Medical School of London*

The word "bronchitis" should correctly be applied to a disease characterized by inflammation of the bronchi. It is used accurately in this sense when applied to those conditions usually described as acute bronchitis, in which, often as a direct or indirect result of a respiratory virus infection, inflammatory changes spread down from the upper respiratory tract to the bronchi. In the condition usually described as chronic bronchitis, so common in Great Britain, it is at least doubtful whether the basic abnormality is essentially inflammatory in nature, even though the acute exacerbations of infective origin which commonly punctuate its course cause inflammatory changes leading to permanent damage of the lungs. In such episodes acute inflammation at bronchiolar level may result in purulent bronchiolitis, foci of pneumonia, and small abscesses. These may partly resolve, but may also lead to fibrotic occlusion of bronchioles, to scars due to organization of pneumonic foci, or to atelectasis beyond occluded bronchioles, and destructive emphysema. These changes result in the final clinical picture usually described in this country as "chronic bronchitis and emphysema." It is with the place of drugs in the management of this condition and of episodes of acute bronchitis that this article deals.

Some other forms of lung damage with emphysema, notably that associated with pneumoconiosis, present in their later stages problems of clinical management rather similar to those presented by chronic bronchitis and emphysema. The progressive bullous type of emphysema and "primary" emphysema affecting persons without previous bronchitis present some different therapeutic problems, which will not be discussed. Similarly, although wheezy dyspnoea due to reversible airway obstruction ("bronchospasm") may occur in chronic bronchitis and measures for relief of this symptom will be discussed, the special problems of the treatment of asthma are outside the scope of this article.

ACUTE BRONCHITIS

Acute bronchitis is most often a consequence of a viral infection, but commonly becomes complicated by added bacterial infection. Sometimes, especially in chronic bronchitic subjects, acute bronchitis appears to be precipitated by irritative rather than infective factors, the most frequent being exposure to a high concentration of atmospheric pollutants as in "smog." Many points in the treatment are common to acute bronchitis occurring in previously healthy persons and to acute exacerbations in chronic bronchitic subjects; in the latter, however, some special features require separate consideration.

Relieving Dry Cough

Certain symptomatic measures may be required. Although it is unwise to suppress a cough in chronic bronchitic subjects who have a constant excess of mucus in the respiratory tract, in the early stages of an acute

tracheo-bronchitis in a previously healthy person there may be a troublesome dry cough which can legitimately be controlled by a suitable linctus. Codeine linctus *B.P.C.*, or, for more troublesome cough, methadone linctus, may be prescribed in the usual dose of 4 ml. At this stage, some patients will get relief from a steam inhalation with benzoin inhalation (vap. benzoin. *B.N.F.*) or menthol and benzoin inhalation *B.P.C.* (vap. menthol. et benzoin. *B.N.F.*). Later in the course of an acute bronchitis when expectoration starts, it may be helped by a suitable expectorant mixture such as the potassium iodide and ammonia mixture *B.P.C.*, or the sodium chloride compound mixture *B.P.C.*, taken in hot water (the Brompton Hospital "hot water medicine"). If wheezing dyspnoea indicative of bronchospasm is a feature, the antispasmodics mentioned below may be helpful, both in relieving this and in facilitating expectoration.

Cyanosis

Acute exacerbations of bronchitis in patients severely disabled with chronic bronchitis and emphysema present special problems. These patients become cyanosed from central anoxia and often have carbon-dioxide retention. Although oxygen is desirable to relieve the anoxia, it may result in such a rise of carbon dioxide tension that disturbances of consciousness and even coma may result. The best compromise in these patients is to give oxygen either in low concentration or intermittently. Nikethamide, given intravenously, is often helpful in stimulating the respiratory centres. Large doses are required, 5 to 10 ml. of the 25% solution being given slowly.

The special problems of the management of right ventricular failure and of the use of assisted respiration in such patients are outside the scope of this article.

Hypnotics

In bronchitic patients with impaired respiratory function, great caution is required in the use of hypnotics. Morphine and its analogues, and even barbiturates, are dangerous, and paraldehyde is probably the best hypnotic in a difficult case. It may be given as paraldehyde draught *B.P.C.*, 1½ fl. oz. (45 ml.), containing 60 minims (4 ml.) of paraldehyde.

Antibiotics

In both groups the question of the use of antibiotics against the bacterial infection arises. In a mild case of simple acute bronchitis it is reasonable to wait a day or so to see whether a phase of bacterial infection evidenced by a purulent sputum supervenes before starting antibacterial drugs. For chronic bronchitic subjects and for patients with more severe simple acute bronchitis it is probably wise to start treatment with a suitable antibiotic at the beginning, in the belief that, even though bacterial infection has not yet occurred,

the prophylaxis of such infection by suitable anti-bacterial drugs is likely to be beneficial.

The two common bacterial pathogens in bronchitis are *Haemophilus influenzae* and pneumococcus. Although the prevalence of these varies from time to time, in general it appears to be *H. influenzae* which is the most frequent pathogen. Nevertheless, if the patient is not gravely ill, it is reasonable to treat him for 24 hours or so as for a pneumococcal infection with penicillin, since the pneumococcus is susceptible to relatively small doses of this antibiotic and does not become resistant. But it is as well to treat more severely ill patients from the beginning as for *H. influenzae* infection. A combination of penicillin 500,000 units and streptomycin 1 g. twice daily is usually effective against *H. influenzae*, and can be continued for 5 days in most cases without ill effects. In older patients there is slight risk of vestibular toxicity from the streptomycin, but this is unlikely to develop within such a short period of administration. Caution is necessary also in patients who have renal damage. If there is nitrogen retention with a raised blood urea, streptomycin will also be retained and the customary dosage may lead to toxic levels in the blood. It is therefore better in such patients to use the alternative method of treatment by tetracycline 0.5 g. 3 or 4 times a day.

In a few patients *H. influenzae* infection may be resistant to either of these regimes. Then, if the sputum remains purulent, indicating the probability of continued lung damage at and beyond bronchiolar level, the use of chloramphenicol is justified in spite of the slight risk of a blood dyscrasia. In an acute case 0.5 g. 4 times a day is appropriate.

Usually there is little practical advantage to be gained from bacteriological studies in acute exacerbations, but the occasional case arises in which information derived from culture of sputum taken before antibacterial treatment begins may be valuable—e.g., in occasional cases a staphylococcus may be responsible. Therefore, if facilities are available it is advantageous to send a specimen of sputum to the laboratory for bacteriological examination before starting antibacterial drugs.

Whatever antibacterial treatment is given in an acute case of bronchitis, full dosage is unlikely to be required for more than 5 days. If at the end of this time the sputum has become clear and mucoid and the patient is not a known chronic bronchitic subject, the treatment can safely be discontinued. In some chronic bronchitic subjects, however, it may be wise to continue for some time after an acute attack with smaller doses of a broad-spectrum antibiotic, as will be discussed below.

CHRONIC BRONCHITIS AND EMPHYSEMA

In the management of chronic bronchitis and the progressive emphysema which eventually accompanies it, two groups of drugs are useful, the antispasmodics and antibacterial agents. The purpose of the antispasmodics is to relieve reversible airway obstruction, usually at bronchiolar level.

Antispasmodics

Some of the antispasmodic drugs are best given as occasion arises to deal with actual or expected bronchospasm. Among these are ephedrine, isoprenaline, and other sympathomimetic drugs. It is a common experience that, if these are taken regularly, they tend to lose their effectiveness. Many chronic bronchitics wake in

the morning with wheezy dyspnoea. They can take ephedrine $\frac{1}{2}$ gr. (30 mg.) or isoprenaline 20 mg. on waking. The patient should be advised to have it ready at his bedside. Ephedrine tablets are swallowed in the usual way, while isoprenaline tablets are allowed to dissolve under the tongue. Similarly, these drugs may be taken before any activity which is known to be likely to bring on wheezing and dyspnoea—e.g., some necessary exertion or going out into the cold air.

The limiting factor to the dosage of both these drugs is usually their effect on the cardiovascular system, patients complaining of palpitations, tachycardia, and sometimes of a feeling of "goose-flesh" from cutaneous vasoconstriction. If these side-effects are not severe, the dose of ephedrine may be increased to 1 gr. (65 mg.). Another untoward effect sometimes caused by these drugs, particularly ephedrine, is that they may cause difficulty in micturition in middle-aged and older men with prostatic enlargement.

Inhalation of 1% isoprenaline from a nebulizer is helpful to some patients, and its use should be timed similarly to that of the oral sympathomimetic drugs.

Theophylline

The various preparations of theophylline suitable for oral administration are probably best given in regular dosage. Of these, choline theophyllinate, 200 mg. thrice a day, is usually well tolerated and may be helpful. The maximum dosage is determined by gastric tolerance, and for patients who tolerate the drug well the dose may be increased to 400 mg. Antispasmodic drugs of both the sympathomimetic and the theophylline groups have a cerebral stimulant effect. For this reason several proprietary antispasmodic preparations contain sub-hypnotic doses of barbiturates. Such are "franol," which contains phenobarbitone $\frac{1}{8}$ gr. (8 mg.) with ephedrine $\frac{3}{20}$ gr. (10 mg.) and theophylline 2 gr. (130 mg.); "tedral," of similar composition but with a larger content ($\frac{3}{8}$ gr. (24 mg.)) of ephedrine; and "amesec," which contains aminophylline 130 mg., ephedrine hydrochloride 25 mg., and amylobarbitone 25 mg. These may be helpful during the day to those patients who experience feelings of anxiety and apprehension after taking the antispasmodic drugs alone, and sometimes to those who are troubled by palpitations. If a hypnotic is required at night, it is best to give an effective dose of a hypnotic drug separately from the antispasmodic.

Secondary Infection

The control of secondary bacterial infection in chronic bronchitis by long-term administration of small doses of broad-spectrum antibiotics has received much attention recently. Such treatment is expensive and carries several risks. The emergence of resistant strains of bacteria, especially staphylococci, is one of them. These organisms are potentially dangerous not only to the patient but also to people he meets, to whom he may pass them on. Fortunately, the pneumococcus almost never and *H. influenzae* only rarely become resistant to antibacterial drugs.

Some patients will develop gastro-intestinal symptoms, particularly diarrhoea, while receiving these drugs, presumably from alteration of the normal bacterial flora of the alimentary tract; but staphylococcal enterocolitis, the most extreme and dangerous variety of this, appears to be rare in bronchitic patients receiving the small doses customarily used for prophylaxis. Against these disadvantages must be set the diminution of

periods of disability and absence from work occasioned by acute inflammatory exacerbations of bacterial origin which many chronic bronchitics suffer during the winter months.

It is probably not possible to generalize about this form of treatment, since the causes of disability in chronic bronchitic subjects vary from patient to patient. Some have their principal disability from persistent dyspnoea due to emphysema and others from persistent bronchospasm of non-inflammatory origin; these will not benefit from long-term antibacterial treatment.

Patients who are usually fit to continue with normal activities and have a non-purulent sputum but suffer a few acute exacerbations each winter are probably best managed by treating each episode promptly, by the administration of tetracycline at the beginning of even apparently trivial upper respiratory infections. Patients whose sputum without treatment is consistently purulent but becomes mucoid and can be maintained so by the administration of a suitable antibiotic, or who have very frequent exacerbations of bacterial infection, may be tried on tetracycline in small doses during the season of the year when acute respiratory infections are frequent. For patients whose sputum is initially mucoid, 0.25 g. twice a day may be sufficient; for those whose sputum is initially purulent, somewhat larger doses should be given at the beginning, say 0.25 g. 4 times a day, the dosage being reduced steadily to the smallest level which maintains a mucoid sputum. If the sputum remains purulent in spite of treatment, it is unlikely that the treatment is doing any good and it should be stopped. For those who benefit, the antibiotic should be continued during the season of prevalence of respiratory infections, say from the beginning of November until the end of March or the middle of April. They probably constitute a minority of the sufferers from this very common disease.

It must be emphasized that this article deals with drug treatment and does not touch upon other important aspects of the management of chronic bronchitis, such as general regime, the avoidance of smoking, and physiotherapeutic methods.

A DECADE OF ANTI-INFLAMMATORY STEROIDS

[FROM A SPECIAL CORRESPONDENT]

Ten years ago cortisone was first given to a patient suffering from rheumatoid arthritis. To mark this occasion a conference was held at the New York Academy of Science on December 15 and 16 to survey "A Decade of Anti-inflammatory Steroids from Cortisone to Dexamethasone." This was a valuable opportunity to review the clinical usefulness of various corticosteroids in a wide variety of diseases, and to assess the benefits of the modifications chemists have made to the molecular structure of cortisone and hydrocortisone in their endeavours to evolve more potent anti-inflammatory compounds with yet fewer side-effects.

Cortisone and Fluorohydrocortisone

The first two sessions of the conference were devoted to the chemical, biological, and metabolic properties of the anti-inflammatory steroids, and were under the chairmanship of Dr. JOSEPH BUNIM and Dr. EDWARD C. KENDALL, whose contributions to the synthesis of cortisone have been recognized in a Nobel prize. Although the mechanism

of its anti-inflammatory action remains undiscovered and despite little being known about the relationships of chemical structure to antiphlogistic action, cortisone might still be the steroid of choice were it not for a number of undesirable side-effects. In large dosage cortisone causes retention of salt and water, inducing in some patients oedema and hypertension. It also has an anti-anabolic effect on protein synthesis, and by depressing the normal maintenance and repair of proteinous tissue, particularly bone, may after prolonged administration cause osteoporosis and pathological fractures of vertebrae. It also influences carbohydrate metabolism and in high dosage may induce a diabetic state which is usually reversible on withdrawing treatment.

It was soon appreciated, however, that these different properties of cortisone might be modified by altering the structure of the steroid molecule. The first major change came in 1952 when a fluorine atom was introduced at the C-9 position. This disproportionately enhanced the sodium-retaining property of the compound, and made fluorohydrocortisone valueless as an anti-inflammatory substance except in the topical treatment of skin diseases. Nevertheless its intense action on sodium metabolism has given it a small but important place in the treatment of Addison's disease and adrenalectomized patients, where it has displaced deoxycortone because it is effective by mouth.

Prednisone and Prednisolone

The second major change, and one that heightened the anti-inflammatory potency of the compound, came in 1954 with the unsaturation of the bond between the first and second carbon atoms in the steroid molecule. The resulting delta compounds (prednisone and prednisolone) proved to have an anti-inflammatory effect some four times as great as cortisone or hydrocortisone on a weight-for-weight basis without a proportionate increase in sodium-retaining activity. Although this reduced the liability to oedema or hypertension, many investigators reported that this benefit had to be balanced against an apparently greater tendency to produce peptic ulceration. The development of gastric ulcers had been observed in patients treated with cortisone, but with the delta compounds this complication of treatment seemed more common, and not infrequently the ulcer was symptomatically silent until it perforated or bled.

Dr. GORDON TOMKINS, of the National Institute of Arthritis and Metabolic Disease at Bethesda, explained that cortisone was largely metabolized in the liver, and that the rate of degradation depended on saturation of the 4-5 double bond by two separate enzyme systems—one a series of soluble reductases, which catalyse the production of 5 β -dihydrosteroids, and a microsomal enzyme which produces 5 α -dihydro compounds. The additional double bond in prednisone and prednisolone between the first and second carbon atoms appeared to increase the *in vivo* stability of the molecule, and this gave it an enhanced anti-inflammatory potency.

These delta compounds have therefore been the starting-point in the search during the last four years for other steroids with greater anti-inflammatory effect but less undesirable side-effects. Such is the structure of the steroid molecule that possible permutations and combinations are almost innumerable, and each new compound synthesized by the chemist has had to be submitted to a long series of exacting biological tests before clinical trials are possible. Only a very few of the many compounds made have shown sufficient promise to merit application in human diseases. Furthermore, since so little is known of the mechanism by which corticosteroids produce their beneficial effect at cellular level, it has proved impossible to predict with any accuracy what will be the effect of adding, for example, a methyl group at any particular location in the steroid molecule.

Triamcinalone and Dexamethasone

The next compound to achieve some clinical importance was triamcinalone, which was a prednisolone molecule with a fluorine atom at the C-9 position and hydroxylation of the