been given for a short time and then restarted after a long interval of treatment by diet alone. In this connexion it is not very uncommon for manifestations of insulin allergy to be associated with a return to insulin therapy. None of our cases showed such manifestations, but the association between allergy and resistance has been noted on a number of occasions (Berne and Wallerstein, 1950). The reason why greater amounts of antibody are not formed in response to insulin treatment may possibly be related to the method of its administration; in no course of prophylactic immunization is antigen given once or more daily over long periods. The restarting of insulin might well be expected to act as a booster dose, and, on general principles, be more likely to lead to greater antibody production.

The results of the P.C.A. and R.D. tests obtained in our cases support the widely held view that there are a number of different causes of insulin resistance. It can be assumed that a serum giving a positive P.C.A. test contains insulin antibodies, whereas the R.D. test is capable of detecting several different types of antagonist. In Case 5 the P.C.A. test was negative and the R.D. test positive, but it is significant that P.C.A. antibodies have not been found when the serum contained no demonstrable antagonist. At present prednisone appears to benefit a group of insulin-resistant diabetics whose daily insulin requirement is nearer 1,000 than 200 units and in whom can be found no apparent cause for the resistance. The time interval between the start of insulin treatment and the development of resistance is usually less than a year, and often between three and six months; in our experience all such cases have had demonstrable insulin antibodies.

Summary

Thirteen cases of insulin-resistant diabetes are presented, six of which have been treated with prednisone. The anti-insulin factors have been studied, and the mouse convulsion test and glucose uptake of the rat diaphragm (R.D.) have been used to demonstrate the presence of insulin antagonists; insulin antibodies have been detected by a reversed passive cutaneous anaphylaxis (P.C.A.) technique. This P.C.A. test is described, with results obtained in normal controls and in insulin-sensitive and insulin-resistant diabetics.

Prednisone produced a dramatic fall in insulin requirement in the four cases in which the P.C.A. test was positive, but had the opposite and more usual effect in the two cases in which this test was negative. The suggestion is made that those diabetics in whom insulin resistance is associated with demonstrable insulin antibodies possess certain common clinical features.

We thank Dr. G. A. Stewart, of the Wellcome Biological Control Laboratories, for carrying out the mouse convulsion tests, Dr. Herbert Levy for allowing us access to Cases 10 and 12, and Dr. J. D. N. Nabarro for permission to publish the details of Case 4. This work was supported by a grant from the Joint Research Committee of King's College Hospital and Medical School.

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CHEMOTHERAPY OF NON-TUBERCULOUS PULMONARY INFECTIONS*

BY

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The acute and chronic non-tuberculous infections of the lung constitute an excellent subject for debate concerning the principles and practice of chemotherapy. The respiratory tract is probably subject to attack by a greater number of species of bacteria and of viruses than any other. The effects of these organisms range from trifling illnesses to disorders which are rapidly fatal. Chemotherapy can claim some of its most brilliant successes in this field, but must also admit to disastrous defeat. If the subject of chemotherapy is really so delightfully logical as our bacteriological colleagues assure us, it should be easy to lay down the principles of treatment for the patient with a pulmonary infection. Unfortunately, clinicians know that there are no simple rules for success and that diagnostic acumen and vigilant observation are demanded by each and every case.

Background for Pulmonary Infections

It is a truism that chemotherapy has transformed the prognosis for the case of ordinary pneumonia and that the mortality from pneumonia has declined dramatically. Yet it is often forgotten that the decline in mortality antedated the introduction in 1938 of the sulphonamides active against the pneumococcus. Since then the mortality from pneumonia has declined further and all age groups have shared in the benefit. Much less change has occurred in the death rate from bronchitis, which, in any case, shows some fluctuation from year to year. The actual numbers of cases of pneumonia are, of course, greatly influenced by influenza epidemics, and it is probably unwise to attribute alterations in prevalence to the effects of therapy. But a great change has undoubtedly occurred in the past twenty years in the clinical presentation of pneumonia. Lobar pneumonia is no longer seen with any frequency in hospital practice. And the situation in general practice has become complex.

Thus the pneumonias of the aged and acute illnesses in those subject to chronic disease such as bronchiectasis

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and chronic bronchitis bulk largely in the total numbers of cases seen in practice. Moreover, the patients with clear-cut signs of consolidation form a minority of all those with acute chest illnesses. The College of General Practitioners (1956) reported that consolidation was found in only 12% of 1,757 cases of acute chest infection seen in general practice. Shaw and Fry (1955) found that radiological changes were often present in patients with localized rales and a severe degree of illness even though signs of consolidation were absent. Truly the diagnostic problem in general practice is now considerable. No one can be sure whether this change results from an evolution in disease perhaps related to host factors or to the effect of chemotherapy on the epidemiology of the naso pharyngeal organisms capable of attacking the lung.

Bacterial Pneumonia

In recent years several careful studies of the sputum from cases of pneumonia have shown that a change has probably occurred in the aetiology of the disease. Studies in London (Crofton *et al.*, 1951), Glasgow (Grist *et al.*, 1952), and Sheffield (Stuart-Harris, 1953) showed that some 20 to 50% of patients with clinical and radiological evidence of pneumonia failed to yield pathogenic bacteria in the sputum (Table I). Yet the response to treatment in these patients was not obviously different from that in patients whose sputum contained an organism such as the pneumococcus. The decline in the bacteriologist's ability to identify the cause of presumed bacterial pneumonia is perhaps a cause of the clinician's discontent at being told to "take a specimen and wait for the sensitivity test." It is certainly unjustifiable to delay therapy in patients with signs of consolidation and one must judge the question much more from the standpoint of the degree of general illness than by whether or not bacteria have been identified.

However, the bacteriological results already quoted are the best guide that we have for the selection of appropriate chemotherapy. Compared with the importance of the pneumococcus and the staphylococcus other bacteria are relatively infrequent causes of pulmonary consolidation though they cannot be wholly ignored. Apart from influenza epidemics, it is clear that the pneumococcus still predominates over all other identifiable bacteria, and even during influenza it causes the majority of the pneumonic complications.

The antibiotic sensitivity of the pneumococcus is a broad one, and the various clinical trials which have been carried out both in this country (Antibiotics Clinical Trials Committee, 1951) and the U.S.A. (Dowling and Lepper, 1951) have failed to show much difference between the efficacy of penicillin and the tetracycline group of antibiotics or of chloramphenicol in pneumococcal pneumonia. Although many clinicians who work in hospital still prefer penicillin there is no doubt that the tetracyclines are often prescribed in domiciliary practice because of their convenience in administration. Nevertheless they are more toxic than penicillin, and pride of place should still go to the latter particularly for those who are gravely ill.

Why do not all cases of pneumococcal pneumonia recover? The mortality of 5% or more which is still recorded is unquestionably due to host factors which are of such importance in pneumonia. Long before the sulphonamide era the significance of age, of previous chronic disease of the lung or coexisting disease of the heart, and of the duration of disease before treatment was realized during attempts to evaluate serum therapy for pneumonia. Such factors are still of importance to-day (Van Metre, 1954), and must not be forgotten whenever it seems that antibiotic therapy is failing in spite of an apparent sensitivity of the bacteria in the sputum to the drug. Fortunately antibiotic resistance has not yet become evident in the case of the pneumococcus.

Staphylococcal Pneumonia

The bacteriological results obtained in cases of pneumonia during the influenza epidemics of 1949 and 1951 (Stuart-Harris, 1953), which were abundantly confirmed during the Asian influenza epidemic, stressed the importance of the *Staphylococcus aureus*. Although staphylococcal pneumonia can occur apart from influenza virus infection, it is the combined infection of the two organisms which presents such a formidable therapeutic problem. This is well shown by analysis of the findings in fatal cases of Asian influenza (Table II). A majority of the cases submitted to post-mortem examination showed a pneumonia often haemorrhagic in type or else a tracheobronchitis. The staphylococcus alone or combined with other organisms was found in 62% of the British cases and in 67% of the Dutch patients. It is clear that influenzal-staphylococcal pneumonia is a formidable problem from the

TABLE I.—*Aetiology of Pneumonia*

Author	No. of Cases	Pathogenic Organisms Identified in the Sputum					No Aetiology Determined
		Pneumococcus	Staphylococcus	H. Streptococcus	Friedländer's Bacillus	Other*	
Crofton *et al.* (1951)	110	29 (26·3%)	10 (9·1%)	—	—	19 (17·2%)	52 (47·2%)
Grist *et al.* (1952)	129	84 (65·1%)	—	—	—	10 (7·7%)	35 (27·1%)
Stuart-Harris (1953) Non-influenzal period	130	104 (80%)	7 (5·3%)	2	0	—	25 (19·2%)
Stuart-Harris (1953) Influenzal period	166	114 (68·6%)	33 (29%)	3	3	—	20 (17·5%)

* The basis for classification of this group differed in the two series quoted.

TABLE II.—*Bacteriology in Fatal Cases of Asian Influenza*

Country	Author	No. of Cases	Pneumococcus		Staphylococcus		H. Streptococcus		*H. influenzae*		Non-pathogenic Organisms Only	Sterile
			Alone	Combined	Alone	Combined	Alone	Combined	Alone	Combined		
Britain	P.H.L.S. (1958)	447	16	12	217	71	3	20	7	23	101 (21·6%)	41 (8·8%)
Holland	Hers *et al.* (1957)	103	3		61·8% 69		1		1		*E. coli* 7	22

therapeutic point of view and at least four reasons can be discerned for this.

1. The staphylococcus may be resistant to penicillin initially or may become resistant after treatment has begun 35% of the staphylococci isolated from patients dying before or within 48 hours of admission to hospital were resistant to penicillin in the recent British series (Public Health Laboratory Service, 1958). Treatment of such penicillin-resistant staphylococci can of course be attempted with either a tetracycline or an erythromycin antibiotic. But the results are much poorer than with penicillin in appropriately sensitive infections.

2. The actual mass of invading cocci, which is considerable, is largely located on the surface of the bronchi and bronchioles in a web of necrotic mucosa, though it later spreads to the alveoli. There is no evidence of bacteriaemia, and metastatic abscesses are not found at necropsy. It seems probable that, at least in the early stages, the infection is relatively inaccessible to antibiotics.

3. Often death appears to be due to the toxic effects of the infection. It is not possible to separate the effects of staphylococci from those of virus, but the considerable number of fatal cases either with sterile lungs or with non-pathogenic bacteria during the recent epidemic is an eloquent testimony of the virulence of the virus alone. Antibiotics are of course useless for bacterial toxaemia, and the effect of the latter on the circulatory system is thus unchecked by treatment. There is no antibiotic yet available against influenza virus.

4. The speed of advance of the infection is often totally unexpected to the clinician, who finds purple lips and panting dyspnoea in a patient who, a few hours before, may not have felt ill enough to go to bed. Absence of pleural pain is another reason for the failure to understand the gravity of the attack in the early stages of staphylococcal pneumonia when treatment ought to begin.

These four reasons fully exemplify the principles which govern success or failure of antibiotic treatment. Moreover, the dangers of indiscriminate antibiotic treatment, at least in cases of influenza, have been stressed by Walker *et al.* (1958) in their analysis of staphylococcal pneumonia. They point out that too broad a spectrum of antibiotic cover may so sterilize the upper respiratory tract that resistant organisms may fill the vacuum created. Cases of influenza may thus become secondarily infected by hospital staphylococci after admission, and these are usually resistant to penicillin and perhaps to other antibiotics as well. In regard to the treatment of patients already infected with staphylococci on admission, it is of the utmost importance to recognize the infection as soon as possible. For this purpose the Gram-stained film of sputum has been useful in my own hands, though it is not infallible and must be followed by cultivation of the sputum and tests of sensitivity to penicillin and the other antibiotics. A combination of penicillin and streptomycin during the first two days after admission can be modified, if necessary, when the results of sensitivity tests are available. If the illness is of a fulminant character erythromycin should be combined with these antibiotics in case the infection is caused by a penicillin-resistant staphylococcus. The question of ancillary treatment by steroids or by staphylococcus antitoxin appears almost irrelevant by the side of the vitally necessary antibiotics. Neither method has really justified its claim for inclusion in the therapeutic regime, and steroids may be positively harmful.

Other Forms of Bacterial or Fungal Pneumonia

Space forbids a detailed discussion of such pneumonias as those due to Friedländer's bacillus, *E. coli*, and fungi of the *Aspergillus* or *Candida* species. Their existence is a justification for continued careful examination of the sputum in cases of pneumonia, and particularly if no immediate response is occurring to treatment with penicillin or the sulphonamides. Streptomycin is a useful antibiotic for pneumonias due to Gram-negative bacteria of the coliform group, and antifungal antibiotics such as nystatin or amphotericin B may be useful in fungal cases, which sometimes develop in the wake of bacterial infections treated by the broad-spectrum antibiotics.

Virus Pneumonias

A great deal has been written and talked about the subject of virus pneumonias in the past few years. Apart from fulminant influenza, psittacosis, and Q fever, the other forms of virus pneumonia are benign, almost trivial, self-limiting conditions which usually require no specific treatment at all. These benign pneumonias are usually diagnosed only when the radiologist reports an unsuspected opacity of the lung fields of a hazy or mottled character in a case previously diagnosed as P.U.O. or acute bronchitis. It seems likely that this is a relatively uncommon disease in civilian practice apart from occasional outbreaks in schools, though it is not rare in Service communities. The diagnosis is often made on grounds of probability and without radiological confirmation in patients with an acute lower respiratory infection which is not responding rapidly to antibiotics. It is a diagnosis which should be resisted lest a more serious condition such as bronchial carcinoma may be ignored. It is also important to avoid the concept of virus infection simply because pathogenic bacteria have not been found in the sputum.

If, however, the radiological picture is suggestive, if general signs of bronchitis are present, or serum agglutinins against group O red cells are found in tests carried out at 4° C., then the diagnosis of atypical or virus pneumonia can be upheld. Even the absence of cold agglutinins is not an absolute bar to the diagnosis, for occasional cases without such agglutinins and due to the adenoviruses have now been described. But the published evidence on the treatment of these infections by the tetracyclines, chloramphenicol, or even by erythromycin (Wolf and Brown, 1956) is on the whole in favour of withholding antibiotics. Control series of patients untreated by antibiotics do just as well as those receiving the latter.

The same cannot be said for psittacosis, of which the variety contracted from parrots is a serious condition. Penicillin and the tetracyclines are both active against psittacosis virus in the laboratory. Q fever due to *Rickettsia burneti* is also said to respond to the tetracyclines, but the organism is less sensitive than the rickettsiae of the typhus fevers. Both psittacosis and Q fever are relatively rare conditions in civilian practice in Great Britain.

Treatment of Acute Bronchitis and Bronchiolitis

The fact that the number of patients with consolidation of the lungs met with in practice or in hospital is only a fraction of the total number ill with acute chest disease has already been stressed. The other infections of the lower respiratory tract consist chiefly of cases of acute tracheobronchitis and of bronchiolitis. The causes of these infections are largely unknown and their response to treatment is equally uncertain.

The problem is greatest in infants and young children in whom the prevalence of bronchitis or bronchiolitis rises during winter epidemics of acute respiratory infection. Such epidemics as are associated with the influenza viruses form only a portion of the total, and there have been several accounts of outbreaks in children unconnected with adult epidemics (Garrow and Fawcett, 1953). There is little doubt that these outbreaks are due to viruses, but there is no certain knowledge of the nature of the latter. Since the discovery of the adenoviruses in 1953, an association has been found between certain of the serological types of adenoviruses and epidemics of pharyngitis with lower respiratory disease as well in children and adults. But such infections do not account for much of the toll from bronchitis.

The next discovery was of the croup or laryngo-tracheo-bronchitis virus recovered by Chanock (1956) in the U.S.A., and by Beale *et al.* (1958) in Toronto. This virus accounts for some cases of obstructive laryngo-tracheo-bronchitis in infants, but it seems unlikely to be a cause of much disease in adults. The J.H. virus of Price (1956), the " U " virus from Uppsala (Philipson, 1958), and the haemagglutinating viruses recovered by Chanock *et al.* (1958) were discovered far too recently for an opinion to have been formed of their relation either to the common cold or to minor respiratory infections. It seems likely that any or all of these viruses may at times be associated with cases of bronchitis or of bronchiolitis. None are known to be sensitive to antibiotics, and it is small wonder that the latter are ineffective against human acute respiratory disease uncomplicated by bacterial infection.

In practice the investigation of acute bronchitis and bronchiolitis in tiny babies and young children is hampered by the difficulty in obtaining a specimen of sputum. Morrison *et al.* (1957) used cough swabs as well as pernasal and throat swabs. A range of organisms similar to that found in pneumonia was recovered from cases of bronchitis, but no pathogenic bacteria were recovered from 23 of 62 cases (37%) of bronchitis or from 27 of 78 cases (34%) of segmental pneumonia and bronchopneumonia. Even when pneumococci, staphylococci, haemolytic streptococci, or *Haemophilus influenzae* are obtained from swabs there is no assurance that they are concerned in the chest disease such as would have been likely if they had been demonstrated in sputum. Nevertheless, it is probable that few clinicians are prepared to withhold antibiotics in the treatment of an acute chest infection in children unless the degree of illness is trifling. The threat of pneumonia and of possible damage to bronchi at a tender age is a justification for therapy even though the latter can only affect a secondary infection. But it is certainly unjustifiable to expose the child to any risk of upset by such therapy, and penicillin or a drug of the tetracycline group is all that should be used

In adults the problem of chronic chest disease, of chronic bronchitis and emphysema, and of bronchiectasis is intermingled with that of acute bronchitis. For, in addition to cases of acute bronchitis in previously healthy persons, the exacerbations of illness in cases of chronic bronchitis are distressingly common and a serious cause of economic disturbance, particularly in industrial areas.

There is some variation in the findings of different workers in this country concerning the relative frequency of the different nasopharyngeal bacteria found in the sputum of patients with chronic bronchitis (Table III). All are agreed that the pneumococcus, *H. influenzae*, and *Staphylococcus aureus* lead all others in frequency and also that the greater the degree of purulence of the sputum the greater the number of bacteria likely to be present. But it is impossible to believe that bacteria are the primary cause of chronic bronchitis, and even acute exacerbations are often initiated by acute upper respiratory infections presumably caused by viruses.

It is reasonable to ask for a precise statement concerning the role of chemotherapy in chronic bronchitis and bronchiectasis. Antibiotics are widely used to treat acute exacerbations of illness; they diminish the amount of sputum and the frequency of coughing. Penicillin either alone or combined with an antibiotic which is more effective than penicillin against *H. influenzae* is the treatment of choice. Oxytetracycline, erythromycin, and chloramphenicol are all active against *H. influenzae* and have all been used in hospital practice. Chloramphenicol probably reduces the amount of sputum most effectively and is preferred to tetracycline drugs for the treatment of acute exacerbations by some (Douglas *et al.*, 1957; Ioannidis and Murdoch, 1957). But the tetracyclines are less hazardous even for short periods of treatment and are also less likely than chloramphenicol to cause an increase in dyspnoea due to excessive viscidity of the sputum in cases of emphysema. Because the exact species of organism associated with bronchitis exacerbations varies from place to place and from time to time, a watch on the sputum is essential. Simpson (1958), for instance, remarked on the recent rise in importance of the staphylococcus in bronchitis following the epidemic in Asian influenza.

An entirely different way of using chemotherapy in patients with chronic chest disease is by long-term administration to prevent relapses—that is, prophylactic administration of the drugs as soon as an upper respiratory infection begins. The evidence from the Brompton Hospital workers (Helm *et al.*, 1954, 1956; May and Oswald, 1956) suggests that oxytetracycline is a useful drug for prolonged therapy in chronic bronchitis. Other workers in London (Elmes *et al.*, 1957) and in Leeds (Edwards *et al.*, 1957) are more doubtful. The case for prophylaxis with antibiotics is not proved. Such therapy is expensive, and in my view hazardous because it encourages the colonization of the respiratory tract with antibiotic-resistant organisms. We should certainly do nothing to impair the value of treatment for acute relapses of infection which may precipitate heart failure or may lead to death from respiratory insufficiency. The best way to use chemotherapy in patients with chronic

TABLE III.—*Cultivation of the Sputum in Cases of Chronic Bronchitis**

Place	No. of Patients	No. of Specimens	Pneumococci	*H. influenzae*	*Str. haemolyticus*	*Staph. pyogenes*	Friedländer's Bacillus	Coliform
Sheffield (Stuart-Harris, 1953) ..	113	172	87 (50·5%)	26 (15%)	8	20 (11·6%)	2	5
Albany, N.Y. (Brown *et al.*, 1954)	20	83	61 (73·5%)	42 (50·6%)	5	2	—	12 (14·4%)
Brompton { May (1953) ..	54	54	31 (57·4%)	14 (25·9%)	—	7	3	4
Hospital { ,, (1954) ..	30	—	6 (20%)	27 (90%)	—	—	—	—

* After Stuart-Harris and Hanley (1957).

chest disease, therefore, is to limit antibiotics to acute phases of illness or to short periods of treatment in those who have undergone slow deterioration as a result of insidious exacerbation of symptoms. In both instances, antibiotics form only a part of the therapeutic armamentarium—a very different statement from the role of antibiotics in pneumonia.

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" United Kingdom exports of drugs and medicines in 1958 did not quite reach their record figure of £39.6m. in 1957, but they were the second highest ever at £37.8m. Antibiotics accounted for £8.3m., miscellaneous proprietary medicines (including those for supply on prescription) £10.6m., and vitamins £2.5m. Exports of alkaloids, aspirin, synthetic antimalarial drugs, ointments and liniments, and sulphonamide preparations all exceeded £1m. Australia was once more the chief overseas market (£3.3m.), followed by Nigeria (£2.1m.). Next came New Zealand (£1.9m.), the Union of South Africa (£1.8m.), India (£1.7m.), the Irish Republic (£1.6m.), and Pakistan (£1.5m.). For the first time exports to the United States of America exceeded £1m., and those to Canada were only just under this figure. In each case the increase over the previous year was in the region of £250,000. Exports to Egypt rose from £84,000 in 1957 to £494,000, and it is hoped that more of this important market will be regained.

" The effect of the financial crisis and increasingly stringent import policy in India was shown by a decrease of exports from £2.9m. to £1.7m."—*The Association of British Pharmaceutical Industry: Annual Report, 1958-9.*

CHEMOTHERAPY OF PULMONARY TUBERCULOSIS*

BY

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The right use of modern methods of chemotherapy now makes it possible to aim at 100% success in the treatment of pulmonary tuberculosis. In all countries from which figures are available there has been a dramatic fall in deaths from tuberculosis since the introduction of chemotherapy in 1947–8. The fall has been well marked in England and Wales but even more impressive in Scotland, where the mortality was previously rising (Fig. 1). That the widespread use of proper methods of chemotherapy can have an effect also on the number of fresh cases of tuberculosis is well shown from the Edinburgh figures (Fig. 2). At the beginning of 1954 an integrated service for tuberculosis was introduced in Edinburgh, with the result that proper methods of chemotherapy were used for all patients requiring treatment. The waiting-list for admission to hospital, which reached a peak of 375 in March, 1954, was virtually abolished during the succeeding year. Nearly all sputum-positive patients were admitted to hospital, and scarcely any were discharged with a positive sputum. Fig. 2 shows how, as a result, a steadily rising incidence of new cases was converted to a dramatic fall. Since March, 1955, there has never been more than 1% of the patients on the Edinburgh Tuberculosis Register out of hospital with a positive sputum.

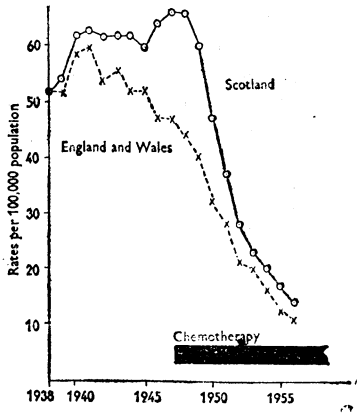

FIG. 1.—Mortality from respiratory tuberculosis, 1938-56.

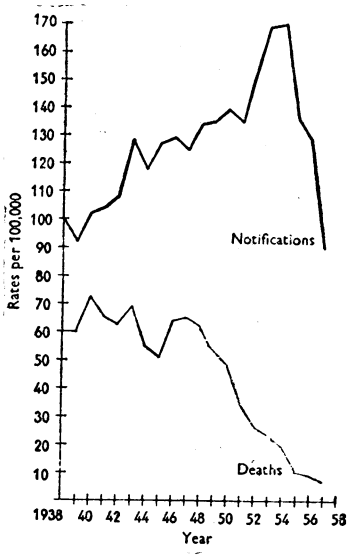

FIG. 2.—Edinburgh: death and notification rates for pulmonary tuberculosis since 1938.

Prophylactic Chemotherapy

There are three groups in which the question of prophylactic chemotherapy might be considered.

1. *Children with a positive tuberculin reaction as the only evidence of infection.*—A controlled trial of

*Read to a Plenary Session at the Annual Meeting of the British Medical Association, Birmingham, 1958.