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TUBERCULOSIS UNDEFEATED*

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I account it a great privilege to be asked to give this lecture in memory of my friend Marc Daniels. From him I first learnt about the epidemiology of tuberculosis and much about the scientific approach to its study. But, for him, tuberculosis was not merely an intellectual interest. He had a passionate concern for the welfare of the men and women behind the facts and figures. It was this underlying passion, coupled with a high and sane intelligence, which enabled him to contribute so much in this field in the course of his short life.

First of all I must excuse the somewhat sententious title of my lecture. I believe that we now have the weapons to defeat tuberculosis finally and completely, but that we could be using these weapons more extensively, more intensively, and more intelligently than at present. In economically developed countries we have certainly made progress, but might not this progress be much more rapid? In this lecture I intend to review the weapons at our disposal and make some suggestions about their better use.

The World Health Organization calculates that at the present time between 0.5 and 1% of the world's population are coughing up tubercle bacilli (Holm, 1959). That is to say, there may be 12 to 25 million infectious cases throughout the world. An estimate based on a large-scale sample survey (Indian Council of Medical Research, 1959) suggests that in India alone there are four to eight million active or probably active cases. Logan and Benjamin (1957) calculate that in England and Wales there are probably about 375,000 cases of respiratory tuberculosis, of which about 45,000 are infectious.

Confronted with such an astronomical computation of distress, it is clear that tuberculosis is very far from being defeated, even in economically developed countries. Indeed, in underdeveloped countries it is often said that little can be done until the standard of living is raised. One can hardly accept that. Skilled anti-tuberculosis measures are even more necessary in such circumstances. Even in the economically developed countries very distinguished specialists aver that a number of patients have disease too advanced or too chronic to respond to treatment. One cannot deny that possibility. All one can say is that, as our knowledge of chemotherapy grows and as we learn to anticipate possible causes of failure, this group of refractory cases dwindles steadily. It seems likely that if we apply present knowledge with sufficient skill and care no patients at all may remain refractory. Indeed, our group in Edinburgh believes that, provided bacilli are sensitive to the standard drugs and that the patient takes the drugs as directed, we should be able to arrest pulmonary tuberculosis and

render the patient's sputum negative in virtually all cases. Our evidence in favour of this view is presented later.

One must admit at once that much can still be learned about how to use our weapons against tuberculosis to the best advantage, especially in underdeveloped countries, but the basic essentials are there. What they contribute depends partly on the knowledge and enthusiasm of specialists in tuberculosis but even more on the will of the community to defeat the disease. As Professor Etienne Bernard, of Paris, said recently, the first country to eliminate tuberculosis will be that country which regards it as a serious problem right to the end. I believe that this country could be the first to achieve this end if we had the will to do so.

Methods Available for Eliminating Tuberculosis

The chief instruments for the elimination of tuberculosis are listed in Table I. Essential tools are miniature

TABLE I.—*Elimination of Tuberculosis*

Elimination of infection:

Bovine sources	{	1. Pasteurization
		2. Tuberculin-tested herds
Human sources	{	1. Miniature radiography
		2. Chemotherapy (surgery for un-cooperative or drug-resistant patients)
		3. Isolation until non-infectious
		4. Improved ventilation
		5. Reduction of overcrowding (a) home, (b) work, (c) play, (d) transport

Raising community resistance:

1. Specific: B.C.G.
2. General improvement in standard of living

radiography and chemotherapy, supplemented by B.C.G. It may be that in underdeveloped countries for some time to come B.C.G. must be the most important tool. It can be assumed that pasteurization and the elimination of tuberculosis from cows will shortly cut off the sources of infection by bovine tubercle bacilli. Thereafter elimination of the disease depends primarily on identifying and curing cases of human pulmonary tuberculosis. These in turn depend on the right use of miniature radiography and chemotherapy. We now know a good deal about chemotherapy and are at last beginning to do some intelligent thinking about miniature radiography.

Meantime our efforts to eliminate the sources of infection can be supplemented in two ways. First of all, unsuspected sources of infection can be made less dangerous by reducing overcrowding and improving ventilation at home, at work, in places of entertainment, and in public transport. We in this country still have much to learn about ventilation. In our passion for keeping our houses chilly, we open the windows and let in some of the coldest and most polluted air in the world. Even the British may not be prepared to tolerate

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this discomfort indefinitely. Besides dealing energetically with the national scandal of atmospheric pollution, let us hope that our engineers will apply their art to reconciling good ventilation with comfort. The epidemiological horrors of the London tube during a rush hour are a standing challenge to preventive medicine.

In addition to reducing the chances of infection from unknown cases of pulmonary tuberculosis, the resistance of the community to the disease can be improved non-specifically by encouraging a general rise in the standard of living—largely a matter for the politicians but partly the concern of health educators—and specifically by the right use of B.C.G.

B.C.G.

The efficacy of B.C.G. as given to 13- to 14-year-old schoolchildren in this country has been established by the carefully controlled trials of the Medical Research Council (1959). It was found that B.C.G. made a child some six times less likely to develop tuberculosis during adolescence. The results of some trials elsewhere have been less impressive. The United States Public Health

FIG. 1.—Tuberculin positivity in 13-year-old school-children.

Service trials in the Southern States (Palmer *et al.*, 1958) showed relatively slight protection, and a recent controlled trial in India (Frimodt-Møller, 1959) no protection at all. Possible reasons for such discrepancies, and indeed the whole problem of B.C.G., have been discussed from the British point of view in an important series of recent papers (Pollock, 1959; Sutherland, 1959; Springett, 1959). It seems that the value of B.C.G. may vary in different epidemiological circumstances, but it is also clear that the efficacy of the particular B.C.G. in use should be kept under constant review, both in the laboratory and in the field.

In this country the value of B.C.G. can be regarded as established, and it may be that there is substance in Pollock's (1959) plea that it might be given at the age of 10 rather than 13, in view of some deceleration in the fall of tuberculin-positivity at the age of 13 in the last few years (Fig. 1). Perhaps this decision should be made in the light of the local figures in each locality.

Miniature Radiography

An outline of the desirable uses of miniature radiography is given in Table II. Until quite recently this weapon has been employed in a most haphazard manner. It has at last been agreed that there should be a policy for its use, and there is a comparatively wide measure of agreement on what that policy should be. In this country we have not yet gone very far in putting it into effect.

Theoretically the ideal is that all adults should have their chests x-rayed annually so that all potential infectors can be identified and treated as early as

possible. This, of course, is quite impracticable, and the important thing is to use the limited facilities to the best advantage. Dramatic large-scale community surveys have recently been carried out in the main Scottish cities, where some 80% of the adult population have been x-rayed within a few weeks (Seiler *et al.*, 1958; Cowan *et al.*, 1958). A similar survey has recently been carried out in Liverpool. In Fig. 2 are

TABLE II.—Use of Miniature Radiography

Community surveys	<ul style="list-style-type: none"> Large-scale Local
High incidence groups	<ul style="list-style-type: none"> Symptom-group Adult contacts Prisons/Borstals Mental institutions Elderly men, especially in lodging-houses Hospital in-patients ? Contacts of tuberculin-positive school-children
"Danger groups"	<ul style="list-style-type: none"> School-teachers Others in contact with children Bus conductors Ticket collectors Shop assistants Barmen Doctors Dentists
Factories and offices	
"Spring-cleaning"

FIG. 2.—Respiratory tuberculosis notifications before, during, and after the Scottish national mass radiography campaign.

shown some relevant notification rates for respiratory tuberculosis in the four main Scottish cities. The maximum post-war rate prior to the campaign is compared with that in the year immediately preceding the campaign, with the rate in the campaign year, and with that in the immediately succeeding year. (The Edinburgh figure for 1959 is calculated from the notifications of the first 10 months.) It will be seen that, although there was a substantial reduction in each city for which there are figures for the year after the campaign, this reduction is perhaps less dramatic than one might have expected considering the preceding fall. It may be that this is partly explained by subsequent evidence of disease activity among patients who had been kept under observation at the clinics because of a doubtful shadow detected during the campaign. It is probably too early

to assess the precise impact that the campaign has had on the epidemiological situation as a whole.

The value of x-raying the high-incidence groups is mainly agreed. Some figures for 1957 are shown in Fig. 3 (derived from the Chief Medical Officer's Report, 1958). In most parts of this country there are now

FIG. 3.—Tuberculosis rates in mass radiography surveys, England and Wales, 1957: 3,514,600 examinations.

adequate facilities both for patients with symptoms and for adult contacts. The cover for prisons, borstals, and mental institutions could probably be greatly improved. The value of x-raying elderly men has been established by the Scottish Mass Radiography Campaigns, and the high incidence in the inhabitants of lodging-houses is now notorious. In the Edinburgh Mass Radiography Campaign the incidence of active pulmonary tuberculosis in men over 60 was 3.39 per 1,000 x-rayed and the incidence of carcinoma of the bronchus in the same group was 2.34. Nevertheless, we have not yet evolved an adequate public policy for the regular x-raying of this group of the population. The high incidence of active pulmonary tuberculosis found on routine radiography in patients admitted to hospital has been well known for years in the United States (U.S. Public Health Service, 1959). In England and Wales overall hospital rates are not impressive (Fig. 3). Higher rates have been recorded in Glasgow (Geddes, 1959). Although further data are required, routine survey of hospital in-patients would probably be well worth while. There are a number of studies suggesting the value of x-raying the home contacts of schoolchildren with positive tuberculin tests, but so far this has not proved a worthwhile procedure in Edinburgh (Medical Officer of Health, Edinburgh, 1958).

The "danger" groups are those groups in which an unknown infector may do most damage. They are therefore those who in their daily work come into contact with the largest number of other people, especially if their contacts are particularly susceptible, as is the case of young children. For school-teachers, a voluntary scheme has been provided in most areas in Scotland for a number of years and such a scheme is being discussed in England. So far as I know, little has been done to organize the regular survey of the other groups. It would be entirely reasonable to make a regular x-ray examination a condition of service in any of these groups, as is done in Russia and, for some groups, in the United States. Although most hospitals now have well-organized schemes for the regular survey of their nurses, the

same is by no means true of the doctors or other hospital employees. One of the most urgent tasks in improving the prevention of tuberculosis is to organize regular radiographs for these "danger" groups.

The surveys of workers in factories and offices, for so long the main occupation of mass radiography units, is now relatively unrewarding (Fig. 3). It may be justifiable to carry out such a survey every three years or so, but annual x-ray examination is probably wasteful.

Finally, it is of great value to have a mobile miniature radiography machine which can be utilized for cleaning up an area, or a place of employment, where several cases of tuberculosis have occurred. Card indices of notifications, classified by place of work and domicile, should be kept so that "blackspots" can be identified and an intensive search made for infectors. For such purposes a machine must be readily on call, and one should be quite prepared to survey a relatively small number of people in a given time in an attempt to identify a dangerous unknown infector.

It is hoped that all areas of the country will appoint small committees, to include chest physicians and medical officers of health, whose business it will be to keep mass radiography policy constantly under review.

Finally, one should recall the view of the Adrian Committee that the advantages of mass radiography, both to the individual and to the community, far outweigh the minute hazards of the radiation involved (Ministry of Health, 1959).

Chemotherapy

Drug Combinations

The value of drug combinations in preventing the emergence of resistant organisms is now generally

DRUG COMBINATION	No of patients	PERCENT PATIENTS WITH RESISTANT TB	
		AT 3 MONTHS	AT 6 MONTHS
1 SM ALONE 2 g./day	42	71	?
2 SM ALONE 1 g./day	53	66	63
2 SM 1 g./day + NaPAS 5g. X 4/day	48	8	7
4 Ditto	219	2	5
3 Ditto	?	7*	6*
3 SM 1 g./day + NaPAS 1.25 or 2.5g. X 4/day	?	19*	34*
4 SM 1 g./day + INH 100mg. X 2/day	120	2	0
5 Ditto	74	0	?
6 Ditto	105	0	0
5 SM 1 g./day X 2/week + INH 100mg. X 2/day	94	3	?
6 Ditto	132	2	5

* Percent of positive cultures

FIG. 4.—Streptomycin resistance with various drug combinations. Data derived from the following reports:

1. Medical Research Council (1948).
2. " (1950).
3. Daniels, M., and Hill, A. B. (1952).
4. Medical Research Council (1953a).
5. " " (1953b).
6. " " (1955).

acknowledged. The most carefully controlled series of comparative trials have been carried out by the Medical Research Council in this country. The results are summarized in Figs. 4, 5, and 6. It is right that we should recall the important part that Marc Daniels played in the initiation and conduct of these trials. Few pieces of research can have saved so many lives. The main conclusions of these trials are the value of daily streptomycin plus isoniazid and of daily isoniazid plus P.A.S.; the high incidence of resistance with single-drug therapy; and the inadequate reduction of resistance when streptomycin is given intermittently with daily isoniazid or when an insufficient dose of P.A.S. is given in combination with streptomycin. From other subsequent evidence, some of it unpublished, it seems likely that the emergence of drug resistance may be higher, at least in severe cases, with daily isoniazid plus P.A.S. than with daily isoniazid plus streptomycin. The latter is almost certainly the best drug combination at present available.

Drug Resistance

The question of what constitutes a clinically important degree of drug resistance is a vital one. In a recent survey of the problem of drug resistance in different countries, carried out on behalf of the International Union against Tuberculosis, we found a chaotic variation in methods of resistance-testing (Rist and Crofton, 1960). Fig. 7 illustrates the range of variation in the size of the inoculum, and in the critical concentrations of the drugs in which growth is regarded as indicating clinically significant resistance. It will be seen that there is a ten-thousandfold variation between different centres in size of inoculum. There is a two-hundredfold variation in the critical concentration of

(modified from RIST and CROFTON 1959)

FIG. 7.—Variation in techniques of resistance-testing in 50/57 centres in 16 countries. (Indirect tests on solid medium.)

DRUG COMBINATION	No. of patients	PERCENT PATIENTS WITH RESISTANT T.B. AT 3 MONTHS	No. of patients	PERCENT PATIENTS WITH RESISTANT T.B. AT 6 MONTHS
INH ALONE 100mg. X 2/day	243	64	48	58
INH 100mg. X 2/day + SM 1g./day	120	2	58	3
Ditto	105	2	60	0
INH 100mg. X 2/day + SM 1g. X 2/week	132	9	64	13
INH 100mg. X 2/day + NaPAS 5g. X 4/day	92	0	47	0
INH 100mg. X 2/day + NaPAS 5g. X 2/day	97	2	27	0

FIG. 5.—Isoniazid resistance with various drug combinations. (References as Fig. 4).

DRUG COMBINATION	No. of patients	PERCENT PATIENTS WITH RESISTANT T.B. AT 3 MONTHS	No. of patients	PERCENT PATIENTS WITH RESISTANT T.B. AT 6 MONTHS
NaPAS alone 5g. X 4/day	?	?	37	32
NaPAS 5g. X 4/day + SM 1g./day	?	?	30	7
NaPAS 5g. X 4/day + INH 100mg. X 2/day	67	1	?	?
Ditto	92	1	47	0
NaPAS 5g. twice daily + INH 100mg. twice daily	65	2	?	?
Ditto	97	1	27	0

FIG. 6.—P.A.S. resistance with various drug combinations (References as Fig. 4.)

streptomycin, a hundredfold variation in that of isoniazid, and a fiftyfold in that of P.A.S. Admittedly, the comparisons between the methods are necessarily oversimplified. The arrows on the diagram indicate approximately the levels used in the tests in our own department, which are similar to those now advocated by the Medical Research Council.

It seems certain that everyone cannot be right, and we have long held that the only way of establishing the critical level of drug resistance is by comparing the progress of patients under treatment with the results of resistance tests. As criteria of failure we adopted clinical deterioration, radiological deterioration, increase of sputum positivity, or the emergence of resistance to a second drug when both drugs were given in a normally successful combination. We have compared in our own material the clinical significance of low and high degrees of drug resistance.

A summary of this material by Dr. Sheila Stewart is illustrated in Fig. 8. Although this is by no means a controlled trial, it does indicate that low degrees of drug resistance are often very important indeed. Those low degrees will often be missed by methods of testing used in many centres. When the bacteriologist informs us that the patient's organisms are sensitive to a drug, we should expect that drug to be effective in all patients. The present methods used in our depart-

FIG. 8.—Incidence of evidence of significance of resistance in patients with low and with high degrees of resistance.

ment do approximate closely to this ideal, but any unexpected result must always be discussed with the bacteriologist. It is only the clinician, knowing the patient, who can detect possible errors or inadequacies in bacteriological techniques.

Size of the Resistance Problem

Because of past errors in chemotherapeutic methods, the prevalence of drug resistance is now a formidable problem in many places. It is important to ensure that current knowledge is properly applied so that such tragedies are prevented in the future. The prevalence of drug resistance found in the International Union survey already mentioned (Rist and Crofton, 1960) is illustrated in Fig. 9. Although the figures represent a very rough sample, they do indicate that the problem is an important one. It is interesting to note the similar pattern of "acquired" and "primary" resistance. The potential importance of "primary" drug resistance in

newly diagnosed patients requires emphasis. It is this danger which has led us in the last few years to utilize all three of the main drugs in newly diagnosed patients ill enough to be admitted to hospital. Pending the results of the pretreatment resistance tests, this ensures that, if the patient's organisms are primarily resistant to one of the three drugs, at least the other two drugs are being utilized as a proper combination. Fortunately the incidence of primary resistance to two or more of the three main drugs is still very small. In areas where effective treatment is being given, the incidence of

FIG. 9.—Drug resistance in treated and untreated patients admitted to hospitals/sanatoria in 1957. Figures for previously treated patients are derived from centres in Austria, Belgium, Brazil, Canada, Czechoslovakia, France, Germany, Holland, India, Japan, Yugoslavia, Poland, Roumania, Switzerland, United Kingdom, and United States. Brazil and India are omitted from the figures for previously untreated patients.

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FIG. 10.—Length of chemotherapy and elimination of tubercle bacilli.

primary drug resistance should decrease. Unfortunately, in many areas of the world bad chemotherapy is being given on a wide scale, and in these areas the incidence of primary resistance will probably increase until present knowledge is properly applied.

FIG. 11.—Chemotherapy used in 348 personal cases rendered sputum-negative, 1952-8.

Results of Chemotherapy

If drug resistance is avoided by proper combinations of drugs it should be possible to render the sputum negative in all cases. Fig. 10 shows the rate of sputum conversion to culture negative in all my own patients with pulmonary tuberculosis, and with organisms sensitive to at least two of the three main drugs, who were admitted between the beginning of 1952 and the end of 1958. Five patients are omitted; four died, still with sensitive organisms, from non-tuberculous causes before sputum conversion. The organisms of a fifth were primarily P.A.S.-resistant; he was treated in a Medical Research Council trial on dual therapy, and sputum conversion was only achieved by surgery. It will be seen that the sputum was converted to culture-negative in all other patients by 10 months. Of these patients, 40% were in the far-advanced category and 49% moderately advanced. The chemotherapy used is indicated in Fig. 11. In the later years treatment was started with all three drugs, for reasons already mentioned, the streptomycin being given intermittently, with daily P.A.S. and isoniazid, to elderly patients more liable to vestibular damage.

Relapse

When we are virtually sure of converting the sputum to negative the next objective is to prevent relapse. Fig. 10 also relates the relapse rate in Edinburgh patients treated in 1953 and 1954 to the duration of their chemotherapy. By 1954 most abbreviations of chemotherapy were due to the patients' default and not to the physician's choice (Ross *et al.*, 1958; Ross, 1959). There is a decreasing rate of relapse with increase in duration of chemotherapy. The rate is only 1% in those who had had 12 to 17 months' treatment and virtually nil in those who had had 18 months' or more. The single relapse occurring in a patient who had had more than 18 months' chemotherapy is omitted from this diagram, although it had to be included in the series on formal definition. It is virtually certain that the relapse was due to the patient's harbouring resistant organisms before admission to hospital. There had previously been a cavity on the opposite side and drug-resistant organisms had emerged under inadequate chemotherapy. Nevertheless the cavity had closed and the sputum had

temporarily become negative. The patient was admitted to hospital once more sputum-positive, but with sensitive organisms. Under good chemotherapy this cavity closed. The eventual relapse was due to the opening of a cavity on the original side from which resistant organisms had been derived, and at the time of relapse the patient's organisms were once more resistant.

The remarkable parallel between the isolation of tubercle bacilli from resected lesions and the relapse rate is also shown in Fig. 10 (derived from Stewart *et al.* (1956, with later additions). It will be noted that, with the probably inadmissible exception discussed above, there were no relapses and no positive isolations in those who had had more than 18 months of chemotherapy.

For reasons given elsewhere (Crofton, 1959) I think there is at present little place for chemoprophylaxis in this country.

The Tuberculosis Service

The weapons available for the defeat of tuberculosis will not be brought to bear with full effect unless there is most enthusiastic co-operation between all branches of the tuberculosis service, using this term in its broad sense. In this context the tuberculosis service must include public-health doctors, health visitors, almoners, mass-radiography workers, in addition to clinicians. In such an inevitable division of responsibility there are endless possibilities for disagreement. It is only when all agree that the only important thing is the end in view, rather than the frontiers of responsibility, that we shall manage finally to get rid of tuberculosis. In fact, even this is not enough. On the broader front, general practitioners and other hospital clinicians must be persuaded to give their full co-operation, and no final success can be achieved unless the public, and this means all sections of the public, can be convinced that this is a battle worth winning and one for which they have a personal responsibility.

No chest physician can obtain a really high rate of sputum conversion unless he has the help of a skilled and well-informed bacteriologist and a skilled and courageous thoracic surgeon to help to salvage those patients who, owing to previous poor chemotherapy, have had their organisms made resistant to the standard drugs. This problem is dealt with elsewhere (Crofton, 1960). In Edinburgh we have been particularly fortunate in all these respects. We have worked with an enthusiastic public health service as well as with bacteriologists, surgeons, and general practitioners of the highest skill. We have still, of course, a long way to go. While we may not be too far from achieving the ideal of no deaths from tuberculosis, we are a long way from having no notifications. However, perhaps we can be immodest enough to suggest that our rate of improvement does indicate that a great deal can be done by careful treatment combined with good team-work on the part of all concerned.

Figs. 12, 13, 14, and 15 compare the trends of mortality in Edinburgh with those in the other major Scottish cities, with certain cities in England and Wales, and with some cities in Europe and North America. It is gratifying to note that Edinburgh mortality has declined from a grimly high place in the order of precedence to a level below that of any other of the cities analysed, with the exception of Amsterdam. I hope that this will be taken as evidence not only of our good fortune in our colleagues in other branches of the

service but also of our claims for the efficacy of chemotherapy and for the substantial contribution it can make to the elimination of tuberculosis.

The importance of both team-work and chemotherapy in decreasing the incidence of the disease is shown by

the changes in notification rates recorded in Figs. 16 and 17. (The figure for Edinburgh in 1959 is estimated from those of the first 10 months.) Up to 1954 the Edinburgh out-patient service had been divided from the in-patient service. From 1954 the same physicians looked after

FIG. 12.—Mortality from pulmonary tuberculosis in the four main Scottish cities, 1946-58.

FIG. 13.—Mortality from pulmonary tuberculosis in Edinburgh and certain other British cities, 1946-58.

FIG. 14.—Mortality from pulmonary tuberculosis in Edinburgh and Northern European cities.

FIG. 15.—Mortality from pulmonary tuberculosis in Edinburgh, New York, and certain European cities.

the patients throughout and good chemotherapy could be brought to all those diagnosed. The dramatic change in the notification rates is obvious, even before the recent mass-radiography campaign. The efficacy of treatment may also be measured by the ratio between notifications and deaths, as shown in Fig. 18.

FIG. 16.—Notifications of pulmonary tuberculosis in main Scottish cities, 1946–58.

FIG. 17.—Notification rates for pulmonary tuberculosis in Edinburgh and certain other British cities, 1946–58.

Conclusions

We are beginning to see how the main weapons against tuberculosis can be applied in economically developed countries in such a way that, provided enthusiasm and public backing continue right to the end, the disease can be eliminated within a measurable period. The problem of applying these techniques to underdeveloped countries is a formidable one. It is heartening to know that the British Medical Research Council is at present making a notable contribution to such studies in Africa and in India. The value of B.C.G., although established in certain favourable circumstances, must not be assumed for all others. The efficacy of the actual vaccine used must be kept under constant review both in the laboratory and in the field. The groups to whom it is given must be determined according to the particular epidemiological situation. Miniature radiography must be used intelligibly. In this country particular attention must be paid to "danger" groups and to certain high-incidence groups which are still insufficiently covered. "Black spots" of high incidence, topographical or occupational, must be identified and attacked.

Techniques of testing for drug resistance are still inadequate in very many centres. In consequence, the clinician may be misled in his choice of drugs, and treatment may fail. Inferior drug combinations are still too often prescribed either initially or later in the course of treatment. Well-advertised remedies may be prescribed before their value has been critically appraised by proper clinical trial. And, finally, we have to fight the new enemy, complacency—complacency by the public, who may fail to volunteer for mass radiography; complacency by administrators, who in some areas may conduct a campaign of attrition on the facilities and morale of the tuberculosis service; and, lastly, complacency in ourselves. I find myself, faced with a new patient, assuming that I can be sure of arresting his disease, but tending to forget that I can be quite certain to do so only if I take an immense amount of trouble over his chemotherapy, his bacteriology, and his social and personal problems.

FIG. 18.—Ratio notifications to deaths from pulmonary tuberculosis in Edinburgh and certain other British cities, 1946–58.

There is little doubt that tuberculosis could be eliminated quite quickly if everyone were prepared to take sufficient trouble. Meantime the only proper attitude, at least in economically developed countries, is that every death from tuberculosis and every new notification is a failure which ought to have been prevented.

Summary

With 12 to 25 million infectious cases of pulmonary tuberculosis in the world the disease is far from being defeated. Even in economically developed countries the elimination of tuberculosis could be proceeding much more rapidly if present knowledge were more widely and more intensively applied.

The main weapons for the defeat of tuberculosis are miniature radiography to detect cases, chemotherapy to cure them, and B.C.G. to raise the individual's resistance to the disease.

It is suggested that B.C.G. has an important, if accessory, part to play in economically developed countries, and might be even more useful in under-developed countries provided the efficacy of the vaccine is kept constantly under review, both in the laboratory and in the field.

The proper use of miniature radiography is reviewed. It is suggested that this weapon could be used with much greater intelligence and effectiveness.

Chemotherapy should be able to ensure the arrest of virtually all newly diagnosed cases of the disease, and there should be little or no relapse. Evidence for this is adduced. Methods for testing for drug resistance are at present chaotic. Failures of therapy are often due to the use of wrong combinations of drugs or to misleading drug-resistance tests.

With good team-work and proper treatment the elimination of tuberculosis could be greatly accelerated. The Edinburgh figures for mortality and morbidity, though by no means perfect, have shown a dramatic change for the better over the last few years and now compare very favourably with other cities in the United Kingdom, Europe, and the United States. This is held to demonstrate the value of team-work, and of scrupulous chemotherapy, in the elimination of the disease.

I am indebted to many people for much of the work on which this lecture is based. I would like particularly to mention my clinical colleagues, Drs. I. W. B. Grant, N. W. Horne, J. D. Ross, and J. Williamson; my bacteriological colleagues, Drs. Sheila Stewart and A. T. Wallace; Mr. Andrew Logan and the Edinburgh thoracic surgeons; Drs. H. E. Seiler and J. M. Mair, of the Edinburgh Public Health Department; and many able past and present assistants. I must thank Drs. J. E. Geddes, R. N. Johnston, Ian M. Macgregor, W. P. Phillips, and V. H. Springett for providing me with certain British figures, and Dr. B. Pirc, of the World Health Organization, for the figures for cities outside Great Britain. I am most grateful to Miss Una Mackie, of the medical illustration department of Edinburgh University, for preparing the diagrams. The Edinburgh research was supported by generous grants from the Royal Victoria Hospital Tuberculosis Trust.

Note.—In the diagrams all Edinburgh figures for 1959 are calculated from the returns for the first 10 months of the year.

REFERENCES

- Chief Medical Officer (1958). *Report of the Ministry of Health, Part II.* H.M.S.O., London.
- Cowan, K., Horne, W. A., Geddes, J. E., Tait, A. W., and Macgregor, I. M. (1958). "Glasgow's X-ray Campaign Against Tuberculosis." Glasgow Corporation, Glasgow.
- Crofton, J. (1959). *Brit. med. J.*, 1, 1610.
- (1960). *Brit. med. Bull.*, 16, 55.
- Daniels, M., and Hill, A. B. (1952). *Brit. med. J.*, 1, 1162.
- Frimodt-Møller, J. (1959). Address at XVth Conference of International Union Against Tuberculosis.
- Geddes, J. E. (1959). *Hlth Bull. (Edinb.)*, 17, 14.
- Holm, J. (1959). Address at XVth Conference of International Union Against Tuberculosis.
- Indian Council of Medical Research (1959). "Tuberculosis in India: A Sample Survey, 1955-58," *Spec. Rep. Ser.*, No. 34. New Delhi.
- Logan, W. P. D., and Benjamin, B. (1957). "Tuberculosis Statistics for England and Wales, 1938 to 1955," General Register Office *Studies on Medical and Population Subjects*, No. 10. H.M.S.O., London.
- Medical Officer of Health, Edinburgh (1958). Annual Report of the Public Health Department.
- Medical Research Council (1948). *Ibid.*, 2, 769.
- (1950). *Ibid.*, 2, 1073.
- (1953a). *Lancet*, 2, 217.
- (1953b). *Brit. med. J.*, 2, 1005.
- (1955). *Ibid.*, 1, 435.
- (1959). *Ibid.*, 2, 379.
- Ministry of Health (1959). *Radiological Hazards to Patients. Interim Report of the Committee.* H.M.S.O., London.
- Palmer, C. E., Shaw, L. W., and Comstock, G. W. (1958). *Amer. Rev. Tuberc.*, 77, 877.
- Pollock, T. M. (1959). *Tubercle (Lond.)*, 40, 399.
- Rist, N., and Crofton, J. (1960). *Bull. Un. int. Tuberc.*, 30, 2.
- Ross, J. D. (1959). *Ibid.*, 29, 710.
- Horne, N. W., Grant, I. W. B., and Crofton, J. W. (1958). *Brit. med. J.*, 1, 237.
- Seiler, H. E., Welstead, A. G., and Williamson, J. (1958). *Tubercle (Lond.)*, 39, 339.
- Springett, V. H. (1959). *Ibid.*, 40, 432.
- Stewart, Sheila, M., Turnbull, F. W. A., and Macgregor, Agnes R. (1956). *Ibid.*, 37, 388.
- Sutherland, I. (1959). *Ibid.*, 40, 413.
- United States Public Health Service (1959). *Tuberculosis Chart Series.* United States Department of Health, Education and Welfare, Washington.

A NEW SYNTHETIC PENICILLIN

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Since the original communications on the therapeutic value of penicillin G (Chain *et al.*, 1940; Abraham *et al.*, 1941) search has been continued for new effective antibiotics. It has become evident that the penicillin-resistant staphylococcus is an organism whose control presents a major problem. Recent papers have emphasized these difficulties, and in a trial at the Postgraduate Hospital, Hammersmith (Barber *et al.*, 1960), penicillin G was actually withdrawn from routine use in an endeavour to reduce the number of staphylococci in the hospital which were penicillin-resistant. The later introduction of erythromycin (McGuire *et al.*, 1952), novobiocin (Smith *et al.*, 1956; Wallick *et al.*, 1956), and vancomycin (McCormick *et al.*, 1956), which are effective against penicillin-resistant staphylococci, have their own disadvantages, such as the rapid development of resistance on the part of the organism or toxic effects on the eighth nerve.

Batchelor *et al.* (1959) announced the isolation of 6-aminopenicillanic acid. An opportunity presented for the development of synthetic penicillins effective against penicillin-resistant staphylococci. The first of these new synthetic penicillins—namely, BRL 1241 ("celbenin")—is the subject of this trial. The chemical formula of this compound is sodium 6-(2,6 dimethoxybenzamido) penicillanate monohydrate.