

**PROGRESS
AGAINST
TUBERCULOSIS**

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FOREWORD

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It is a pleasure to write a short Preface to the first booklet issued by the Office of Health Economics. For too long our attitude to the economics of medicine has been limited to a simple computation of costs without much attempt to assess the economic saving, as well as the humanitarian benefits, which accrue from improved medical care. The cost of drugs receives great publicity nowadays—and it must be confessed that our drug bill is a formidable one—but it must be remembered that the economic benefit to England and Wales resulting from the use of the anti-tubercular drugs alone is approximately £55 million a year, or more than half the cost of the expenditure of the National Health Service on all drugs to treat all disease. Other specific drugs against other major diseases have already achieved human and economic savings of a somewhat similar magnitude.

The aims of the Office of Health Economics are clearly stated elsewhere in this booklet, and its success could lead to an improvement in our understanding of the many complicated factors that determine, and the wide repercussions which result from, health and disease.

The present booklet discusses in a lucid fashion the economic advantages resulting from the control of tuberculosis. I have found it particularly interesting, as I have been fortunate to practise and teach medicine during this era in which the disease, from being a major cause of death and morbidity—particularly amongst the young—has been controlled and to some extent eliminated by a combination of improved standards of living and, more importantly, by the effective use of drugs. The economic and social advantages of this need no further emphasis from me.

The pharmaceutical industry is to be congratulated on taking the initiative in sponsoring the Office of Health Economics. I sincerely hope it will have the success it merits.

D. M. Dunlop

PROGRESS AGAINST TUBERCULOSIS

Tuberculosis is the disease selected by the novelist or librettist whenever he wishes to tell a romantic story ending in tragedy. Throughout the ages it has been linked with tales of youth and beauty and of high promise cut off in its prime. Of all diseases it has inspired the most sympathy. It has been said that of the millions of species of living organisms on earth the two about which most has been written are man himself and the tubercle bacillus. Such terms as the 'white scourge' and the 'chief of the captains of the army of death' have been applied to it. These stories of tuberculosis were not based on imagination alone; they sprang from the lives of real people. A Lady of the Camellias inspired the story and the opera; Mimi lived and died before 'La Boheme' was written—her grave can still be seen. Keats was describing his own, the classic, symptoms of tuberculosis when he wrote of 'the weariness, the fever and the fret' and foretelling his own end in the later lines from the same poem, 'where youth grows pale, and spectre-thin, and dies'.

The tragic certainty of the outcome, the slow progression of the disease, the temporary improvements, bringing a false hint of happier days to come, the 'spes physthica'—the classic 'hope of the tuberculous' that lasts until death itself, these are the very stuff of tragedy. Usually death came in the last chapter. For as Sir Macfarlane Burnet has said: 'Up to 1939 there is little to indicate that treatment did more than delay the fatal event in those who would have died without treatment'. No apology is made

for beginning what is intended to be a scientific article on this histrionic note. The tragedy of disease is human tragedy and the true measure of scientific achievement is in the suffering that it relieves and in the happiness it brings. The story that follows is one of the most exciting in these eventful years of great therapeutic advance, when new drugs are being developed so rapidly. Now victory over tuberculosis is a practical possibility.

The Size of the Problem. Some Facts.

Nearly 1 per cent of the people of the world are coughing up tubercle bacilli (¹). There may be 25 million infectious cases. For instance, a national survey suggests that in India alone there are 5 million cases of tuberculosis, many of which are infectious; the problem is equally acute in town and country. Traditional hospital treatment is out of the question there. 30,000 beds are available, up to one million would be needed. But it should not be assumed that the problem is confined to underprivileged communities. It is probable that there are still 375,000 cases, of which 45,000 are infectious, in England and Wales (²).

At the end of the 19th century tuberculosis in Britain caused more deaths than any other disease. One in every five deaths was due to it; a dreadful total of over 60,000 people each year. And, worst of all, most of these deaths occurred in children and young adults. Today the death rate in Britain from tuberculosis is down to one in every 80, and most of these are old people. In 1960 only 400 persons under the age of 40 died from tuberculosis.

The decline in mortality from 1900 till 1945 was at about 3 per cent per year in Britain and the United States, apart from the years of the two world wars in Britain (Figure 1). After 1948, however, the previously steady decline abruptly accelerated to an average of 15 per cent per year in both countries up till the present time. If the new rate of decline continues—and there are good reasons for expecting it to do so—tuberculosis as a cause of death in our country will have virtually disappeared by 1975, providing complacency does not develop.

The steady but slow success in the battle against tuberculosis in the early decades of the 20th century

was due to many factors, including an increasing understanding of the disease, application of preventive measures and particularly the increasing prosperity of the population. The abrupt and persistent increase in the speed of improvement after 1948, however, was the result of a single dramatic new factor—the discovery and widespread use of effective anti-tubercular drugs. It is the use of these drugs, combined with traditional methods of treatment, that has opened up the possibility of the final defeat of tuberculosis in Britain within 15 years.

THE DISEASE AND ITS CONTROL

The novelist selected tuberculosis as the disease of tragedy for good reasons. In most infectious diseases there is a short severe conflict between the defence mechanism of man and the invading bacteria, which results in death or recovery. But in tuberculosis, although the same general principles are involved, the processes are very slow. This is because the tubercle bacillus is an inactive organism. The typhoid bacillus will double its numbers in less than half an hour; the tubercle bacillus takes a day or so. This may be due to a thick wax coat which surrounds the organism and which interferes with diffusion of food into the bacteria and of excreta and poisonous substances out of the bacteria. As a result, the surface of the tubercle bacillus provides little irritation to the tissues as it grows in the body. In many ways, it behaves like an inert foreign body, such as a splinter of glass or a thorn.

This wax coat also protects the bacillus from drugs or disinfectants intended to kill it and from the defence mechanisms of the body. Because of it, the bacillus may remain alive but inactive in the tissues for years, to resume activity when the health of the patient declines for some other reason, such as fatigue or a bout of influenza. Before 1946, it could be said that 'tuberculosis is never cured, only halted'. The main purpose of sanatoria was to educate patients to conduct, discipline and restrict their lives so as to keep the disease 'halted'.

This slow and insidious disease is therefore usually difficult to detect, particularly in the early stages and in patients with mild or chronic disease. These

people, in particular, may go about their business, virtually free from symptoms, other than slight cough, though they are highly infectious. The detection and treatment of these people provides one of the most important aspects of the control of this disease. The senile tuberculous patients provide an important source of infection.

The Tuberculin Reaction

In addition to the waxy coat, there is another substance in the tubercle bacillus of great importance, a protein called tuberculin. When a patient becomes infected with tubercle bacilli, antibodies to tuberculin develop which have the ability to unite with tuberculin so that when the latter is injected into the skin, a red patch of inflammation appears. This is called the 'Tuberculin Test' which provides an important method of detecting people infected with tubercle bacilli. It is believed that this process of 'sensitization' to tuberculin is part of a defence mechanism produced by the body, which prevents the spread of infection. It must be very effective in the vast majority of people, because in many parts of the world up to 90 per cent of the population can be shown by this test to have been infected with tubercle bacilli before they are twenty years old, but most suffer no ill-effects at all and only a few become ill.

Susceptibility to the Disease

The most important single factor in deciding whether a patient infected with tubercle bacilli will become ill or not is believed to be genetic. The body's ability to deal with tuberculous infection is believed to be largely inherited. In communities where tuberculosis has existed for centuries, particularly during the years of the industrial revolution, there was a high death rate amongst those with an inherited susceptibility to tuberculosis; the resistant population survived and reproduced. The percentage of resistant people therefore steadily increased and the mortality from the disease gradually fell. But whenever a new non-immune population met the tubercle bacillus for the first time, they developed an acute, rapidly progressive and fatal type of tuberculosis. This was seen among West African troops brought into Great Britain during

the 1914-1918 war. The North American Indians responded in this way to tuberculosis introduced by white people. The coloured South Africans, particularly those working in mines where conditions are favourable to the spread of infection, also develop acute tuberculosis, whereas the white population do not do so. In many parts of the world where tuberculosis is a new disease, natural immunity is lacking. This magnifies the problem of control of the disease. Moreover, because tremendous advances have been made in the drug treatment of tuberculosis and those that would have died now live, the proportion of any population that is susceptible to the disease will increase and provide a potential threat in any new outbreak. These people will reproduce and the percentage of susceptible people will increase.

B.C.G. Vaccine

The problem of artificially producing and maintaining immunity to tuberculosis has therefore attracted a great deal of attention. In 1906 Charles Calmette and Camille Guerin first began to grow their particular strain of tubercle bacillus (Bacille Calmette Guerin—B.C.G.) in a wooden shed in Lille. Great Britain was one of the last countries in the world to introduce B.C.G. but having decided to study the vaccine, did so with a thoroughness and skill that surpassed any previous work in this field. A British pharmaceutical company developed a 'freeze dried' vaccine which was safer to use than the wet vaccine, and also had the advantage of stability so that it could be kept for long periods and easily distributed and exported. During the various stages of this development there was close co-operation between the scientists of the Medical Research Council and those in the industry and it is unlikely that this valuable work could have been done as rapidly and effectively by any other means.

The Defeat of Tuberculosis

The essential part of any programme for the elimination of tuberculosis is the identification and cure of all cases. If this were done, the disease would be conquered. Other measures are supplementary safeguards. The main methods for the elimination of

tuberculosis are summarised in the Table at the end of this article. Anyone wishing to consider the problems in greater detail than is possible here should read the Marc Daniels Lecture for 1960 of the Royal College of Physicians of London, entitled 'Tuberculosis Undeafated', given by Professor John Crofton of the University of Edinburgh (*).

Miniature Radiography

In ideal circumstances, the entire population should be X-rayed annually so that early cases would be identified and treated. This is impractical. Miniature radiography should be used to survey groups of people in the community with an increased risk of infection: obviously, and most important, all known contacts of a case of infectious tuberculosis starting with the family of the patients; all institutions, mental homes, prisons; all immigrants, particularly those from countries with a high susceptibility to the disease (this includes both white and coloured races). In general, people from countries with a small population in which agriculture is the main industry are susceptible to tuberculosis—Ireland is an example. The Industrial revolution in most of the countries of Western Europe, with resulting overcrowding and poor nutrition killed most people susceptible to tuberculosis in the nineteenth century, leaving a relatively immune population behind.

Miniature radiography should be used also to survey all those with an increased risk of contracting the disease or, if infected, of spreading it to others: nurses, doctors, dentists, school teachers and others in contact with children. Areas with a higher incidence of tuberculosis than the country as a whole might be subjected to large-scale community surveys. This has been done very successfully in Scotland and in Liverpool. Professor Crofton (*) has made an important plea for 'a mobile miniature radiography machine which can be utilised 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 'black spots' 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.' It is to be hoped that such wise counsel will be followed.

Drug Treatment

Although in theory the disease would die out if every infectious case were isolated, the cost of such a procedure makes it virtually impossible. To apply it the State would have to maintain both patients and their dependants. Quite apart from this, the suffering to families caused by separating one or more members from the others for long periods of time is very great, particularly in milder cases of the disease. In the past, many doctors who detected early cases were very distressed by the financial hardships suffered by the patient's family while the patient was treated. The triumph of the new drugs must be measured against this background. A survey to find patients in order to isolate them for long periods of time is one thing, a survey to find patients in order to cure them, many while they are still at work, is another. This is a vitally important point.

The Role of the Pharmaceutical Industry

The discovery in 1935 of the sulphonamides by Domagk in Germany and their subsequent success in the treatment of many infections created a climate which encouraged the search for other new and specific compounds. Thus by 1941 Fleming's discovery of penicillin in Great Britain was found to have a most important application. In 1943 Waksman in the U.S.A., working in collaboration with the pharmaceutical industry, had isolated streptomycin—another antibiotic—which he showed to be active against tubercle bacillus. Unfortunately, though this was a major advance, the bacillus developed resistance and furthermore in the dosage which had to be used the drug caused some toxic effects in a proportion of patients. Fortunately by 1946 Lehmann, working in Scandinavia, demonstrated that a new compound, P.A.S., was highly

effective against human tubercle bacilli: a great therapeutic advance had been made. More recently two pharmaceutical companies, one American and the other Swiss, simultaneously discovered Isoniazid which is probably the most powerful of all the compounds used in the treatment of tuberculosis and which has the remarkable property of diffusing widely through the body thereby increasing its effectiveness against the invading organisms.

Much attention has been paid to the possible use of corticosteroids with the anti-tubercular drugs, as in certain circumstances they enable the drugs to reach the bacteria more readily. It has been suggested that corticosteroids used in this way are of value in some gravely ill patients, for example in tuberculous laryngitis.

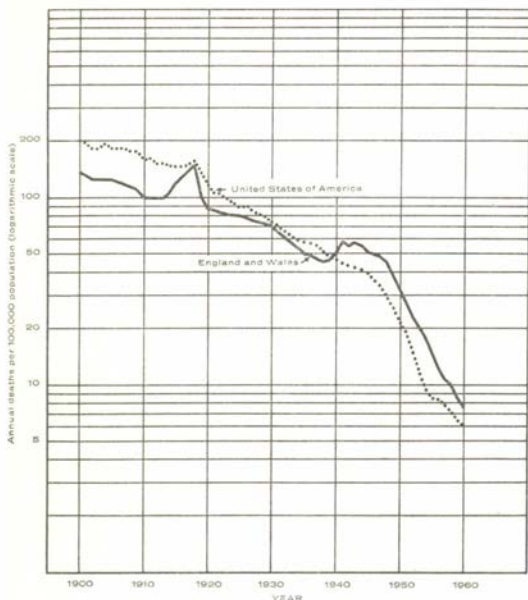
So far it has been found that the use of one drug alone rapidly leads to the development of resistant organisms but this can be prevented by using suitable combinations of drugs. Very good results are obtained when this is done (4). Non-infectious patients with mild disease can continue at work while they are undergoing treatment.

Tubercle bacilli infecting some patients become resistant to a drug during treatment. Other patients become infected with organisms that are already resistant. In either case, when such a state of resistance is known to exist a choice has to be made from the many new anti-tubercular drugs developed by the industry. Though their final place in the treatment of tuberculosis is still to be clearly defined, examples of these newer drugs are capreomycin, viomycin, kanamycin, cycloserine, pyrazinamide and ethambutol (4), (5), (7).

THE HUMAN AND ECONOMIC RESULTS

The startling effects of the anti-tubercular drugs in the campaign against the disease are now becoming apparent. The slow but steady downward trend of 3 per cent per year in mortality from tuberculosis (*Figure 1.*) from 1900-1948, patiently achieved by improved standards of living, public health measures and sanatorium treatment rapidly accelerated as the new drugs came into use. Since the use of anti-tubercu-

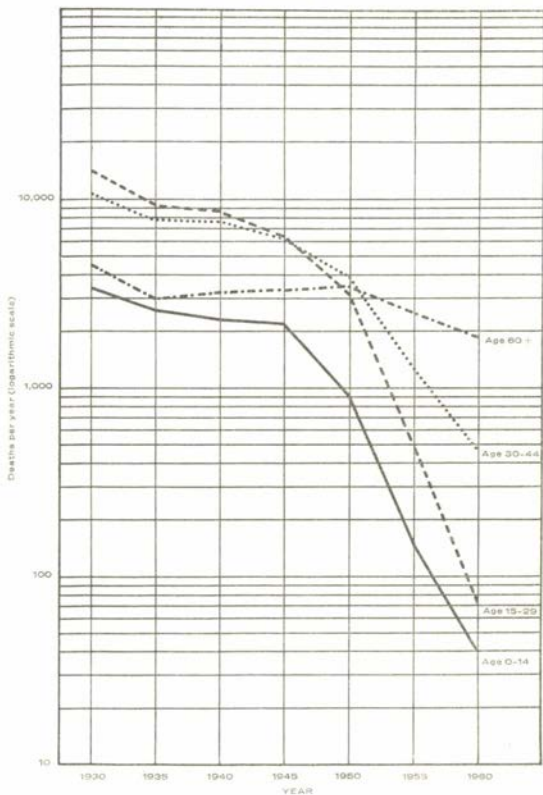
Fig. 1 Mortality Rate from Tuberculosis.
 England and Wales, and U.S.A. 1900-1960.
 Sources: Ministry of Health, London.
 National Office of Vital Statistics, Washington.



lar drugs became widespread, mortality has declined by 15 per cent per year.

Of even greater importance than the decline in overall mortality has been the much faster decline amongst the elderly. In 1930, 14,010 persons aged between 15 and 29 died from tuberculosis in England and Wales, but in 1960 only 75 deaths occurred in this age group (*Figure 2*). Between 1930 and 1950, the annual rate of decline averaged 4 per

Fig. 2 Deaths from Tuberculosis by age groups.
 England and Wales 1930-1960.
 Source: Registrar General.



cent per year, but in the last ten years it has averaged 30 per cent per year.

The fall in deaths amongst the elderly has been much less striking and the majority now occur over the age of 50. 4,670 died who were aged over 60 in 1930, but in 1960 there were still 1,850 deaths in this age group (*Figure 2.*).

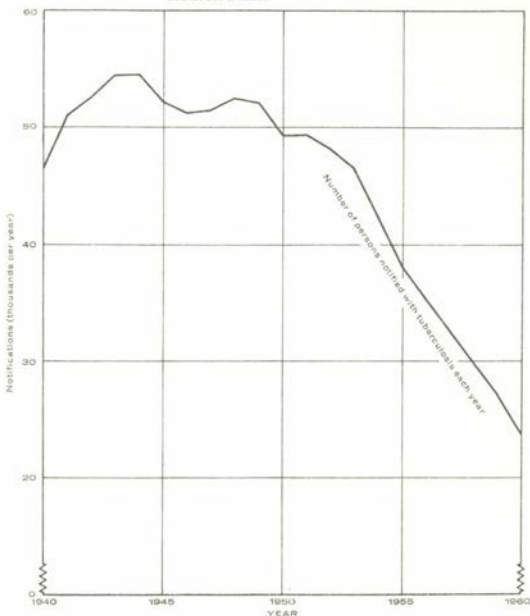
The reason for the disparity of the mortality in the different age groups is that fewer and fewer young people are developing the disease, and many of those that do have since been rapidly cured by the use of effective new drugs. Tuberculosis, however, is a disease that in the past usually took many years to run its course, and many of the elderly who are now dying first developed the disease many years ago before modern drugs were available. The advent of new drugs then enabled them to live on a number of years, even though they had already been severely affected, and death finally occurred later in life.

A further change is now occurring. With fewer young people developing the disease the 'supply' of those affected living on to later life is diminishing. As the elderly already affected die, they are not being replaced by the same numbers of others with tuberculosis, and so the mortality amongst the elderly will also start falling more rapidly, and this is just beginning to occur (*Figure 2.*).

As the 'reservoir' of patients with tuberculosis gets smaller the chance of others becoming infected also diminishes. Measures to prevent the disease spreading therefore tend towards eventual elimination. In the case of tuberculosis cure is itself a form of prevention because the existence of patients with active pulmonary tuberculosis is necessary if new cases are to occur. Most patients who have the disease can now be cured by drugs, and they are then no longer a source of infection. Prevention is better than cure is a well-known adage, but with tuberculosis it is equally true that cure is prevention. Combination of preventive and curative measures by eliminating the reservoir of infection will eventually abolish tuberculosis as completely as elimination of the reservoir of malarial parasites has abolished malaria in many parts of the world.

Fig. 3 Notifications of Tuberculosis.
England and Wales 1940-1960.

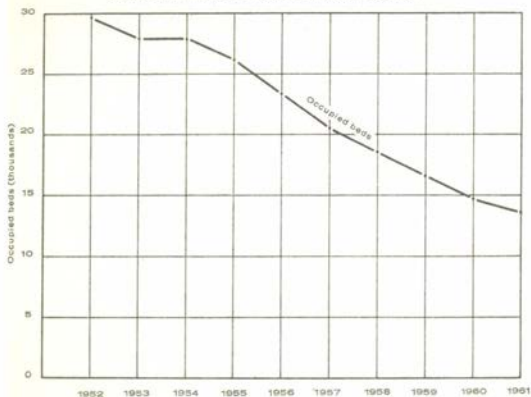
Source: Ministry of Health (1961) *Annual Report* (Part II) for 1960, P.127.



The decline in the number of new cases developing active tuberculosis did not occur until a few years after the introduction of the new drugs because the number of patients with active disease was at first only slowly reduced. At the time it was noted that mortality was falling, but the new drugs seemed to be having no effect on the incidence of the disease. In England and Wales new cases were continuing to occur at about 50,000 per year throughout the 1940's and up till 1952 (*Figure 3.*). Then abruptly there was a

Fig. 4 Occupied Hospital Beds: Diseases of the Chest.
England and Wales 1952-1961.

Source: Ministry of Health. *Annual Reports*.

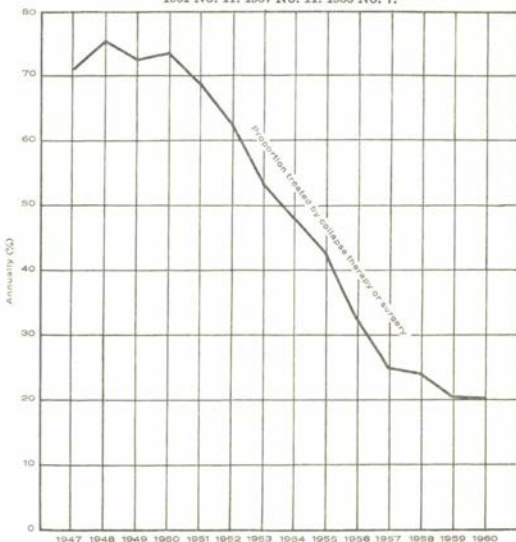


decline which continues and by 1960 new cases were nearly down to 20,000. Testing with tuberculin has also shown that the number of young persons becoming infected at all with tubercle bacilli has also fallen rapidly in the last ten years. The rapid fall in new cases will continue as the sources of infection disappear.

The new drugs have reduced the incidence of tuberculosis, they have shortened the duration of treatment and enabled many patients to be treated at home instead of in hospital. They have solved one of the most pressing problems besetting the Health Service in its early years. In 1950, there were 10,000 patients with tuberculosis waiting for admission to hospital in Britain and plans were drawn up for extension of hospital facilities for the tuberculous. By 1955, however, the number waiting admission had fallen to below a thousand and the plans for expansion were rendered redundant. The number of occupied beds in hospital departments for diseases of the chest had fallen from 29,000 in 1952 to 14,000 in 1960 (*Figure 4.*),

Fig. 5 Proportion of patients in Hospital with Pulmonary Tuberculosis by Collapse Therapy or Surgery. Switzerland 1947-1960.

Source: F. Kaufmann, *Blätter gegen die Tuberkulose*, 1961 No. 11, 1957 No. 11, 1953 No. 7.

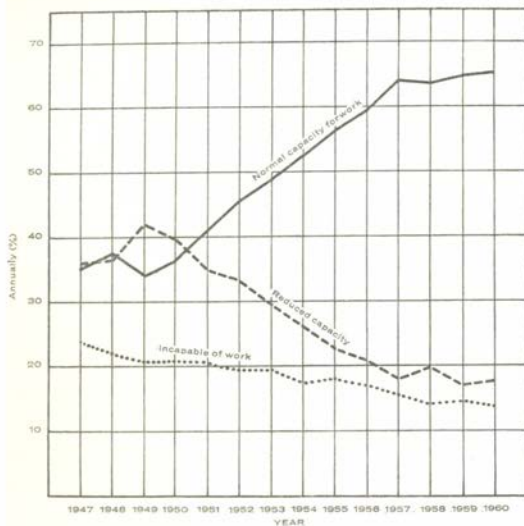


and a steadily rising proportion of the patients in them are suffering from chest diseases other than tuberculosis. In Britain many sanatoria have been closed and some already sold by the Ministry of Health. In Switzerland in the last ten years 19 public sanatoria have been converted to other uses, six of them being made into hotels.

The anti-tubercular drugs have also greatly diminished the need for older forms of treatment such as collapse therapy and surgical resection. In Switzerland the proportion of tuberculosis patients in public sanatoria treated in such ways has fallen from 75 per cent in 1948 to 20 per cent in 1960 (*Figure 5*). Numerous

Fig. 6 Capacity for Work of Patients discharged from Hospital. Tuberculosis of Lung. Switzerland 1947-1960.

Source: F. Kaufmann. *Blätter gegen die Tuberkulose*. 1961 No. 11. 1967 No. 11. 1963 No. 7.



patients have thus been saved from operative procedures which, besides being dangerous, were sometimes mutilating.

The ability of drugs to produce complete cure more often than earlier methods of treatment is indicated by the increase in the proportion of those discharged from hospitals with normal capacity for work from 35 per cent in 1949 to 65 per cent in 1960 (*Figure 6.*).

In the prosperous countries of the world tuberculosis which was the leading cause of death only 60 years ago, is thus well on the way to becoming as unusual as diphtheria or smallpox already are. In many of the under-developed countries, however, the disease is

still a major scourge. As living standards are raised, the combination of public health measures, new drugs, and our modern knowledge should, with proper organisation, be able to bring the disease under control even more quickly than it has been in our own country.

The benefits which flow from the conquest of tuberculosis are both humanitarian and economic. The tragedy of the prolonged illness and death of a young mother or father and the consequent hardship to a whole family is too obvious to require emphasis. But it is often forgotten that the disease also causes great economic loss to a nation which is avoided as it is brought under control. Prolonged illness renders a person unable to undertake productive employment and premature death represents the loss of many years of economic activity. Not only are these losses avoided by the conquest of tuberculosis, but the hospital and medical resources previously devoted to its treatment are released for use elsewhere. The economic benefits have greatly exceeded the cost of obtaining them.

After making due allowance for the steady progress of public health measures, sanatorium treatment, and improved standard of living, it has been estimated that the development of these new drugs has already saved the lives in England and Wales alone of about 100,000 people. This figure has been arrived at by calculating the number of people who would have died each year if the rate of decline in deaths from tuberculosis had continued at the steady rate existing before the anti-tubercular drugs came into use and deducting from these figures the actual number of deaths that did in fact occur.

Because high mortality from tuberculosis was in the age groups below 45, it is reasonable to assume that the 100,000 people who would otherwise be dead would include a higher proportion of economically productive persons than is present in the general population. The average contribution to the gross national product per head of the entire population is about £400 per annum. Thus, the new methods of treating tuberculosis are currently providing an additional contribution to the gross national product of at least £40 million per annum.

To this must be added the annual saving in the cost

of tuberculosis and chest hospital beds not now needed, and for England and Wales this is an additional £15 million per annum. Thus, the anti-tubercular drugs would appear to provide an economic benefit to England and Wales alone of at least £55 million per annum (8).

An economic benefit of £55 million per annum is a large one. It is more than half the cost of N.H.S. expenditure on all drugs to treat all diseases. The Committee on the Cost of Prescribing (1959) under the chairmanship of Sir Henry Hinchliffe were alive to social and economic gains flowing from the development and use of new drugs, commenting:—

'It must not be overlooked that the community as a whole derives tremendous benefits from the growing use of the pharmaceutical service, not only in terms of relief of suffering and saving of life but also financially' (9).

and

'The hospital service would probably be costing a great deal more but for the use which general practitioners are now able to make of new drugs. Patients are now often treated at home for conditions which were formerly treated in hospital' (9).

TABLE—THE ELIMINATION OF TUBERCULOSIS.

1. INCREASE RESISTANCE TO TUBERCULOSIS OF
THE COMMUNITY
 - A. *Specific Resistance*
 - B.C.G. Vaccine
 - B. *Non-Specific Resistance*
 - Clean Air, Ventilation, Overcrowding, Tobacco,
Raise General Standard of Living.
2. SEPARATE INFECTIOUS FROM NON-
INFECTIOUS PEOPLE
 - A. *Non-Infectious People*
 - i. Tuberculin Test Negative
 - Consider giving B.C.G. Vaccine
 - ii. Tuberculin Test Positive
 - a) No evidence of disease
 - Ideally miniature X-ray at regular inter-
vals of time.
 - b) Disease active.
 - Cure with drugs.
 - B. *Infectious People*
 - i. Isolate from non-infectious until non-
infectious.
 - ii. Cure
 - a) Treatment with drugs.
 - b) Surgical methods may be needed in
addition to chemotherapy in a few patients
3. BOVINE TUBERCULOSIS
 - A. *Tuberculin test herds*
 - B. *Pasteurize all milk.*
4. IMMIGRANTS
 - A. *Must be proved to be non-tuberculous.*
 - B. *May be very susceptible to infection. If so:*
 - i. B.C.G. Vaccine.
 - ii. Miniature X-ray at regular intervals.

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Office of Health Economics

The Office of Health Economics was founded in 1962 by the Association of the British Pharmaceutical Industry with the following terms of reference:

- 1 To undertake research to evaluate the economic aspects of medical care.
- 2 To investigate, from time to time, other health and social problems.
- 3 To collect data on experience in other countries.
- 4 To publish results, data and conclusions relevant to the above.

The Office of Health Economics welcomes financial support from any persons or bodies interested in its work.