Methods of discovery in the fight against disease : Robert Boyle memorial lecture 1938 / by Sir Edward Mellanby.

METHODS OF DISCOVERY IN THE FIGHT AGAINST DISEASE

Robert Boyle Memorial Lecture
1938

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METHODS OF DISCOVERY IN THE FIGHT AGAINST DISEASE

I SHOULD like in the first place to pay tribute to Robert Boyle, the great man in whose honour this lecture has been instituted. I have always had feelings of benevolence towards Boyle since my early days, for the simple reason that of the many laws with which I was inculcated from childhood onwards, his was one of the few that I thought I understood. Its simplicity of expression suited me. It was with great regret, therefore, that I noticed that physicists have questioned its infallibility under certain conditions and that in its modification it has acquired more symbols. Boyle was a man of such great versatility that it is difficult to believe nowadays that such a man could exist. Although a physicist at heart, yet described by some of his biographers as an eminent chemist, it is pleasant to know that he was also a doctor of medicine of Oxford University. Among his numerous works are three volumes of *Medicinal Experiments* and *Memoirs for the Natural History of the Human Blood*. His *Sceptical Chymist* is an elucidation of the true method of scientific inquiry. Clearly, then, he took all natural science as his province, a characteristic which makes him the ideal patron saint for a university society devoted to the study of scientific problems.

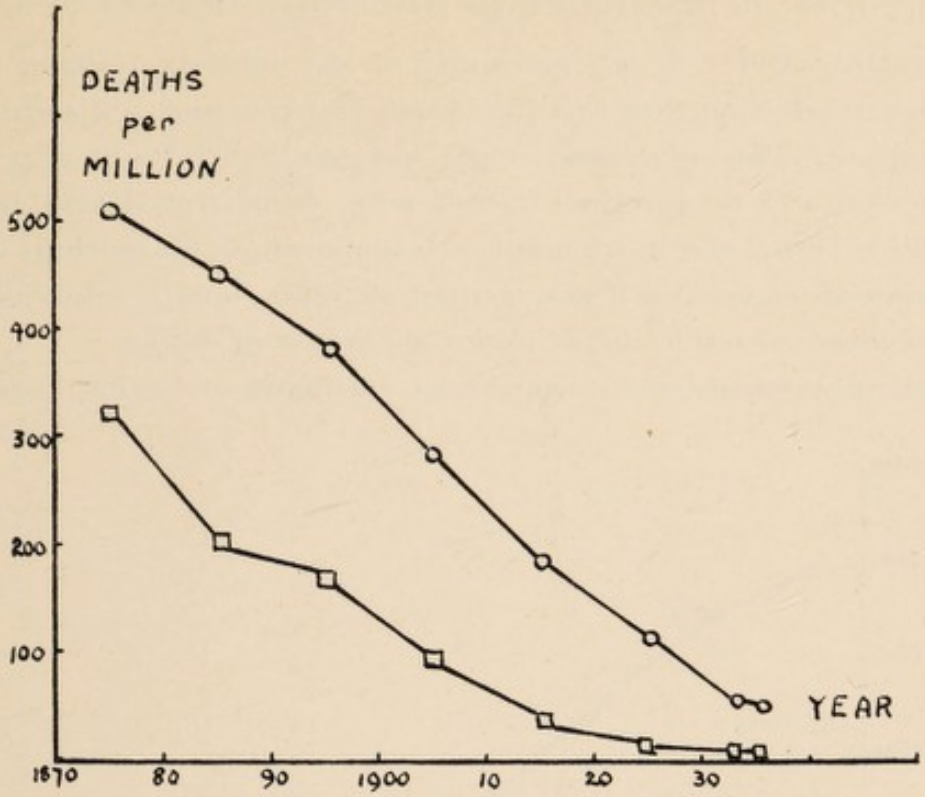
In this lecture to-night I wish to give you some evidence of the great advance in medical science in recent times. Knowledge of the advances in physical science cannot be avoided because of their domestic and public manifestations, such as motor-cars, aeroplanes, wireless, and television. The advances in the conquest of disease have been no less important, but they do not thrust themselves upon the public and, indeed, their greatest triumphs are often completely obscured, partly because it is unusual for medical men to talk in public about their subject and partly because the greatest triumphs of medical research do not lead to manifestations but to the disappearance of diseases and the consequent forgetfulness of anything related to them. The great advances in understanding of disease in recent times, as compared with the stagnation of previous eras, can probably be appreciated when it is remembered that, up to about sixty years ago or even less, the average doctor treated his patients on the same lines as Hippocrates, though probably not quite so well.

If Hippocrates walked into a large general hospital now and saw what was happening, he would no doubt feel very perplexed and astonished.

I am anxious not to mislead you on the subject of medical discovery by the particular form which this lecture will take. In a popular lecture of this type, it is necessary to choose the more interesting and possibly even the dramatic side of the subject, and the only part of medicine which is of this nature is, of course, the curative side of the subject. Before, however, any patient can be cured, it is clear that his condition must be diagnosed and the underlying causes understood. The accumulation of knowledge and the investigations that have been necessary to bring the art of diagnosis to its present position are, of course, numerous. When a patient comes to a doctor complaining of recurrent headaches, the cause of these headaches has first to be diagnosed. They may be due to one of many causes and correct treatment depends upon proper diagnosis. Similarly, a patient may have a pain in the abdomen and the treatment again must depend upon the correct diagnosis of the cause of this symptom. This part of a doctor's work and the accumulated knowledge upon which he bases his decisions do not lend themselves to popular exposition but are none the less important for that. Again, it must be recognized that the aim of medical research is to rid the community of disease. This can only be done in the case of any particular disease by precise and intimate knowledge of its causation. In the course of the last hundred years we have seen many diseases disappear from this country, but few people ever think anything more about them. On the other hand, there has been a tremendous advance in methods of diagnosis and treatment of the diseases still occurring. It is important to realize that these two lines of advance in knowledge have opposite effects in public life. The first, which brings about the elimination of disease, does away with the need for hospitals and doctors, and nurses, and all the other paraphernalia associated with medical treatment. As examples of this line of advance we might think of the decreased incidence of rickets and scurvy. On the other hand, improvement in knowledge of diagnosis and treatment as such usually means more and bigger hospitals, more doctors, more nurses, and more equipment. Since it is clear that the medical personnel of the country is largely increasing and the hospitals are improving both in quantity and quality, it might be thought

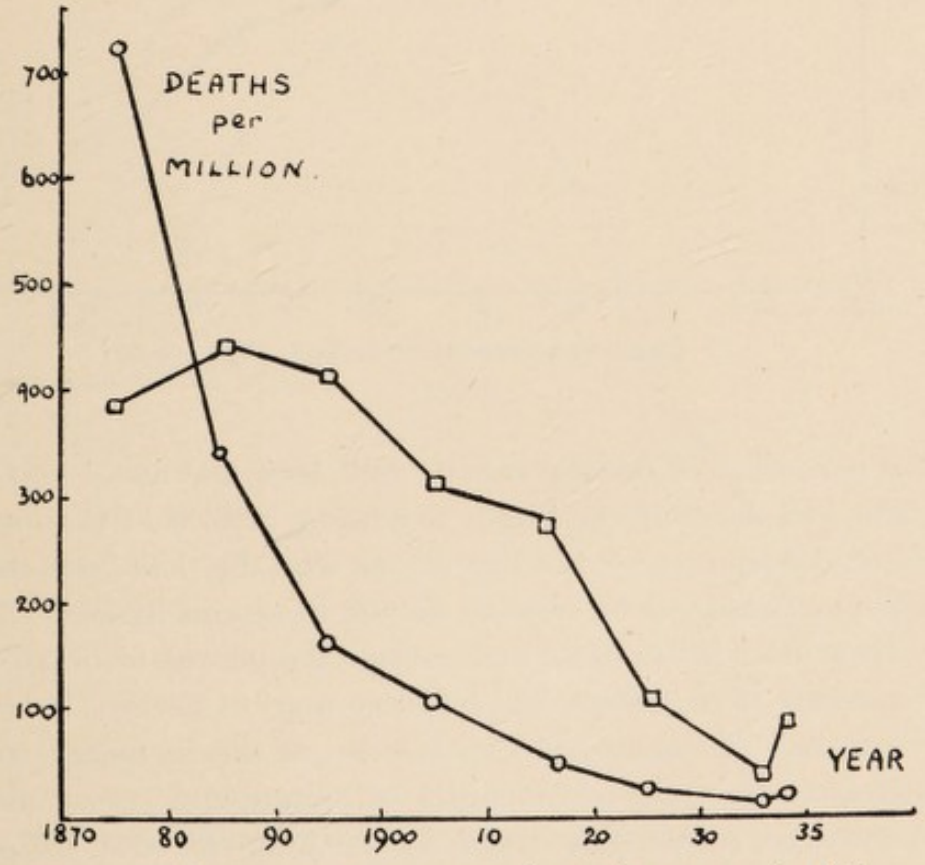
that the modern discoveries of treatment are greatly outweighing the preventive discoveries. For the moment this may be so, but there is nothing more certain than that in the course of the next fifty years or so the preventive aspect will become more and more important and there will be less need for the treatment side of the problem. How little do we now think, or rather, perhaps, we do not even know, of the great scourges of a hundred years ago, of such diseases as cholera, plague, malaria, small-pox, and typhus fever. We now give little thought to these diseases, much less to the means whereby they have been made to disappear. Typhoid fever is another disease which comes under the same category, although the recent scare at Croydon, when a few people died of this condition, was sufficiently great to suggest that we ought occasionally to count our blessings in this respect. Nowadays we hear little of gout and stone in the bladder, descriptions of which filled the ordinary literature of bygone days. Most of us in this room have in our time seen the incidence of such diseases as rickets, chlorosis, epidemic diarrhoea, and vomiting in children reduced from enormous numbers to relatively insignificant figures. The point I wish to emphasize is that the greatest triumphs of medical science, because they lead to the disappearance of disease, pass with the disease into oblivion, whereas the curative remedial discoveries, some of which I will mention in this lecture, though possessing dramatic qualities, do not eliminate the disease they remedy, and so they remain in men's minds.

Let me illustrate some of the modern developments in this fight against disease by showing you specific and detailed examples of the great reduction in modern times in death-rate due to certain infective diseases. In Figs. 1, 2, and 3 can be seen the relative mortality rates due to typhoid fever, whooping cough, scarlet fever, measles, and tuberculosis. The almost complete elimination of death from typhoid fever can be seen in Fig. 1, while in all the other examples, especially scarlet fever and tuberculosis, the mortality rates have come down tremendously in recent years. As regards the death incidence from tuberculosis, you will see that in the past seventy years the mortality rate has been reduced to one-fifth, so that, whereas in 1855 the mortality rate was 3,500, in 1936 it was something of the order of 500 per million. You will notice that the decline throughout all this period has been a straight one, and if this rate of disappearance is maintained there ought to be little or no tuberculosis in this country



Death-rates from whooping-cough (o) and typhoid fever (□).

FIG. 1

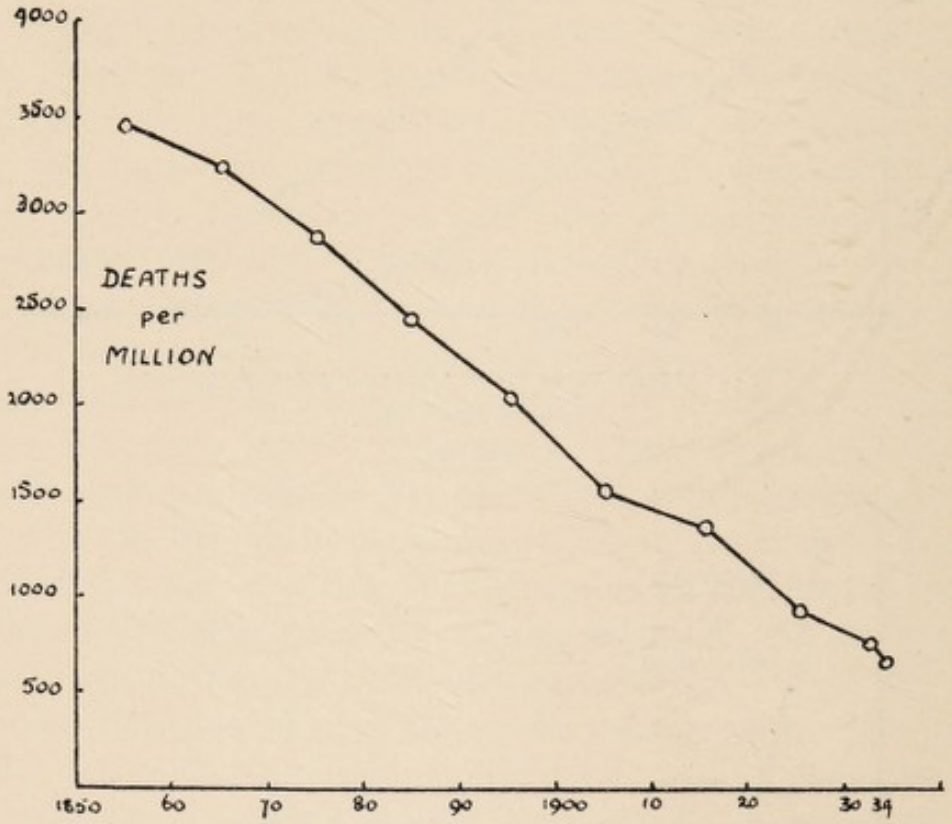


Death-rates from scarlet-fever (o) and measles (□).

FIG. 2

by the year 1960. I can see some of the mathematicians in my audience predicting that this line must continue and will shortly cut the abscissa. This, of course, might happen, but I doubt very much whether it will or whether it will even bend round and become asymptotic until the incidence has become much lower than it is at the moment, especially if the control of public health remains at its present level, which it shows every likelihood of doing.

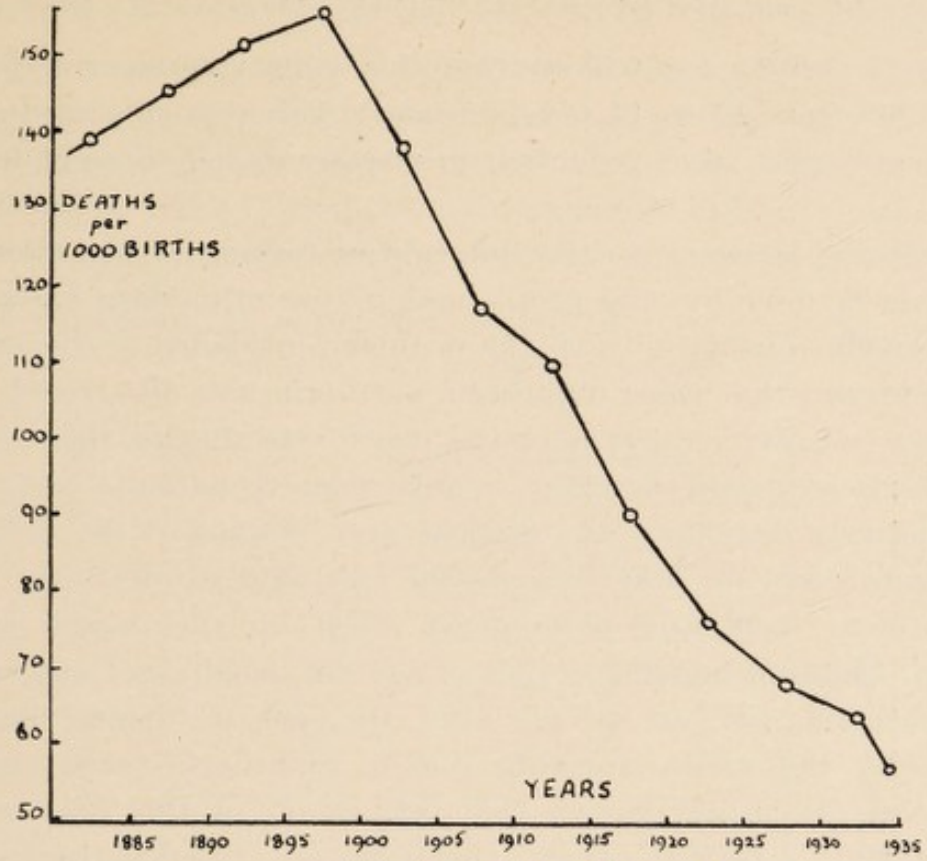
Another measure of the improved standard of health associated



Death-rate from tuberculosis, 1850-1934.

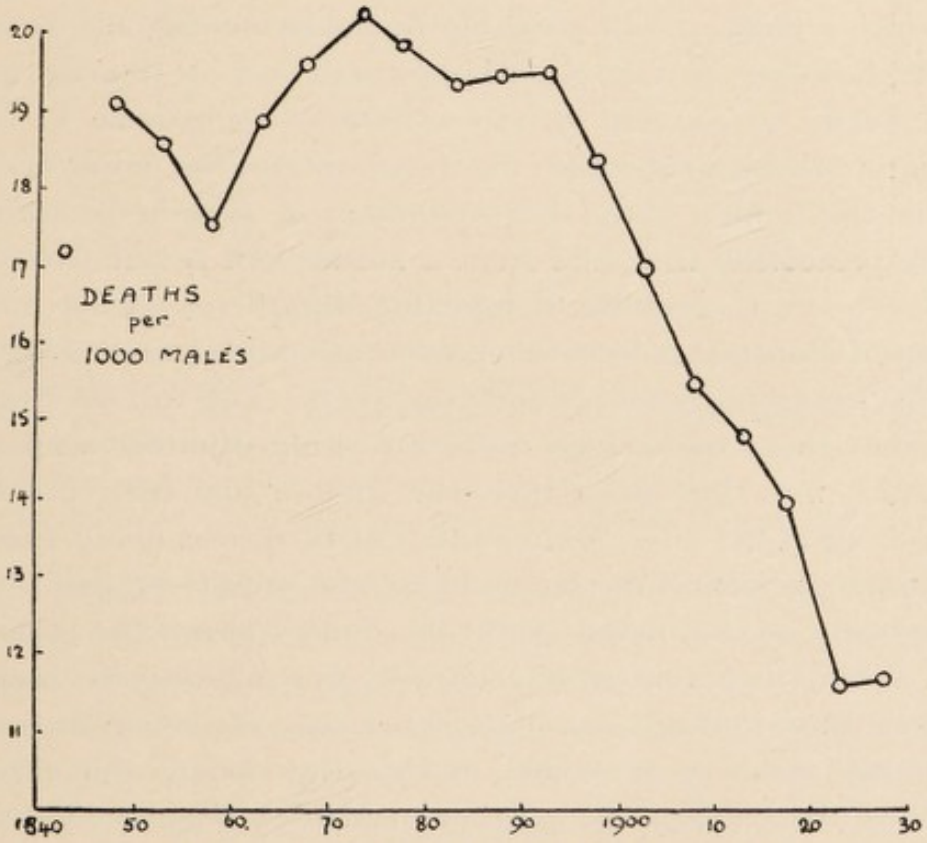
FIG. 3

with the reduction of disease can be well seen in Figs. 4 and 5. In Fig. 4 you will see that the infant mortality rate, that is to say the number of children under the age of one who die, has been reduced from 160 per thousand in 1900 to 56 per thousand in 1936. I have heard it said that in the past it was more dangerous to be an infant under one year than a front line infantry man in battle. It is sometimes said that the increased expectation of life in recent times is due entirely to the reduced mortality of infants and young children. Fig. 5, however, shows that this is not entirely the case, for in that graph which expresses the mortality rates of adults between the



Infant mortality, 1880–1934.

FIG. 4



Mortality rates, males aged forty-five to fifty-five, 1840 to 1930

FIG. 5

ages of 45 and 55, you will see that this death-rate has come down since 1905 from 17 to 11 per thousand. This can only mean that there has been a great reduction in disease among those of middle life.

To return, however, to the question of fevers, let me show you what can be done by wise people making use of modern knowledge and actively interfering with the ordinary incidence of disease. It is well known that since diphtheria antitoxin was discovered there has been a great reduction in the death-rate due to this disease. Diphtheria antitoxin, however, is only given to patients when they have actively developed the disease, and because of the difficulty of diagnosis and for other reasons the antitoxin is often only given too late to have any pronounced effect on the course of the disease. Children under one year of age are usually not susceptible to diphtheria, nor are people after the age of fifteen, therefore practically the whole mortality due to diphtheria takes place in childhood. It is now known that one attack of this disease protects against a further attack, that is to say, the diphtheria toxin produced in the first attack evokes the production in the individual of an antibody known as the antitoxin. If diphtheria toxin be injected into a child, it will probably be made severely ill. It is now possible, however, to take diphtheria toxin and by treating it with formaldehyde to convert it into a harmless substance known as diphtheria toxoid, a substance which still retains the power of calling forth in the human body the production of diphtheria antitoxin, thereby protecting the child from a subsequent severe attack. In Fig. 6 you see the results of injecting diphtheria toxoid into the children of Montreal, where this preventative measure has been employed systematically for a number of years. You will see from this graph that there was a high death-rate from diphtheria up to the year 1928, but that since then the disease has been practically stamped out of the city. Many other Canadian and many American cities present results of the same kind, and it is quite evident that this disease could be eliminated from this country also if the practice of giving diphtheria toxoid prophylactically were extensively used. The results indicate that not less than 50 per cent. of the children in any community must be protected in this way before the disease is controlled and reduced to negligible incidence. Some 3,000 to 4,000 children die annually of diphtheria in this country out of about

50,000 or more (this figure is a guess) who contract the disease. Just think what a boon it would be to eliminate all this waste of life, all this sickness by the simple practicable means now available.

I should now like to give you a few examples of modern discoveries in the treatment of disease rather than in its prevention, but let me

Diphtheria Mortality Rate in Montreal, with number of Deaths at each point of the Curve.

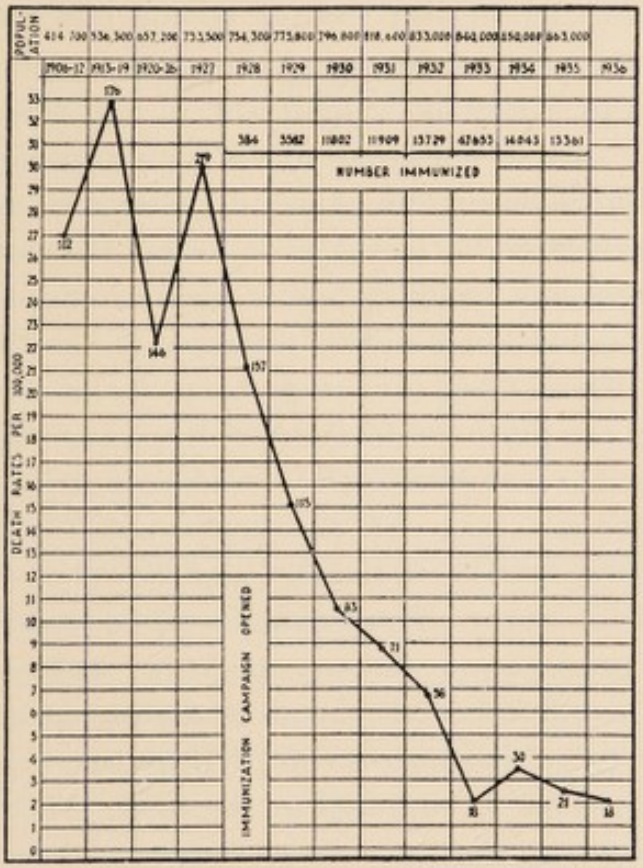


FIG. 6. Summary of results of large-scale voluntary protective inoculations against diphtheria in New York and in Canadian cities and provinces. Wherever the necessary 50 per cent. or more of children under 15 years have been inoculated diphtheria has been reduced to small proportions of the previous rates within about a single decade, and in smaller towns altogether eliminated.

(*By courtesy of Dr. Graham Forbes and the 'British Medical Journal'.*)

again emphasize that the dramatic nature of some of these results is not the only or the best method of illustrating the advances in medical discovery of modern times. As I should like to choose methods of treatment which contrast with one another in their type and scientific character, let me first say a word about the general causation of disease in man. The causation of disease may be crudely divided into two groups: (1) diseases due to infection, and (2) non-

infective diseases, namely those due to chemical derangement, including nutritional deficiencies. In the first group the invading infection which produces disease may be of various types. It may be due to a virus, such as is responsible for small-pox, measles, and epidemic influenza; it may be of bacterial nature, such as is responsible for diphtheria, anthrax, or gonorrhea; or it may be protozoan, such as is responsible for syphilis, malaria, and sleeping-sickness.

As regards the second large group of diseases, due to chemical derangement, this again may be due to the fact that there is too much or too little of some essential chemical factor or hormone, or more probably to a lack of adjustment in the delicately balanced interplay of the various hormones in the body. In one large group of such diseases the chemical substance in question is something which is normally synthesized in the body, and when the elaboration of this goes wrong there may result a disease such as exophthalmic goitre, in which there is too much active principle of the thyroid at work, or acromegaly, where there is excessive activity of certain cells of the anterior lobe of the pituitary body, or of hyperparathyroidism where there is excessive parathyroid gland hormone in action. On the other hand, the deficiency of a specific chemical substance in the body may be responsible for Addison's disease—deficiency of the active principle of the cortex of the suprarenals, or myxoedema—deficiency of thyroid active principle, or diabetes mellitus—deficiency of insulin.

The second subdivision of chemical derangement concerns the lack of one or more substances, not synthesized by the body and which therefore must be supplied in the food. This includes, then, all dietetic deficiency diseases such as rickets, certain forms of anaemia, simple goitre, scurvy, &c. Sometimes, of course, the infective diseases are associated with these disorders due to chemical derangement, and there are undoubtedly other diseases which do not fall into either category. On the whole, however, most ordinary diseases can be so included.

The first of these about which I propose to say a few words is an infective disorder due to a virus, namely measles. Measles is still a deadly disease in this country and kills about three to four thousand children under the age of three annually. It appears in epidemic form biennially and the death-rate in alternate years due to measles is always high. If death were the only result, it would be bad enough. But what makes it much worse, from a social standpoint, is that it

leaves so many sequelae, especially in the form of bronchial pneumonia and infection of the middle ear. Many children and adults, who have to go through life with running ears and subsequent deafness, owe these disabilities to an attack of measles in early life. Fig. 7 illustrates, by means of a temperature chart, the history of measles. It will be seen that the attack does not begin till about the 11th day after exposure to a source of infection. The temperature then rises rapidly and in an uncomplicated attack does not come back to normal till about the 19th day. Two things may happen before the

Measles

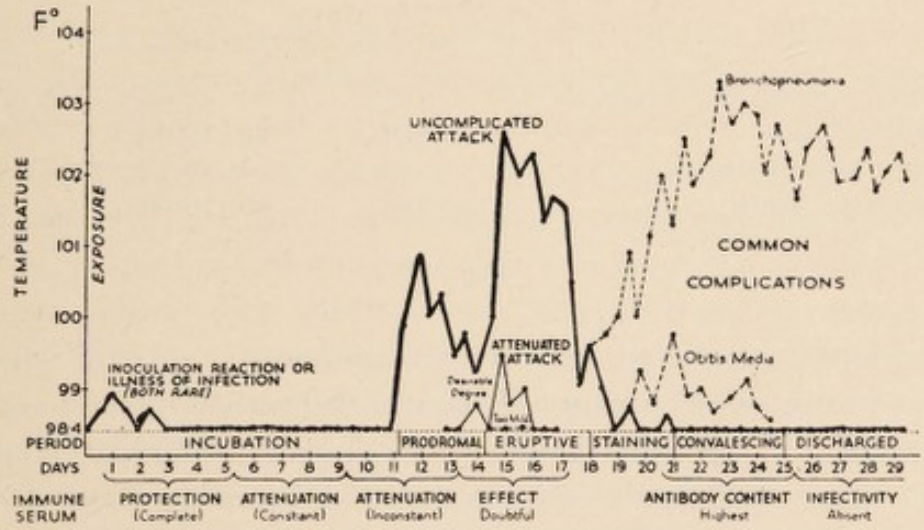


FIG. 7. Synoptic chart showing the typical course of measles: (1) uncomplicated, (2) with the two commonest complications, (3) attenuated by immune sera (*a*) to the desirable degree and (*b*) to an undesirable degree with an attack too mild to confer lasting immunity.

case is cured, both of which occurrences are reflected in Fig. 7. The temperature may suddenly rise again about the 17th day after infection, owing to the development of broncho-pneumonia, or it may rise to a lesser degree above normal on the 18th or 19th day, owing to the development of otitis media. Broncho-pneumonia often results in death, otitis media or middle-ear disease in discharging ears and deafness.

When children are exposed to infection, about 75 per cent. of them take the disease, but one attack usually protects permanently against a second attack, and this fact indicates the line of action in the prevention of the disease. Since after an attack of the disease the blood contains an antibody to the measles virus, it is possible by injecting the serum of an individual who has had measles to modify

the attack in a child exposed to the disease. There are two types of sera; one known as the convalescent type, which is obtained from individuals recovering from the disease, and the other known as the adult type, obtained from anybody who in childhood has had measles. If 10 c.c. of the adult measles serum is injected into a child under three years of age, who has been exposed to infection, the child will

MEASLES

Complication and Mortality Rates. Non-serum versus Serum Treatment

	Number of patients	*Complications*	*Deaths*
I. Control group (no serum) .	101	57 (36·65%)	5 (4·95%)
II. Adult serum . . .	324	32 (10·0%)	Nil
III. Convalescent serum . .	75	8 (10·7%)	Nil
IV. All serum cases . . .	399	40 (10·03%)	Nil

FIG. 8

be completely protected during one epidemic, provided that the serum is administered within five days of the earliest known exposure to infection. On the other hand, if it is desired to modify the attack and not to prevent it, this can be done by injecting about 5 c.c. of adult serum into the child between the 6th and 9th day after exposure to infection.

There is a great difference in the subsequent resistance or immunity of the child to measles according to whether it has been completely protected or allowed to develop a modified attack. After protection against an attack, the immunity only lasts for three or four weeks, that is, over one epidemic. On the other hand, if the attack is only modified, that is, reduced in severity, the individual is permanently immune for the rest of his life. It is therefore clearly desirable to allow a modified attack if possible. On the other hand, measles is a very dangerous disease to all children under three and therefore in such children it is necessary to protect them completely at that age. It has been shown in the London County Council fever hospitals that death resulting from measles can be almost completely eliminated by this treatment of children in the early stage, and also that the complications due to broncho-pneumonia and middle-ear disease can be greatly reduced (see Fig. 8). It will also be seen that the

method can be applied to any community such as a school at the early stages of an infective attack, and every member of the school can be allowed by this means to have a very slight modified attack under safe conditions, and each individual then be immune for the rest of his life.

The second disease, the results of recent developments in the treatment of which I want to put before you, is puerperal or childbed fever. There has been great public discussion about this disease in recent years, because the mortality rate has not come down in line with other diseases, in spite of the greater precautions of modern management of childbirth. Until the last year about 1,200 women have died each year in childbirth as a result of this infective condition. Modern research has shown that the pathogenic forms of streptococci, which prove so fatal to these women, whom we must regard as very important members of the community, are not normally present in the birth canal, but are conveyed there from the throats of people with throat infection and from the skin and other extraneous places. The infection may, for instance, be carried from the throat of the doctor or midwife attending the case, or from the patient's own throat or from septic sores on her skin.

Up to about thirty years ago most drugs used in medicine for the treatment of disease were naturally-occurring substances, for instance, morphine from poppies, digitalis from foxgloves, and quinine from cinchona bark. In 1905 a new type of drug for treating disease was introduced into medical science when Ehrlich discovered salvarsan for the treatment of syphilis. Salvarsan is an organic arsenical compound which Ehrlich discovered had the power to kill spirochaetes which were responsible for certain infections of animals and men. This drug is one of a large group of substances now commonly called chemotherapeutic compounds, which have been synthesized in the laboratory and proved to have specific killing effects on certain micro-organisms. For instance, atebrin and plasmoquin are chemotherapeutic compounds used in malaria, while Bayer 205 or germanin kills the trypanosomes of sleeping-sickness. Until recently all the triumphs of chemotherapy had been associated with diseases due to protozoa and in no instance had a chemotherapeutic agent having a specific effect on bacteria been obtained, although many attempts had been made to find such compounds. Some years ago two German workers, Mietsch and Klarer, synthesized a substance which was

found by Domagk to kill streptococci in mice and thereby to prevent the death of the mice from streptococcal infection. This substance was known as prontosil, of which there were two varieties—'red prontosil' or just prontosil and 'prontosil soluble'. Later it was found by three French workers, Tréfouël, Nitti, and Bovet, that a substance called sulphanilamide had the same preventative action as prontosil in mice infected with streptococci. The formulae of these three substances are shown in Fig. 9.

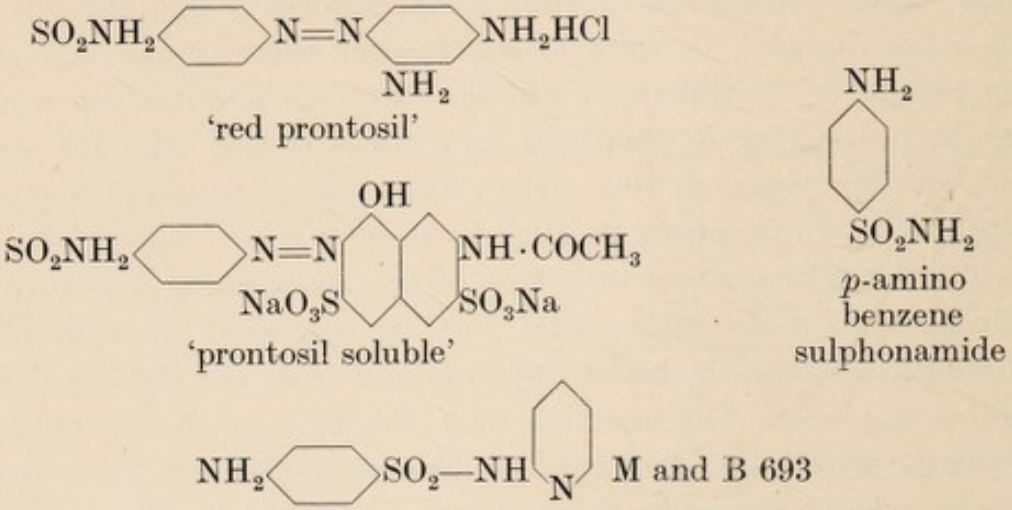


FIG. 9

The next stage in the development of this interesting story was when Dr. Colebrook, working at Queen Charlotte's hospital, showed that these substances also had specific curative effects on puerperal fever in women. In the five years from 1931 to 1935, the average maternal mortality among the women suffering from childbed fever in Queen Charlotte's hospital was 22·8 per cent.; during the first eight months of 1936 there were sixty-four cases of this disease treated by these drugs and the mortality rate was only 4·7 per cent. (see Fig. 10). Since this time, Dr. Colebrook has treated many other cases and the mortality rate has kept down to 5–6 per cent. It is generally recognized now that sulphanilamide drugs have an extraordinary effect in streptococcal infections, including puerperal sepsis. For instance, they have a specific curative effect in streptococcal meningitis, streptococcal sore throats and acute tonsilitis, and in erysipelas. They have also been shown to have curative effects in diseases due to other infective organisms such, for instance, as gonorrhea, infections of the genito-urinary tract, and in meningococcal meningitis. Recent

results have also suggested that an allied sulphanilamide derivative known as M and B 693 (see Fig. 9) has great curative effects in pneumonia.

Although all this development has been very recent, we know sufficient to be sure that the discovery of this series of sulphanilamide compounds is one of the greatest advances made in medical science, and the new form of treatment by these compounds promises to confer untold blessings on mankind.

Treatment of Childbed Fever by Prontosil

	Number of cases	*Deaths*	
1931	98	31 = 31·6 per cent.	Average 22·8 per cent.
1932	90	19 = 21·0 per cent.	
1933	97	20 = 20·6 per cent.	
1934	120	20 = 16·6 per cent.	
1935	90	22 = 24·4 per cent.	
1936 (Jan. to Aug.)	64	3 = 4·7 per cent.	Prontosil treatment introduced.

FIG. 10

For my third example I wish to choose quite a different type of disease to illustrate modern therapeutic methods. This disease belongs to my second group, it is a chemical derangement, and is known as general osteitis fibrosa of von Recklinghausen (hyperparathyroidism). In this rare condition there is great swelling and tenderness of the bones. The bones also become deformed and sometimes fracture spontaneously. There is great muscular weakness. The patient loses appetite, feels sick, and may vomit. There are also abdominal cramps. Usually the patient is very thirsty and excretes large quantities of dilute urine. There is much wasting in advanced cases. The kind of deformities that one gets in the bones of such patients may be seen in Fig. 11. The bones usually become very brittle owing to the removal of the calcium salts by certain cells called osteoclasts which are present in large numbers. If the blood of such people be examined, it will be found that they have a very high calcium content and a low phosphorus content, and it is this condition of hypercalcaemia which is responsible for the sickness and weakness of the patients. This disease was first described in 1891, and in 1907 it was discovered by post-mortem examination that these patients had an

enlargement of one or more parathyroid glands—small glands placed behind the thyroid gland in the neck. Their position and relative

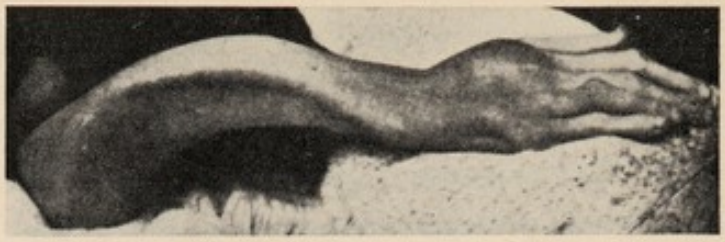


FIG. 11. Antero-external curvature of the forearm. Large bony swelling on dorsum of right hand. (June 1930.)

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size is shown in Fig. 12. In 1926 Mandl, a Viennese surgeon, decided that this swelling of the parathyroid gland was probably the cause of the bone and other defects in the patient. It was impossible, of

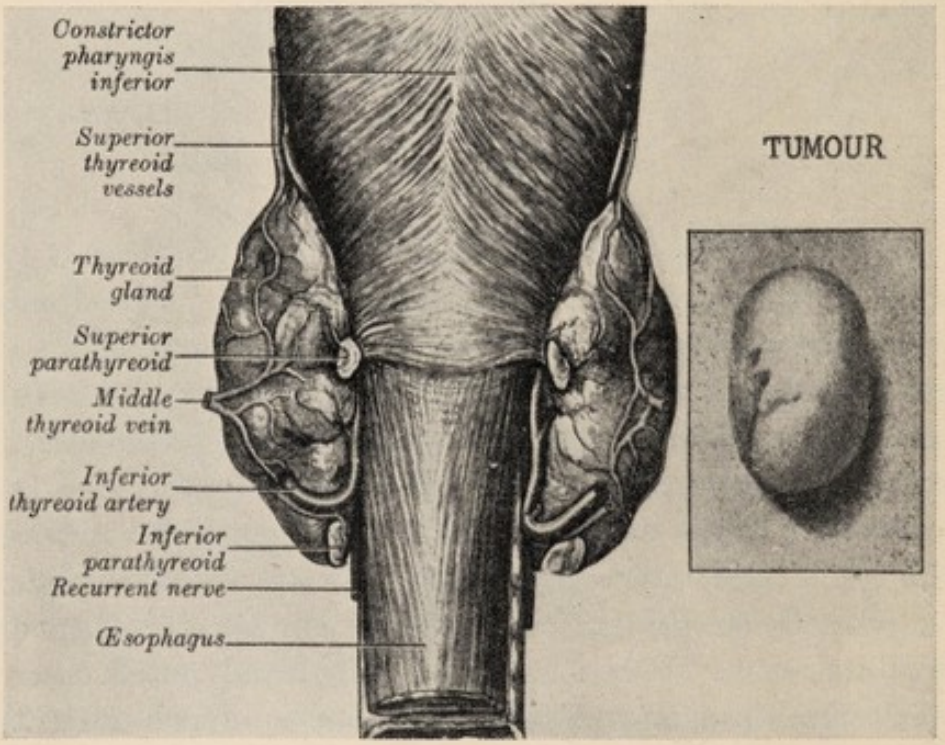

FIG. 12. Showing position and relative size of the parathyroid glands in man. The tumour of the parathyroid, actual size, was removed from the case whose history is described in the text.

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course, to say whether the gland was hypertrophying as a reaction against the disease or whether the hypertrophy of the gland caused the disease. Mandl removed four parathyroid glands from a healthy fatal accident case and transplanted these into the abdominal wall

of a patient suffering from osteitis fibrosa. No improvement was brought about by this treatment. He then explored the neck of the patient and found a parathyroid tumour and removed it. Within a few days all pain and sickness had disappeared and the patient felt greatly improved. The calcium in the blood was lowered and the calcium excretion also diminished. After $3\frac{1}{2}$ years the patient was

Hyperparathyroidism

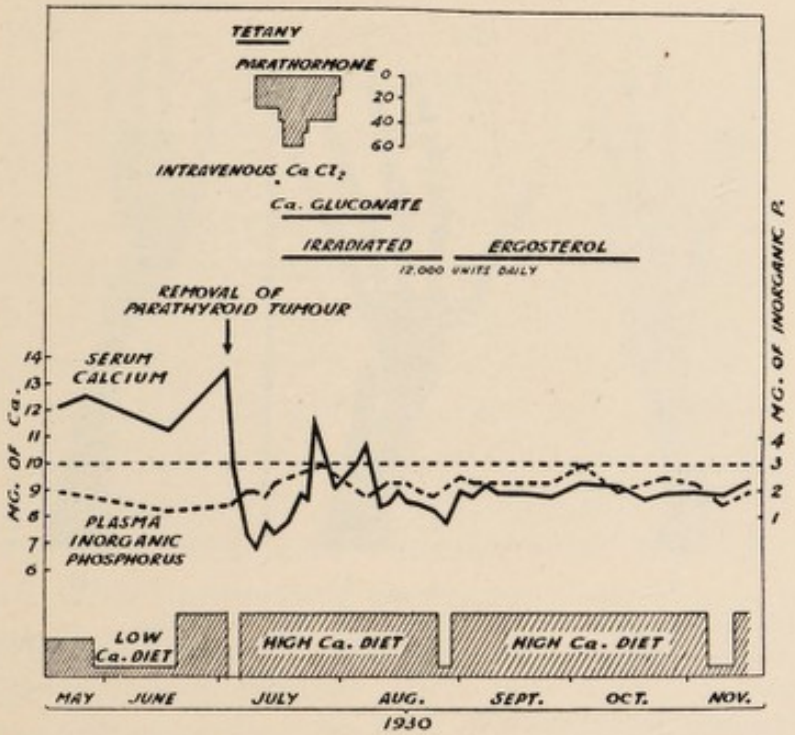

FIG. 13. *Chemistry of the blood:* The blood was examined at intervals for two months before and for five months after operation. The low calcium diet was that given during the investigation of the calcium balance. The high calcium diet was not weighed. It included four pints of milk daily, together with ice cream, cheese, and eggs. The scale indicating the dosage of parathormone represents units per day. The dosage of intravenous calcium chloride was 10 c.c. of a 5 per cent. solution. The dosage of calcium gluconate was 10 c.c. of a 10 per cent. solution daily, given by intramuscular injection. The dosage of irradiated ergosterol was measured in anti-rachitic rat units.

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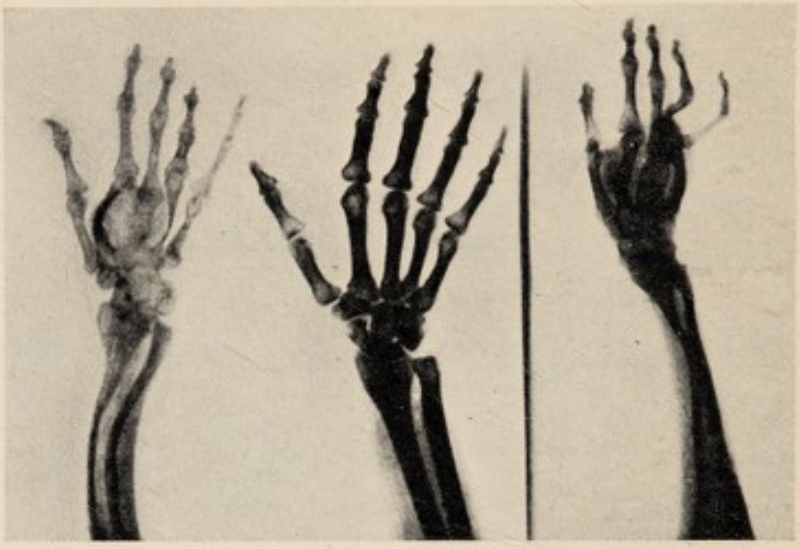
able to walk about. Fig. 13 is a chart showing the serum calcium changes as the result of operative removal of a parathyroid tumour depicted in actual size in Fig. 12 in a case of general osteitis fibrosa. The sudden fall in calcium in the blood will be obvious following operation. Usually these people, immediately after operation, develop a condition known as tetany, owing to a deficiency of calcium in the blood, and for some weeks after operation it is necessary to give them extra calcium in their food together with vitamin D to ensure

its absorption and utilization. These together bring about an increase of calcium in the blood and cure the tetany. After some weeks the patients usually progress without any further treatment. As might be expected, it generally takes months or even years for the bones to recover their normal condition. In Fig. 14 the X-rays show the structure of a normal hand with that of a hand of a patient suffering from osteitis fibrosa before removal of the parathyroid



A C B

FIG. 14. Controlled radiograms of right hand and forearm.

A. Case of hyperparathyroidism (same as Fig. 11) before operation. Note marked decalcification.

C. Control normal for comparison.

B. Same as A after operation and treatment as described in text. Note remineralization of bone.

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gland. The third X-ray shows the hardening of the bones of this case one year after the operation.

It will be seen that this third type of illustration which I have given represents the treatment of a disease due to the over-production in the body of a substance normally present. In the normal individual the parathyroid gland is always manufacturing and sending out into the blood a certain quantity of this calcium-regulating substance, parathormone, as it is called. In general osteitis fibrosa an excess of this substance is produced, and this causes the denudation of the bones of their calcium content. As soon as this excess production is prevented by removal of part of the gland and a good calcifying diet provided, the bones recover their normal hardness.

The last condition I wish to refer to in this lecture is the disease

known as myasthenia gravis, and I have chosen it because of the dramatic way in which it responds to modern treatment. In this disease the individuals' voluntary muscles become weaker and weaker, so that they cannot walk or use their arms and ultimately become so weak that their lips are useless for talking and they cannot even raise their eyelids. Until recently it has not been possible to do anything to cure this condition and the weakness spread until it affected the muscles of respiration and the patients died. Some years ago, Dr. Mary Walker found that the injection of a drug called physostigmin produced immediate but temporary improvement in patients suffering from this disease. This drug, however, had other unpleasant effects and a drug of a simpler but similar nature to physostigmin, known as prostigmin, was then tried instead, because it was known that the undesirable effects on the alimentary canal were not so great in the case of prostigmin. We still do not know how prostigmin acts in these people, but the recent work of Sir Henry Dale and his colleagues suggests that for some reason the normal mechanism for the transmission of the nervous impulse across the neuro-muscular junction which involves the liberation of acetyl choline, cannot function in this disease, hence the inability to use the muscles. This transmitting agent, acetyl choline, is, subsequent to the passage of the impulse, normally removed by the action of an enzyme, acetyl choline esterase. Now it is known that prostigmin has the power of preventing the action of this esterase and it may be that this inhibitory effect is the explanation of the action of prostigmin in myasthenia gravis. You will see in the following film how dramatic is the effect of prostigmin on a patient suffering from myasthenia gravis. You will see that before the injection she cannot walk, she cannot raise herself in bed, she cannot feed herself, her grip is very weak, and she can barely lift her eyelids. She is given a small dose of 2·5 mg. of prostigmin together with atropine. After five minutes she can sit up in bed, and after fifteen minutes she can feed herself, get out of bed, and walk about. At a slightly later stage you see her sweeping the floor of her bedroom. The alleviating effect of the drug reaches its maximum in about one hour after the injection. In eight hours she is back in the condition she was in at the beginning of the film before the injection and is again like a log. It is, however, possible, if these people are given two or three smaller injections suitably spaced during the day, to keep them almost normal, and

there are now instances of persons with this disease who have been kept living a more or less normal life for some years.

These, then, are but a few instances showing the great advance of medicine in recent years. You will realize why medical research, often hand in hand with chemical research, is carried on nowadays with such a spirit of optimism and expectancy, for most problems affecting the animal body give some hope of being ultimately solved. There are still, of course, many problems of disease awaiting solution, especially chronic disease, but the rate at which knowledge is accumulating as the result of medical research is so great that the ultimate outlook in this fight against disease and the warding off of death except by accident or violence is very bright.