

The experimental method in the conquest of disease / by Sir Edward Mellanby.

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Mellanby, Edward, Sir, 1884-

Publication/Creation

[Place of publication not identified] : [publisher not identified], [1939?]

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THE THIRTEENTH STEPHEN PAGET MEMORIAL LECTURE.
"THE EXPERIMENTAL METHOD IN THE CONQUEST OF
DISEASE."

BY

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*(Delivered at the Annual General Meeting of the Research Defence Society,
on Tuesday, June 13th, 1939.)*

In thanking the Research Defence Society for the great honour of being invited to give the thirteenth Stephen Paget Memorial Lecture, may I first say what a great pleasure it is to me, as indeed it must have been to all my predecessors who have held this office, to recall to memory the distinguished founder of this Society? Many of us still remember Stephen Paget when he was giving the best of his life to this movement. In those days the investigator in medical science was fighting for the right to work in his own way, and no man did more to bring about those conditions, which have allowed the continuation of such research and its complete justification in the eyes of mankind. If ever a man has deserved permanent and highly-honoured remembrance because of the benefits that he brought to his fellow men by vision combined with unselfishness and public spirit, that man is Stephen Paget.

With the passing of years, this annual meeting is gradually altering its character. At one time we were more on the defensive, and it was regarded as important that the Stephen Paget lecturer should supply ammunition for the use of those in the front line who were protecting men and women actively engaged in medical research. Those days are passing: the general public can now see at every turn the enormous benefits to mankind that have come from such research. This annual meeting is becoming more and more, not a meeting of the general staff of workers preparing for offensive or defensive battle, but a place where we can count the blessings we and our fellow men have secured as the result of the wide adoption of experimental science and offer up thanks for our good fortune in being allowed to use this method. Some of us have not to rely on this annual meeting to be reminded of these blessings. It is my usual habit to pass down Whitehall on the top of a bus at 9.45 each morning. Whatever may have been my daydreams up to this point, I am suddenly brought to life by seeing in a shop window models of some of my own rachitic dogs exposed to the public view. I realise then that I have not always spent my days in an office, and I remember that it is just because it is possible to see these models of deformed dogs that it is difficult to

see the same kind of deformities in *children* throughout the country.* In the memory of many of us, stunted children with bandy legs were so common as either to pass unnoticed or be a source of amusement. If we saw them now we would be angry, because we would realise they were the products of ignorance or negligence. Many women whose pelves are contracted or of abnormal shape owing to rickets in childhood are still paying the toll of this disease either by their own death in childbirth or by that of their babies. As the present generation of girls become mothers, it is certain that this particular disability will greatly diminish.

Let me now say a little about the words "experimental method" and "experiment." Most of us know what we mean when we use these words, but there is still evidence of confusion in the minds of some people as to the difference between experiment and observation. Thus, Abraham Flexner in his book on Medical Education says: "Yet, strictly speaking the experiment is only controlled, accelerated, and multiplied observation—more fertile, because it takes place under conditions that can be more carefully regulated, repeated and statistically tabulated. But no new senses and powers have been created." Surely this is a wrong way of expressing the difference between the meaning of the words "experiment" and "observation." An observation leads to knowledge of itself, and it is true that, for an experiment to be fruitful, it must be followed by observation. The experiment, however, consists essentially of changing a condition or conditions by active interference, whereby any effect produced by these changes can be tested.

Active interference or varying the conditions is the essential nature of experiment to the scientist. Claude Bernard in his book "Experimental Medicine" discusses from this point of view the relative nature of the work of a physiologist, who establishes a gastric fistula in an animal, with that of Dr. Beaumont on the stomach of Alexis St. Martin, whose fistula was produced by a point blank gun shot in the left hypochondrium. He points out that the end result is the same, whether the exposed hole in the stomach is produced by active interference, as in the case of the physiologist, or by accident, in the case of Dr. Beaumont's patients. It seems to me that so long as Dr. Beaumont simply looked into and examined the contents of the Canadian's stomach he was only making observations. When he actively interfered and, by controlling and altering the conditions of digestion, he compared for instance the stomach's reaction to a meal of meat with that to a meal of potatoes, he was making experiments. When a physiologist first made a gastric fistula in an animal to see whether it produced a normal secretion and whether an animal so operated on could exist in a healthy condition, he was making an experiment. If his ultimate object was to study the mechanism of gastric secretion and its reaction to diet, the actual making of the fistula could only be regarded as a preliminary to or part of the experiment. When Frederick the Second, Emperor of

*Figs. 1 and 2 show photographs of children with natural rickets. Fig. 3 shows dogs with and without rickets produced under experimental conditions.



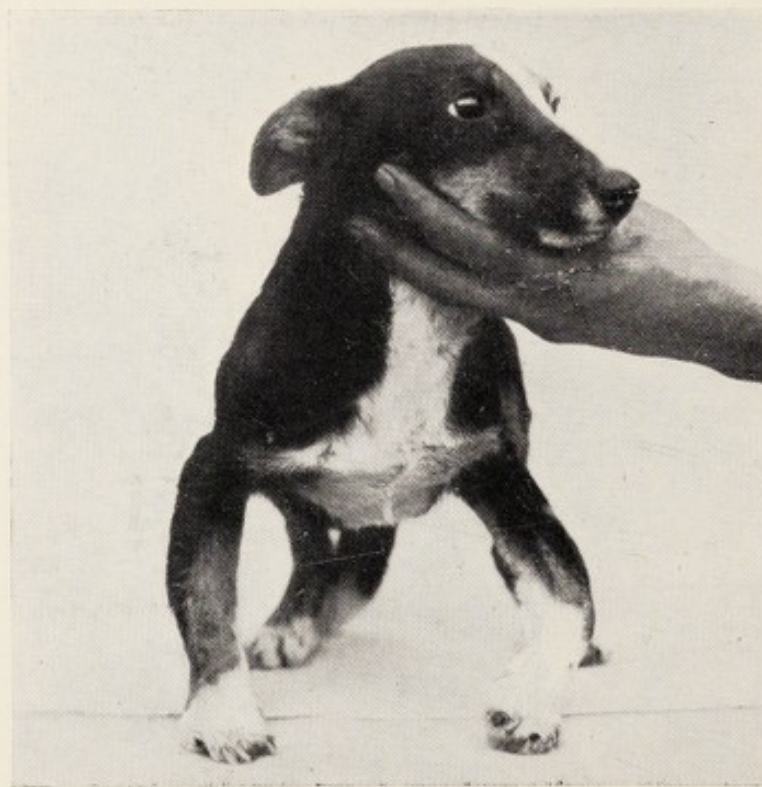
FIG. 1.—Two brothers with rickets.



FIG. 2.—Children 6 years of age showing severe rachitic deformities compared with normally grown child (centre) of the same age. Vienna, 1920. Amerikanische Kinderheilstätte.



FIG. 3.—(a) A normal dog reared on a good diet rich in fat-soluble vitamins A and D (cod-liver oil) during a period of confinement.



(b) A rickety dog brought up on a diet similar to that of (a) except that it was deficient in fat-soluble vitamins and especially in antirachitic vitamin D.

the Romans, King of Sicily and Jerusalem, who lived A.D. 1192-1250, found himself suffering from indigestion, he was making an observation. When his active mind demanded an answer to the question whether indigestion was prevented or increased by exercise, he made an experiment. He took two knights, gave them the same meal, sent one to bed and the other out hunting. At the end of a few hours he killed both and, by comparing the state of the contents of their alimentary canals, decided that rest in bed promoted digestion more than did exercise. It may be remembered that this particular king was called "Stupor Mundi"—the world's wonder—and no wonder.

The difference between a condition produced by intention and one presented by nature represents the essential difference between the work of the physiologist and the clinician. The one by experiment questions nature and forces her to unveil herself; the second observes and listens to nature.

Let us see the relative parts played by the experimental and observational methods in obtaining information about the working of the body by taking as an example a human disease where the lesion is so simple and superficial that the observational method ought to be more effective.

I suppose medical men or their equivalents have seen cases of what is now known as Bell's palsy, since man first appeared on the earth. In this common disease all the muscles of one side of the face, except those working the jaws, are paralysed. No clinical condition could have a simpler pathological basis and yet these medical men cannot have known what they were looking at throughout the ages till Charles Bell took the matter in hand in 1844. His interest was aroused by noticing that in some people suffering from the disease there was an obvious lesion near the seventh nerve as it issues from the skull. In one case where there was a tumour near the ear he remarked that "the man could not whistle to his horse"; in a second case of suppuration in the parotid region he made a *post-mortem* examination and found the seventh nerve involved. It must be remembered that in most cases of Bell's palsy there is no obvious swelling or lesion. When Bell made an anatomical examination of the nerves that might be affected in this disease, he was troubled by the observation that every branch of the seventh nerve after leaving the skull was joined by divisions of the fifth nerve. He then proceeds: "having taken the assistance that the knowledge of the human structure and comparative anatomy affords, we are prepared to decide the matter by experiment. If an ass be thrown and the portio dura be cut across where it emerges upon the face before the ear, all the muscles of the face except those of the jaws will be affected. There is no sign of pain or in no degree equal to the result of division of the fifth nerve." By this means it became known (for ever) that Bell's palsy was essentially a paralysis of the seventh nerve and further, that the seventh nerve was the motor nerve of certain muscles of the face and not of other facial muscles.

You notice that this problem of probably a million years' standing was settled by the experimental method immediately it was used for this purpose. This instance—one of thousands—forms a striking example of the relative power of the experimental and observational methods to supply information about the body. If all the clinical conditions encountered by the physician were as simple as Bell's palsy, the need for animal experiments would be greatly reduced although, even in such cases, animal experimentation would be necessary to determine the function of the nerves and other organs at fault. Usually the physician only recognises what he is looking at because of the knowledge brought to him by the experimenter who, by simplifying his experimentally produced conditions and analysing their effect, has been able to teach the clinician the functions of each structure and what happens when this structure is absent or abnormal.

The acquisition of knowledge *by making comparisons* is common both to the experimental and observational methods, and it is this factor which again often introduces confusion as to what constitutes an experiment. In the case of an experiment a condition of affairs is noted, and the object of the experimenter is to determine any change that takes place as a result of altering one or more of the conditions. In observational enquiry an individual notes any differences there may be under natural but uncontrolled circumstances. It is of interest, for instance, to find that Claude Bernard regarded the recording of the pressure at the base of a tower and comparing it with the pressure at the top of a tower as an experiment. In this case, however, although there is comparison, there is no question of actively altering the environment. Nowadays it would probably be said that such an operation would be regarded only as a comparison of two observations and not in the nature of an experiment. Similarly, a clinician may find that the blood pressure in the artery of the foot is higher than the blood pressure in an artery in the arm, but the mere recording of this difference does not involve experiment but only two observations. If, however, the clinician compares the differences in pressure between the hand and foot when the patient is sitting down and when standing on his head, he is doing an experiment, because he is altering the environmental conditions and determining the effect of this alteration on the differences in blood pressure. In other words, by actively interfering and choosing his conditions he is being taught by nature the effect of alteration in posture on a certain physiological phenomenon. When he observes differences in pressure between the radial artery and the foot artery, he is only observing and comparing and, although he may think that this difference is due to posture, he cannot know this until he has done the actual experiment.

One of the fundamental properties of the experimental method is that a particular experiment always records the absolute truth. The words "good" and "bad" in connection with an experiment have no meaning at all, except in so far as they reflect the goodness and the badness of the experimenter. The actual effect of the alteration of conditions during any experiment is determined and certain, whatever may be the ability of the

experimenter, and the end result, whether rightly observed or not, is the only possible result of the conditions of the reaction, and its record is strictly true. An experiment may be a bad one for many reasons; the idea or hypothesis which caused the experimenter to do the experiment may be a wrong one or the conditions of the experiment may not be such as the experimenter thinks. The result of the experiment may not be observed or may be observed wrongly, or may be wrongly interpreted. For any one or more of these reasons the experiment may be a failure, but these have nothing to do with the changes of the reacting material of the actual experiment. It is this sense of certainty and reliability of the experimental method, throwing as it does the complete onus of the work on to the experimenter, which gives such great intellectual satisfaction to the investigator and puts him on his mettle. It makes or ought to make the medical scientist who uses this method a very careful and humble person, because he realises that success or failure depends entirely on himself. He recognises the enormous difficulties of the experimental method in biological investigation, due to the complexity of the interacting materials, which have prevented the establishment of simple laws such as the physicist and chemist know. He assumes, however, that the absence of biological laws is only due to complexity of structures and functions of the material used and that, apart from this, there are no forces interfering with the reactions beyond those that are peculiar to highly complicated chemical substances. His success has warranted this assumption.

Every experimenter in medical science knows that nature always plays fair and that his own mental ability is the limiting factor in his work. All of us remember with discomfort times when we have failed for one reason or another to get the true benefit of some experiment or series of experiments on which we may have spent much time and trouble, because of our own inadequacy. Each of us can recount many occasions when his fallibility has been conspicuous in preventing the full fruits of an experimental enquiry being obtained.

I should like to recall one instance out of many of my own failures to use this method of research properly. When the work of Huldschinsky, in which he showed that light and particularly ultra-violet radiations cured rickets, became known in this country in 1921, all people engaged in the study of rickets recognised the need for bringing together the facts which demonstrated that there was an anti-rachitic vitamin and this new fact discovered by Huldschinsky. Very soon I began an experiment to see whether the exposure of a non-calcifying fat like olive oil to ultra-violet radiations gave it calcifying properties. Having no mercury-vapour lamp at the time, I enquired at the Physics Laboratory whether they had such a thing and, if so, whether they could lend it to me. Receiving an affirmative answer to both questions, I asked a colleague, who was a first-class worker but who had no detailed knowledge of my object, to fix up this mercury-vapour lamp and to expose olive oil in thin layers to its radiations for a period of one hour. This he did and a litter of four puppies was

then placed on the same rickets-producing diet, except that two puppies received the non-irradiated olive oil and two the irradiated oil. The experiment was continued for some months and at the end of that time it was clear by X-ray examination that all the dogs had the same degree of rickets. I deduced from this that exposure of olive oil to ultra-violet radiations was ineffective in producing antirachitic properties in this oil. Two years later, that is to say in 1924, the work of Steenbock and Black was published, in which they showed just the opposite, namely, that exposing non-active fats to a mercury-vapour lamp endowed them with high calcifying qualities similar to those of fats naturally rich in anti-rachitic vitamin. This result seemed to me amazing, in view of my own complete failure to demonstrate this action, and I sought for an explanation. I went to the Physics Laboratory and asked to see the mercury-vapour lamp they had lent me and found it had a thick glass cover and was therefore incapable of giving out any ultra-violet radiations. They had not enquired for what purpose I wanted the lamp, which had always been used in that laboratory for the production of a mercury spectrum for spectrographic purposes. I had assumed that the function of a mercury-vapour lamp was to give off ultra-violet radiations. This, you will see, was a bad experiment and the badness consisted, not in the fact that the result did not represent the absolute truth, but in my own carelessness in not noticing that the lamp supplied was made of glass and that it could not give out the type of ray, namely the ultra-violet radiation, which was known to act on the skin of children with rickets. You will also realise from the subsequent history of this phenomenon, especially on the commercial side, that the experiment was not only bad but that it was tragic.

It is, however, needless to emphasise further the infallibility and power of the experimental method in contrast to the fallibility of the experimenter. Fortunately the mistakes are generally in the nature of the deductions made rather than of the facts observed in the experiment, and these are quickly remedied by other investigators. There is a belief widely held by the public that medical men, including those engaged in research work, form a kind of closed ring and not only support each other, whether right or wrong, but prevent any recognition of discoveries made by others outside the ring. Little do these people know of the real state of affairs. I suppose next to making a discovery itself, the greatest mental satisfaction comes to the investigator who disproves the facts or theories of his fellow worker and more especially is this the case if, by adding another fact or another idea, he can put the whole problem on to a proper basis.

The free publication of all his discoveries and ideas related thereto by every reputable person engaged in medical research without any thought of personal reward ensures not only free discussion but also repetition and testing throughout the world. All we ask is that every discovery relating to the body, whether made by medical or non-medical persons, orthodox or unorthodox, should be submitted to the same stringent rules as regards full publication and exposure to criticism.

It is evident that the clinician has always been, and probably always will be handicapped by the limited amount of experiment that can be made on man himself. He has had to depend almost entirely on observation and I am sure you will be prepared to join with me in acknowledging the great amount of knowledge of disease and of its structural and other effects on the body that has been accumulated as the result of these observations at the bedside and in the *post-mortem* room. For thousands of years the doctor had the further handicap of an atmosphere pervaded with the thought that sickness was due to evil spirits which had to be ejected from the body for the restoration of health. The classification of disease, knowledge of its natural history, and the morbid anatomical changes that accompany it, represent an enormous achievement, and in these investigations the clinician has had to work largely by observation and without the aid of experiment. Whereas this kind of knowledge brings satisfaction to the doctor and is the basis upon which the early structure of medical diagnosis was built, it does but little either to restore the sick to health or to prevent ill-health except possibly in the case of certain diseases of epidemiological interest.

Recently we have seen a movement develop in this country for the promotion of clinical science as an experimental subject of study. This movement has emphasised the fact that medicine is indeed a science, that there is still scope for legitimate experiment in clinical work, even in the case of sick individuals, and that animal experiment, so far as disease is concerned, although it has provided most of the knowledge available to the physician about the human body, is the servant and not the master of medical science. While all this is true, it is quite certain that additions to knowledge must depend in the future, as they have in the past, on experiments on animals. The guiding principle in determining whether any test should be made on human beings must be the simple question: "Would the doctor allow this to be done on himself or on some member of his family?" If he would not, then the experiment ought not to be done. This limitation will soon bring the realisation of the small scope allowed to the clinician in his investigation on human beings.

In view of the great restrictions in experimenting on man himself, it is clear that it is much more likely that the cause and sequence of events associated with any particular pathological condition in man will be elucidated if a similar pathological condition can be produced in an animal. Immediately the investigator can obtain this, his opportunity of study is widened and he can take each point in turn and by means of animal experiments he may be able to track down the factors operating to produce the disease. We have again and again seen this method of attack lead to the knowledge of the causation and control of disease. More especially has it been successful in the study of nutritional diseases such as beri-beri, scurvy, rickets, pellagra, xerophthalmia, and defective formation of teeth. In the study of infectious diseases also the animal experimental method has formed the keystone of knowledge, although in

this group much knowledge has also been obtained by the study of the natural history of each disease independently of experiment. Even in this case, however, our knowledge would have been meagre indeed without the aid of animal experiment. The study of cowpox and vaccinia, of epidemic influenza in ferrets, mice and pigs, of distemper in dogs, has been of inestimable value in shedding light on these diseases and on the whole subject of virus disease in general.

In some cases it has not been possible to reproduce the infectious human diseases in animals, and yet only by their use have fundamental facts been obtained. The nature of diphtheria toxin and toxoid and the possibility of producing antitoxin became known as the result of animal experiments. There is every reason to believe that the proper use of the present knowledge of the actions of these substances would result in the disappearance of diphtheria from this country as it has done in parts of Canada and the United States. When, as in the case of measles, no animal experimental method has been available for the production of the disease, and no method is even known of growing the virus outside the human body, knowledge of methods of controlling the disease has been delayed. Every experiment has had to be done on patients suffering from the disease. Fortunately, information obtained by animal experiment in other virus diseases allowed certain limited tests to be safely made on human beings which have led to the use of human immune serum in measles, so that it is now possible either to suppress the disease or modify its intensity, according to the wishes of the doctor, if cases come under treatment early in the infective state. It is only in recent years that virus diseases have been studied as a group and the advance in knowledge has been very great in this brief time.

The part played by animal experiment in laying bare the causation and processes of disease has indeed been so great as to make it almost superfluous to record. Nearly everything we know about diseases of the endocrine glands has resulted from animal experiment—hyperthyroidism and hypothyroidism, diseases of the parathyroid, suprarenal, pituitary glands and the gonads would have remained completely unintelligible, had we not been able to study the functions of these organs and their products by experiment on animals. Indeed there is hardly a function of any organ in the body that has not been originally disclosed by animal experiment and no doctor, even if he be an anti-vivisectionist, can discuss intelligently any process of a physiological or pathological nature without using knowledge acquired by such experiments.

The measure of success in acquiring knowledge of a particular human disease by experiments on animals often depends on the identity in ætiology of the experimentally produced disease in a particular animal with the human condition. Occasionally, it is possible—as in the case of scurvy—to apply practically every fact gained by the animal experiment directly to the human disease. When Holst and Frölich published their work on scurvy in guinea pigs in 1907, there was already a general belief that this disease

in human beings was due to absence from the diet of fresh food, especially fruit and vegetables. There must, however, have been some doubt about the need for "freshness" of the food, for I was interested to see in lecture notes which I took on scurvy in 1908, at a time when Holst and Frölich's work was not generally known in this country, that scurvy was probably due to an insufficiency of intake of potassium salts or malic acid; it is difficult to see how these substances could be destroyed by lack of freshness. All the facts discovered about scurvy by the use of guinea pigs, both by Holst and Frölich and by every subsequent worker in this subject, have been found to hold true in human scurvy—the fact that it is due to insufficient antiscorbutic vitamin (vitamin C), the distribution of the vitamin in different foods, its easy destruction by heat, its formation in dried pulses and cereals on germination, and the ultimate isolation and synthesis of ascorbic acid, facts established by the aid of animal experiment, are of equal applicability to the human disease.

The same kind of identity of experimental and natural disease is seen in the case of rickets in dogs (but not in rats), in xerophthalmia and night blindness in rats, in epidemic influenza in ferrets and some other infective conditions.

But the mere production of a particular pathological condition by an experimental method in an animal does not always necessarily mean that the same condition in man has an identical cause, although there is generally some relationship or connecting link between the two. An outstanding instance that comes to my mind on this point is the experimental production of middle ear disease in rats by depriving them of vitamin A. Clearly, in human beings there must be other causes than vitamin A deficiency responsible for this condition, for it commonly occurs in children with abundant vitamin A in the diet. Possibly a common factor in this localised infection in animal and man is the blocking up of the Eustachian tube and other passages of the middle ear; by hyperplastic epithelium in the case of the rat and inflammatory exudate in the case of the child. In any case, it is not improbable that a closer study of the actual process of infection in the rat with an experimentally produced infection of the middle ear would throw much light on the same disease in man.

Sometimes the experimental work on an animal disease, although it is of great value in bringing about the control of a human disease, may not prove to have the complete identity with the human disease originally thought. For instance, few experimental investigations can have turned out to be more successful in helping mankind than Eijkman's work on polyneuritis in fowls. The results immediately became applicable to the prevention and cure of beri-beri and ultimately to the possibility of cure of alcoholic and certain other forms of neuritis and of Korsakoff's psychosis by vitamin B₁. It is, however, extraordinary that, in spite of many efforts, there is still no clear evidence that a pure vitamin B₁ deficiency in either birds or animals ever produces a real neuritis with medullary degeneration of the nerve fibres, such as occurs in beri-beri and alcoholic neuritis in

human beings. That vitamin B₁ deficiency affects the nervous system is indeed certain, but the laboratory work has emphasised at every stage that the defect produced is acute, that if continued it is incompatible with life and that recovery is very rapid if the vitamin is administered. The work of Peters and his colleagues, which has established the fact that, in the absence of vitamin B₁ carbohydrate metabolism is interfered with at the stage of pyruvate oxidation, has explained clearly the experimental observations on vitamin B₁ in animal and bird studies. It is of even greater interest to know that in human beri-beri there is an increase of pyruvic acid in the blood as there is in the experimental animal suffering from vitamin B₁ deficiency. The fact remains that there is still a gap to be filled between the results obtained by animal experiment on vitamin B₁ deficiency, which has always emphasised the acute and rapidly produced and rapidly cured side of this problem, and the chronic conditions associated with vitamin B₁ deficiency, such as polyneuritis, which has proved of interest to the clinicians.

The recent work on alcoholic neuritis and its cure by vitamin B₁ may lead to the filling of this gap. It will be remembered that Wechsler and others have now shown that even if a large amount of alcohol continues to be consumed by the patient suffering from alcoholic neuritis, large doses of vitamin B₁ will cure the condition. Neither alcohol nor vitamin B₁ deficiency in itself seems to cause the neuritis but, either by interfering with the absorption of vitamin B₁ or by bringing about a condition which makes the demand of vitamin B₁ in nerves greater than the supply, alcohol causes chronic degenerative conditions of the peripheral nerves. It may be that in beri-beri also there is some additional factor acting in a similar way to alcohol as well as vitamin B₁ deficiency.

A better instance, where the clinical application of an animal experimental enquiry has been different from that expected, is the discovery of the curative factor of pernicious anæmia in mammalian liver by Minot and Murphy. When these investigators repeated on human beings the work of Whipple, which demonstrated the effect of foodstuffs on the regeneration of red blood corpuscles and hæmoglobin in secondary anæmia in dogs, they expected positive results with liver in the case of secondary anæmia and negative results in pernicious anæmia. Their surprise can be imagined when the first of these effects, *i.e.*, on secondary anæmia, was relatively slight, while the liver effect on cases on pernicious anæmia was great. This was undoubtedly one of the most dramatic results ever obtained by clinical trial and its importance was none the less great because it was completely unexpected, so far as the animal experimental results obtained by Whipple, which formed its basis, were concerned.

I should at this point like to indicate a further consequence of this clinical work, because many laboratory workers seem to have the impression that investigation in the wards seldom or never leads directly to important physiological discovery. The clinical work on pernicious anæmia in man has in itself opened up again the whole question of red blood formation in

the bone marrow, and it is impossible for any physiologist nowadays to study the problem of bone marrow formation without taking into account the hæmopoietic action of a liver active principle. More than this, there is now good evidence that larger doses of the same liver substance which promotes restoration of the red blood cells in the case of a patient suffering from pernicious anæmia, also stops the progress of combined system disease of the spinal cord and brings about great functional improvement in early cases. Since simple anæmia of equal severity, so far as the hæmoglobin content of the blood is concerned, is not associated with extensive degenerative changes in the cord, it is evident that another important physiological relation between the substance which controls red blood cell formation in the bone marrow and the structure and function of the nervous system awaits elucidation. Here again the shuttlecock is thrown back to the physiologist and experimental pathologist and it will probably be the laboratory worker who will, by the experimental method, find means of relating the processes of red blood cell maturation with the proper functioning of tracts in the central nervous system. Note the sequence of events in these investigations. First, there are the clinical observations of the blood condition in the anæmias. These suggest experimental enquiry in the laboratory, which leads in turn to the acquisition of information of the stimulus given by certain foodstuffs to red blood cell and hæmoglobin formation. The clinician applies this information to his anæmic patients and finds evidence of dietetic ingredients which specifically affect the maturation of red blood cells in the bone marrow. Combined laboratory and clinical work show the chemical nature of this substance. Further clinical tests demonstrate that this substance also acts directly or indirectly on the central nervous system and stops degenerative processes. The clinician is now held up by the limited means of experimental enquiry on patients at his disposal, so back comes the problem for further investigation in the laboratory. In the meantime the clinician has the satisfaction of knowing that he can now control two widely different pathological conditions—pernicious anæmia and subacute combined degeneration of the cord—two conditions always previously fatal, and in addition has indicated to the physiologist two important normal functions of the bodily organs which urgently require the further application of the experimental method.

These happy results, gained by the extension of the results of animal experiment designed to throw light on a condition other than that for which they have proved to be of immense value, illustrate another important fact in medical research. Here is an instance where a remedy for pernicious anæmia, which makes all the difference between a healthy life and rapid and certain death, was discovered at a time when nothing of the causation and but little of the pathology of the disease were known.

The same applies to other controllable diseases such as diabetes mellitus, myotonia, myasthenia gravis and, in the case of surgical treatment, enlarged and infected tonsils, appendicitis and exophthalmic goitre. Knowledge of the causes of these diseases is very small and yet they can be

controlled to a greater or less extent by the medical man. On the other hand, the information that has come to light as the result of experiments in the last thirty years about cancer is enormous and a number of ways in which cancer can be produced are definitely known, and yet the degree of control or cure of this disease in man is still small. In other words, there is often no relation between the curative control of a disease and the amount of knowledge about that disease. The great standby of the anti-vivisectionist nowadays is the failure of the investigator to find a cure for cancer in spite of all the animals sacrificed to experiments on this disease. It is pointed out that the lack of success is a certain proof of the futility of animal experimentation. Nobody is more conscious of the failure to discover methods of preventing and curing cancer than those engaged in this work. Their labours have impressed upon them that this is the hardest problem in both medicine and biology yet encountered. They are certain, however, that the experimental method is the principal method which can lead to the requisite knowledge and they are hopeful that this problem also will submit ultimately to this type of investigation, as has happened in the case of so many other diseases. The anti-vivisectionist may not always be able to jeer at the relative lack of success of the experimenter in discovering a means of controlling cancer. Probably even now it may be of interest to point out to them a cloud, or what they only will recognise as a cloud—of the size of a man's hand—that has recently appeared on the horizon of the investigator, which may ultimately overwhelm, even if it does not silence them. Bittner has recently found that certain strains of mice, 65 per cent. of which normally develop cancer of the breast remain free from this disease if breast-fed by mice of a strain that does not develop cancer. On the other hand, mice of a non-cancerous strain have been found to develop cancer of the breast in large number if breast-fed in early life by cancer-susceptible mothers. This observation, which has been confirmed, is one of the most promising of the many recent discoveries obtained in cancer research. Of the multitude of ideas that have been held to throw light on the cause of cancer it has never previously been imagined, much less demonstrated, as has happened in this case, that the precancerous stage is sometimes determined by the diet in early life.

After all, it is only a matter of three years or so since we were in the same predicament as regards streptococcal infections. When Lord Linlithgow was appointed Viceroy of India four years ago and thereupon retired from the chairmanship of the Medical Research Council, almost the last words he said to me were: "Do you think we shall ever find a method of curing streptococcal infections?" Within a year of this question, the work of Domagk, followed by the clinical tests of Leonard Colebrook, soon showed the world that the back of this immense problem was broken. Not only the work of Domagk in discovering the chemotherapeutic effect of prontosil on streptococcal infections but that of Tréfouel, Nitti and Bouvet, who extended this action to sulphanilamide and that of Whitby, who established the protective effect of M & B 693, prepared by Ewins, on both streptococcal

and pneumococcal infections, involved the use of hundreds of infected mice. In each case the technique was to find the number of micro-organisms lethal to mice and then to determine how many times this lethal dose could be multiplied with safety to the animals when the mice were injected with the chemotherapeutic agent under test. Had the direct bactericidal effect of prontosil alone been tried without the use of the infected mice, its action could not have been discovered. I do not know how the life of bacteria, as compared with that of mice and rats, stands in the affection of anti-vivisectionists, but they may as well realise that the sacrifice of hundreds and possibly of thousands of mice in these investigations will involve the further death of hundreds of millions of deadly micro-organisms. Incidentally, very many human lives are being and will continue to be saved by the knowledge gained.

It is pleasant to think that, as the result of these discoveries by animal experiment, on the average only four or five out of every 100 women who develop puerperal sepsis need now die, instead of the 22 or more per 100 previously killed by this disease: that, whereas 17 out of 100 people under 50 years of age who contracted pneumonia and did not receive the treatment died, that number has now been reduced in Birmingham and probably elsewhere to under 2 per 100: that the cure of gonorrhoea, which used to take five or more months constant and disagreeable medical treatment for a cure to be effected now takes in most cases only a week or so: that cerebro-spinal meningitis, from which previously 80 per cent. of those attacked died, now has a mortality rate of only 5 to 10 per cent.: that in streptococcal and pneumococcal meningitis, from which practically everybody died, many lives are now being saved: that genito-urinary infections, which up to recent times have always proved most refractory to treatment can now be rapidly and successfully treated. These are some of the catch landed by the net of chemotherapy, the discovery and fabrication of which were determined solely by animal experiment. Is there any man of sense still alive who thinks that the sacrifice of possibly thousands of mice was too high a price for these discoveries? Can any man or woman still assert that animal experiments are a futile waste of time?

The medical scientist is attacked by anti-vivisectionists by every verbal weapon that is available—legitimate and illegitimate—but on the whole their condemnations can be stated as follows:—

- (1) experiments on animals never have led and never will lead to increased control of disease;
- (2) where investigators have claimed the discovery of methods which increase the control of disease, these methods have been either untrue or, if true, obvious without any experiment;
- (3) there have been enormous numbers of animal experiments made on disease which have not led to any increase in control of the disease investigated.

The first of these criticisms is so obviously untrue that it merits no attention.

The third is certainly true but, as we have seen, this is not due to any failure of the experimental method, but to the limitation of the human intellect and to the fact that discovery of knowledge of the human body in health and disease is the hardest task ever faced by man. Time and opportunity for further experiments will allow this criticism to be met in the case of many unsolved problems of disease as has proved to be the case where success has been obtained.

Only the second criticism needs consideration, namely, that any new method of preventing or curing disease or any new physiological or pathological fact, discovered in the course of medical research by animal experiment, is either wrong or useless or, if true and useful, was known or could have been easily prophesied by an intelligent man. Obviously this statement is also crazy in most cases. By what possible means could human intelligence alone have foreseen the mechanism of blood coagulation or that of the transmission of a nervous impulse across a synapse or nerve ending. I suppose the answer of the anti-vivisectionist would be that in such cases the knowledge is useless. This is certainly not so in the case of blood coagulation and, even in the case of the problem of transmission of the nervous impulse, it is interesting to remember that, since its discovery by Dale and his colleagues, two previously uncontrollable diseases of man, myasthenia gravis and myotonia, are now controllable. It is curious, however, how often the experimenter has a feeling when he has made a discovery that, if he had been more intelligent, he could have more quickly foreseen the particular process under study. Nature's methods seem so inevitable when once discovered—but only when established by experiment. How quickly would we give up animal experimentation if intelligence alone could give us the necessary knowledge!

Let me deal with this criticism by giving a single example out of my own experience in which observation and intelligence not only failed throughout many centuries of human experience to reveal the truth but had come to conclusions quite contrary to the truth.

Since bones and teeth are made up principally of calcium and phosphorus, it seemed obvious to the "intelligent" man that a foodstuff like oatmeal which contains 0.069 per cent. calcium and 0.392 per cent. phosphorus would form far better bones and teeth than, say, white flour which contains only 0.02 per cent. calcium and 0.092 per cent. phosphorus. You may remember that this "intelligent" anticipation did not prove to be the case, and that, when oatmeal formed a large part of certain diets, bones and teeth much worse in structure were found than when a similar amount of white flour was eaten. In order to explain these results, it was necessary to postulate that oatmeal was richer than white flour in a substance whose identity I did not know but which actively interfered with teeth and bone calcification and that this deleterious effect could be antagonised by adding vitamin D or extra calcium or better still, both these substances. I called it a "toxamin" to indicate that it was a toxic substance, whose action could be counteracted by a vitamin.

The next stage in this story was the work of Bruce and Callow who in 1934 found that, if compounds of phytic acid were added to diets of rats, the phosphorus was unabsorbed from the alimentary canal and apparently unavailable. If, for instance, such rats were given a rickets-producing diet, rich in calcium, poor in phosphorus and deficient in vitamin D, then the addition of phytic acid salts did not reduce the rickets, whereas a simple phosphate like sodium phosphate had this effect. Their experiments only proved that phytic acid was not absorbed from the alimentary canal. But the point at issue is not whether phosphorus was available or not, since the diets of the dogs, as indeed is the case with the usual diet which produces rickets in children, were rich in available phosphorus: rickets in children cannot be cured by giving phosphates. The essential condition to be explained was that oatmeal contained a substance which actively prevented the animal body from incorporating calcium salts in its bones and teeth. Recently Professor D. C. Harrison and I have shown that phytin—the calcium magnesium salt of inositol hexaphosphoric acid, the form in which phytic acid is usually supposed to be present in food—does not produce rickets and may indeed have a slight antirachitic action. If, however, phytic acid or its sodium salt, sodium inositol hexaphosphoric acid, prepared from oatmeal, be added in small quantities to diets which produce slight rickets in puppies, the degree of rickets is greatly intensified. Only part of the phytic acid of oatmeal appears to be present as phytin and it is now probable that the hypothetical rachitogenic toxamin in oatmeal is phytic acid or one of its compounds other than phytin and that it exerts a toxic action not simply because its phosphorus is unabsorbed and therefore unavailable, but also because it prevents other calcium constituents of the food from being available for bone and tooth formation. If extra calcium is added to the food beyond that stolen by the phytic acid compounds, the cereals are rendered harmless so far as calcium metabolism is concerned. There is also some evidence that cereals can actually drag calcium out of fully formed bones, if the diet is deficient in calcium, so great are their claims on this element as it passes down the alimentary canal. As in the case of oxalic acid, the toxic effect of phytic acid is therefore due to its great power to immobilise calcium but, whereas oxalic acid is rapidly absorbed from the alimentary canal and quickly kills by depriving the blood and other tissues of their calcium, phytic acid, being unabsorbed, can act directly only on the calcium of the alimentary canal, and the loss of calcium from the body is more gradual.

This is just one small example of a practical problem which, at first sight, seemed explicable by intelligence but which on testing by experiment proved to be quite wrong in fact and complicated in explanation.

I have endeavoured to give a brief account in this lecture of what the experimental method of investigation means, of how much more effective it is than the only other method—the observational method—whereby man can acquire information of himself and his environment. It is the royal road to discovery and its acceptance and wide practice for the

solution of problems affecting both animate and inanimate matter is the greatest intellectual contribution ever made in the history of mankind for the promotion of his bodily and material welfare. During the hundred years or so when its power and usefulness have been generally recognised, it has transformed the life of civilised man. It has been the means whereby man has been provided with practically all his present knowledge of the bodily functions. It has led to the prevention and cure of disease affecting millions of animals and men; it has prolonged life and warded off death: it has improved the physique and general health: it has reduced the tragedies and griefs of mankind which come from sickness and untimely death: it has afforded the means of greater enjoyment of the benefits and beauties of life. Is there any other human activity that can compare in fruitfulness with that of the practice of the experimental method? While all these benefits are obvious, there is still a wide gap between the knowledge now placed at the service of mankind by the experimental method and that in general use. It is not the task of the experimenter to popularise his discoveries and it ought not to be his job to defend himself and his methods against the attack of a minute section of the public. He does not complain, however, for he sees medical men in practice and even the general public becoming more and more inclined to listen to his teachings and the voice of opposition against his methods of discovery is becoming fainter.

However much the experimental method has done for the welfare of men and animals in the past, it will do more in the future. The tempo of discovery is increasing rapidly throughout the world and man's control of his own destiny, so far as health and disease are concerned, is becoming correspondingly greater.