ADDRESS IN MEDICINE

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THE TOXIC ORIGIN OF DISEASE.

WHEN this Association last met in Edinburgh the Address in Medicine was delivered by the accomplished and universally beloved physician, Dr. Warburton Begbie, and notwithstanding the lapse of time, I can still recall—and there are others here also able to recall—the thesis which formed the subject of the address, expressed in the inquiry, Has the practice of medicine made a single step since the time of Hippocrates?

In dealing with this thesis, Dr. Begbie described the history of medicine from its beginnings, as only could be done by one who had not only carefully studied the writings of the Fathers of medicine, but had also made himself familiar with the work of their successors. The doctrines regarding the nature of disease, which successively replaced each other during the twenty-three centuries dealt with, were clearly described, and, as was to be expected from the practical physician, he fully discussed the bearings of these doctrines upon treatment, and pointed to the more conspicuous acquisitions in the healing art which had enriched practical medicine.

He had the opportunity of showing how greatly medical doctrine had been transformed by Harvey's discovery of the circulation of the blood; how the diagnosis of pulmonary and cardiac disease had received an extension and previously unknown definition from Laennec's discovery of auscultation; how the memorable discoveries and courageous applications of nitrous oxide, ether, and chloroform, by Horace Wells, Morton, and Simpson, had deprived the knife of the surgeon and the reproduction of animal life of much of their former terrors and anxieties; and how by that vaccination, which will ever be associated with the name of Jenner—the first and still unsurpassed means of restricting the ravages of a fatal infectious disease—an almost incalculable benefit had been conferred upon the human race.

From his elaborate survey of the history of medicine, he concluded that no general doctrine—chemical, physical, humoral or physiological—had been propounded which satisfactorily explained the nature and production of disease; that therapeutic advancement had been obtained, chiefly by the observation of patients, by adhesion to the classic method of rational empiricism; and that by this method such valuable accessions to the means of treating disease had been gained as the administration of turpentine in pulmonary gangrene and bronchitic affections; of quinine in intermittent fever; of iodide of potassium in syphilitic periostitis and thoracic aneurysm; of bromide of potassium in epilepsy; and of cod-liver oil in pulmonary tubercle.

It may not be without interest to consider to-day how far, and in what directions, this great and wide subject of medicine has chiefly advanced since Dr. Begbie delivered his address. The intervening period is the relatively brief one of scarcely a quarter of a century. It has, however, been signalised by a great increase of knowledge regarding the fundamental sciences of chemistry, physiology, and morbid anatomy; by the creation of pharmacology as a science of the action of remedies; by steady advance in symptomatology and diagnosis, and above all by so remarkable a development in our conceptions of the nature and production of many diseases, that we appear almost to have attained a position, vainly sought for during centuries by our predecessors, of being able to formulate a doctrine of disease, founded upon the satisfactory basis of experimental demonstration, and sufficient to explain many of its forms and to already provide us with assured means and principles for its prevention and treatment.

While fully acknowledging the merits of the workers in medical science and practice by whom this gratifying progress

has been made, it cannot be forgotten that the necessary pioneer work was undertaken amid difficulties of exploration in dark and unknown regions; and that but for this pioneer work the present generation would not have been able to reap so prolific a harvest of medical discovery.

This indebtedness to our predecessors is nowhere more conspicuously shown than in the advancements that have been made in the diagnosis of disease. Observation, careful and intelligent, practised by the Fathers of medicine, had already constructed a nosology sufficient to distinguish the great majority of diseases, and so complete that it is doubtful if much advance could have been made had the methods in use at the commencement of this quarter of a century alone been trusted to. The introduction, however, of physical aids to our senses, and of chemical applications and methods—each rendered possible by the growth of collateral science—has placed us in a position from which we have been able to advance in accuracy of diagnosis, and even in the discovery of new diseases.

By the apparatus now in use for blood determinations the condition of this fluid in regard to many of its most important constituents can be exactly determined, and information can be obtained valuable for treatment, and previously unattainable by any perfection of intelligent observation by means of the unaided senses. The sphygmograph depicts with precision of detail changes in the pulse which are difficult to apprehend by the unaided finger, even after a long apprenticeship, and above all increases the usefulness of the physician by indicating the characters which, without its use, he should be trained to detect. He is thus enabled to appreciate changes, which are not only of the highest value in prognosis, but are also frequently sufficient, either in themselves or aided by the most superficial of further observation, to justify without auscultation the diagnosis of the cardiac lesion which is present. The ophthalmoscope has increased the certainty of diagnosis of many nervous affections and toxic processes, and some of the difficulties of clinical observation have been overcome by radiography, whose capabilities, however, are as yet undeveloped.

By the introduction of chemical processes applied especially to the examination of the stomach contents, and of the urinary and other secretions, diagnosis has also been advanced, and previously unknown precision has been obtained. The agglutinating effects of the blood serum in certain infective diseases, as typhoid, Malta, and relapsing fevers, and in cholera and anthrax, upon their respective pathogenic organisms; and the application of chemical pigments to reveal the existence of the microscopically minute organisms of such diseases as pulmonary tubercle, pneumonia, and diphtheria has removed many of the perplexities of diagnosis and rendered identification almost a mechanical art.

While by these and other means the diagnosis of diseases—a fundamental work in the art of medicine—has conspicuously advanced during the last quarter of a century, this advancement, however great, does not in itself justify any claim to a nearer approach to the realisation of the highest aims and objects of medicine. Diagnosis, for the most part, deals only with symptoms, it has no immediate concern with the true nature of the malady, and until this has been determined progress in treatment can only be tardy and unsatisfactory. The history of medicine has shown that the advance in these two departments has rarely, if ever, been parallel or equal. The one may reach a position of almost ideal perfection, while the other still remains in the initial stage of vague speculation. This is exemplified by the present state of knowledge of nervous diseases. Minute symptoms have been identified, and have been so arranged in groups as to constitute special diseases, and thus numerous forms of disease associated with morbid lesions of parts of the spinal cord or brain have been created. The elaboration is a remarkable triumph of painstaking and skilful observation in symptomatology and in morbid anatomy. It presents a field for the training of the powers of observation and reason, probably unsurpassed by any other problems in practical medicine, and the solution of these problems is undoubtedly a cause of satisfaction to the physician, as it frequently also is to the patient. To what extent, however, is the patient a gainer? To what extent is the object of diagnosis and of all medical knowledge fulfilled? It must be admitted that the gain in most cases

is disappointing. The natural course of the disease is no doubt often beneficially modified, but usually to only a slight extent, unless surgical treatment be successfully applied, which even the scientific discoveries of Ferrier and Horsley and the surgical skill of Durante, Kocher, Macewen, and others have rendered possible in relatively few cases. Whether the investigation of the condition of the patient leads to the diagnosis of acute ascending paralysis or anterior cornual degeneration, of spastic paraplegia or locomotor ataxia, of syringomyelia or bulbar paralysis, the methods of treatment are much the same; and while we may have some satisfaction in adopting measures to relieve symptoms or to protect the patient against conditions favourable to the progress of the disease, or to increase the general powers of resistance, we most frequently find ourselves in the mortifying position of being unable to cure the disease. In those cases, on the other hand, where it is possible to advance from diagnosis to the determination of the actual cause of the disease, when remedies are employed which have been proved to be curative as regards that cause, the disease, whatever be its position in the artificial nosology of nerve affections, may in many instances be arrested in its progress, and may even be cured, provided the affected tissues have not already undergone incurable destruction.

At the present epoch in medicine it is especially interesting to recognise that the latter gratifying results are to be obtained when there is reason to believe that the disease has been caused by a toxic substance present in the body, and that according as this substance is the poison of syphilis, or of rheumatism, or of malaria, is the cure effected by remedies which have been proved capable of annulling the toxic effects of these poisons. It is thereby shown that the disease is not truly a product of the structural alterations which are present, but of a hurtful substance or poison capable among other effects of producing these structural alterations. Similar facts are observed with many ordinary poisons, and an association, highly significant in regard to the production of disease, is thus indicated. Many of the more common poisons also produce changes in structure closely simulating the changes of disease, as the peripheral neuritis, anterior cornual degeneration, granulo-fatty degenerations, and arterial sclerosis of lead; the liver steatosis and yellow atrophy of phosphorus; and the fatty degenerations and diffuse sclerotic hyperplasia of the liver, the peripheral neuritis and the atheromatous changes in blood vessels produced by alcohol.

By such facts, acquisitions of modern pathology, it is strongly suggested that the structural changes found in many diseases may, after all, be mere manifestations, associated with other effects, of a cause which would thus assume the importance of being the essence, the *vera causa*, of the disease, and that this essence is a toxic substance. This idea is rapidly becoming the predominant doctrine of the present-day conception of disease, and as investigation proceeds it is almost daily receiving support from new facts. It has been demonstrated that the body is constantly subjected to the risks of poisons produced within itself, as well as of poisons introduced into it from without. Many of the poisons produced in the body, such as the ptomaines and leucomaines, are of the chemical nature of the previously known alkaloids, and not a few of them rival the vegetable alkaloids in toxic power and reproduce their leading effects. Nervine, for instance, is lethal in minute doses, and acts in many respects like pilocarpin; while muscarin finds its analogue in the active principle elaborated by poisonous fungi.

The organism, even in a state of health, is a veritable storehouse of these toxic substances. Many of its normal constituents, such as potash salts and carbonic acid, are well-recognised poisons; many of the products of its glands, such as saliva and bile, contain toxic ingredients; many of the substances formed in the processes of disassimilation, and which enter such secretions as the urine and the intestinal canal, are capable of disordering health and even of endangering life; and in disorders of function, even if they amount to little more than mere disturbance of nutrition, poisons not found in the healthy body are generated and produce the symptoms of disease. By such toxic influences the symptoms of cholæmia, gout, rheumatism, uræmia, diabetic coma, stercoræmia, and probably also of chorea, sunstroke, neurasthenia, asthma and the idiopathic anemias

receive a sufficient explanation, even although the toxic substances have not in all cases been identified.

The doctrine of the toxic origin of disease has also been applied to mental affections. Auto-intoxication from poisons produced in the intestinal canal is believed to be an important factor in the causation of insanity, and already neurologists, such as Nissl and Van Giesen, have expressed the opinion that the toxæmic theory is destined to clear away much of the present vagueness regarding the pathogenesis of mental disease. Further, it is not improbable that in cancer, auto-intoxication by a poison generated in the cancer cells, equally with, and in some instances to a greater extent than, structural degenerations of invaded tissues, accounts for the symptoms and for the fatal termination—a probability which has been strengthened by the separation from cancer of a substance possessing a hyperthermic and powerfully lethal action.

The widely acting pathogenic influence of poisonous substances has, however, received its most definite and convincing support from the remarkable discoveries in bacteriology which have signalised this period. The gravity and wide prevalence of infective diseases had rendered them a subject of special study from the earliest period. Rhazes in the seventeenth century propounded the view that small-pox was essentially a fermentative disease, and thus originated the doctrine of the fermentative nature of all infectious disease. Previously to this time a theory of the parasitic origin of these diseases had been propounded, and its more enthusiastic supporters gave a reality to their views by such statements as that syphilis was caused by a minute worm, and measles, small-pox, and plague by infusorial animals or invisibly minute insects. With the introduction of the compound microscope the parasitic theory disappeared in this gross form of it, and the fermentative theory was again adopted. It was not, however, until 1861, when Pasteur's great discovery of the nature of butyric fermentation was made public, that the sufficiency of the theory became revealed. His demonstration of the essential part played by minute living structures in the transformations which constitute the process of fermentation at length removed the process from the mysteries which had previously surrounded it, and opened up applications to the pathogenesis of infective diseases which have revolutionised medicine. He pointed out that the organisms of fermentation are similar to those which had already been discovered by Rayer and Davaine in anthrax. He subsequently demonstrated the virulent nature of the microbes of pyæmia and infected gangrene, and, following Koch's work on the cultivation outside of the body of the bacillus of anthrax, he proved also that this bacillus, as well as that of fowl cholera, is able, when grown in suitable media, to reproduce itself almost indefinitely, and to retain for many generations its power to cause the symptoms of the original disease when inoculated into animals.

The way was thus opened up for important additions to the knowledge of the etiology of infective diseases, and, in rapid succession, the pathogenic micro-organisms of swine fever, glanders, tubercle, Asiatic cholera, septicæmia, erysipelas, pneumonia, and numerous other infective diseases were discovered.

The pathogenic action of the microbes was at first attributed either to mechanical obstruction of the blood vessels, caused by their accumulation in them, which resulted in asphyxia of organs essential to life; or to a biological action which enabled them to appropriate nutritive materials destined for the tissues of the body, and thus to deprive these tissues of life. While, in the case of a few of them, both of these actions may to a slight extent explain their effects, it was subsequently proved that these effects are mainly caused by the poisons which they produce. The poisons are of complex composition; some are alkaloids, and others modified proteids, and others, again, have altogether unknown chemical composition. Many of them are of extreme and almost indefinitely great activity: one milligramme, for instance, of the dry poisonous constituents of tetanus toxin is sufficient to kill a horse, or 600 million times its weight of living tissue; while the hyperthermal effects of tubercle toxin are appreciable when the dry toxin in doses of from one to two-tenths

of a milligramme, is injected, representing a strong reaction on 60 trillions of its weight of living human substance. Like other poisons, further, they are capable of producing structural changes, exemplified in the skin eruptions produced by many infectious diseases; the focal necrosis of peripheral nerves produced by the diphtheria poison; the fatty changes and longitudinal fibrillation of the heart muscle produced by this poison, and also by that of anthrax; the cerebro-spinal meningitis produced by the poison of influenza; the anterior cornual and muscle degenerations and the neuritis produced by the poisons of tetanus and diphtheria; the acute parenchymatous and hæmorrhagic nephritis produced by serpents' venom; and in the production of nodules in the lungs, reproducing the characteristics of pulmonary tuberculosis, by dead tubercle bacilli.

The demonstration of the toxic origin of infectious diseases has thus added greatly to the number of diseases which are caused by poisons, and has thereby been largely instrumental in establishing the doctrine of the toxic origin of disease. Unlike the older doctrines of the iatro-chemists, humoralists, and physiologists, this doctrine is supported by an abundance of convincing facts; and it may confidently be anticipated that it will have an endurance which former systems of medicine have not possessed.

Large numbers of disease-producing poisons are thus ever present in the body, created by the normal processes of life, and abundantly produced by departures, even in themselves unimportant, from these processes. Many substances well known to have poisonous properties are intentionally introduced into the body, such as alcohol, tobacco, tea, and opium, while others, such as lead, accidentally find their way into it. The respiratory passages and intestinal canal are crowded with micro-organisms, and they teem in the soil, air, and articles of food. Many of them are producers of virulent poisons, and when they effect a lodgment in the body and find conditions congenial to development, they proliferate with so great rapidity that a single bacterium may in twenty-four hours have multiplied itself into many millions of separate toxin-producing organisms.

In these circumstances, it is of interest to inquire what defence man and other animals can oppose to the disease and death-producing poisons by which they are so constantly endangered? Instances have long been known of the possession of defensive powers against the ordinary poisons, organic and inorganic. Certain animals are by hereditary endowment able to receive with impunity large quantities of poisons, which in minute quantities are hurtful to other animals, well exemplified in the enormous quantities of belladonna and opium which may be administered without injury to herbivora. It is also notorious that man and other animals may become so habituated to the action of several toxic substances that, in the course of time, doses greatly in excess of the minimum lethal are no longer able to cause death or even much inconvenience. Such acquired powers of defence are produced against arsenic, opium, alcohol, and tobacco, and they are also illustrated in the effects of nitrile ethers.

Explanations for these exceptional powers of defence have been found in the special activity of the processes of elimination, and particularly of elimination by the kidneys, whereby the quantity of poison requisite to cause injury is prevented from being present in the blood; in an unusual power of producing decomposition, probably dependent on special chemical conditions of the blood, by which, for example, herbivorous animals are enabled to convert very large quantities of atropine into relatively inert tropine substances; and on the property which certain organs, and especially the liver, possess of absorbing and retaining toxic substances and of thus preventing their access to the structures on which they act in quantity sufficient to be hurtful. In the case, further, of many organic poisons, absorption and diffusion are impeded by the walls of cells, as in the instance of the slow absorption of strychnine through the stomach walls and of many albuminoid poisons through the intestinal epidermis.

These explanations, however, do not account for all the observed phenomena, and it must in the meantime be assumed that tissues may gradually become accustomed, possibly by exhaustion, to the perturbations produced by substances which modify their normal condition, so that by-and-by a tolerance is induced.

Anticipating some statements which will afterwards be made, a fundamental difference exists between both congenital and acquired defence against ordinary poisons and that resulting from the action of disease toxins, venoms, and such-like poisons, in so far that in the former there is not produced in the blood any substance which plays the part of an efficient counter-poison or antitoxin.

The subject has, however, gained a new importance from the remarkable facts discovered in connection with the poisons generated by pathogenic micro-organisms, and in connection also with other poisons of very similar chemical composition, represented especially by the venom of serpents and by the vegetable products abrin and ricin.

It had long been known that many infectious diseases conferred upon those who had suffered from them a power of resistance against subsequent attacks of the same disease. After the discovery had been made—and to this I have already alluded—of the microbial origin of infective diseases, it was experimentally shown that if the microbes constituting the cause of any infective disease were inoculated into animals, not only were symptoms of the disease produced, but also that the animal, if it survived, reproduced still further the events of an infectious illness, by acquiring a power of successfully resisting the morbid influence of the same microbes subsequently inoculated. It has likewise been found that each of these events could be reproduced by the filtered, and therefore microbe-free, solution, in which the pathogenic microbes had been cultivated, and thus it was demonstrated that neither the original disease nor the subsequently acquired production was actually due to the microbe, but to toxic substances produced by it.

From this position the further great advance was made that the blood serum of protected animals, itself destitute of poisonous properties, when introduced into non-protected animals conferred upon them a resisting power which might be so great that even large lethal doses of the virulent micro-organism and of its toxin no longer produced death or even symptoms of poisoning.

These remarkable results of experiment deservedly claim much attention. They irrefutably demonstrate that infectious diseases are in their essence poisonings; they throw much light on the mystery, previously shrouded in metaphysical phrases, of the nature of the protection acquired by attacks of infectious disease or conferred by vaccination; and they have not only at once led to valuable therapeutic results, but they indicate further applications, both in the prevention and treatment of disease, exceeding in their possibilities any expectations that had previously been originated by discovery in medical science.

Inquiry into the nature and cause of this protection has thereby been removed from the position of speculation long occupied by it to one in which experimental methods could be pursued with some hope of solving the problems. Many of the results, however, are yet difficult to explain, and considering that new facts bearing upon them are almost daily being obtained, it is not to be expected that altogether satisfactory solutions had been found or unanimity of opinion obtained. More especially does this apply to the nature of the process whereby protection or immunisation is obtained, to the origin of the protection-producing substances or antitoxins, and to the manner in which they act as curative or therapeutic agents.

As in the case of some of the ordinary poisons, mineral and vegetable, it may be admitted that a portion of the acquired protection is due to the tolerance brought about by the accustoming of the structures of the body to the action of the poison, but this tolerance could not continue for the long periods during which acquired immunity sometimes persists after the infected disease has been recovered from. It may also be admitted that pathogenic micro-organisms absorb and thus remove from the body certain constituents necessary for their growth and vitality, whose removal may, to some slight extent, render the body unsuited for the further growth of these organisms; but, apart from other objections that might be advanced, it is inconceivable that this cause could operate in the bodies of animals which so rapidly change the composition of all their constituent parts, and that therefore the substances which have been removed would not very soon be again restored to the body, and thus render it vulnerable to

fresh infections. The doctrine of phagocytosis, enunciated and ably and strenuously supported by Metchnikoff, in which protection is attributed to the power possessed by leucocytes of absorbing and destroying microbes, may to a limited extent account for the destruction of living microbes, but it probably accounts to a greater extent for their disappearance after life is extinct; while it can have but little influence upon the soluble toxins which, since the introduction of the theory of phagocytosis, have been proved to be in most cases the true cause of the disease symptoms.

The frequent persistency of immunity, not only exemplified in the after-history of patients who have recovered from certain of the infectious diseases, but also in vaccination against small-pox, as it alone serves to disprove each explanation yet advanced of the essential nature of acquired protection, must be taken into account in formulating explanations. The micro-organism of an infected disease introduced into the body produces the characteristic symptoms of the disease, and, if the animal recovers, subsequent inoculations of this micro-organism no longer produce any injury. The animal has become protected against the disease, and there is abundant clinical evidence to show that in the case of the majority of infectious diseases the immunity lasts for many years. The pathogenic organism of the same disease cultivated outside the body produces a toxin which when administered to an animal likewise reproduces the symptoms of the disease, and if the animal recovers, and further quantities of the toxin are successively administered, an immunity may be acquired so great that the animal suffers but little inconvenience when 50 times the minimum-lethal dose, or even a larger quantity, of this toxin is now administered to it. The immunity acquired in the latter case is, however, only of short duration. I do not know if the duration of it has been defined with any of the toxins of disease, except with the toxin of diphtheria, and Roux and Klein have shown that with this toxin it lasts only from five to seven days. Enough, at least, has been done to show that it is brief when compared with the immunity produced by the microbes from which the toxins had originated, and Klein remarks that a serum which may be relied on to afford any durable protection is still a desideratum. It is also interesting to note that Monckton Copeman has found that lymph filtered so as to remove from it all solid particles, and therefore presumably all micro-organisms, can produce only a briefly lasting protection against unfiltered vaccine lymph of normal potency. In the case of the venoms of serpents—which in composition, and in other important respects, are analogous to the toxins of disease—the duration of immunity has, however, been defined; and experiments have shown that if an animal be protected so as to survive the minimum-lethal dose of the cobra venom, the protection produced against the same dose of venom does not last longer than a few hours; and even when the process of the immunisation has been carried so far that the animal can survive four times the minimum lethal, the protection against this dose of venom exists for only thirty days.

The protecting substance, antitoxin or antivenin, which appears in the blood after inoculation with pathogenic microbes, or after the injection of toxins or venoms, is chemically unstable, and is subject also to the general processes of elimination. Its presence in the body, even when the quantity of toxic substance to which it owes its origin is greatly above the quantity of toxin which has been elaborated in a case of infectious disease by the pathogenic organisms of that disease, is to be measured by days only; and, nevertheless, the protection produced in a patient by an infectious disease may apparently endure for a lifetime, and the immunity from small-pox gained by vaccination for at least seven years. It appears to me impossible to explain these contrasting facts on any other supposition than that, in the instances of prolonged immunity, successive supplies of the antitoxin of the disease, or of small-pox, must be furnished to the body during the time that protection continues. It is not possible, however, that these supplies could emanate from the pathogenic organism itself, for the life of the host would not endure were it retained in the body in its condition of original virulence. Jenner himself believed that vaccinia is a modified small-pox. The microbe of small-pox, like all other microbes, is greatly influenced by its surroundings. When

transferred from man to the calf, it is now known that it may gradually acquire the characteristics of vaccinia, and elaborate substances which reproduce in man the protective effects of inoculation with human vaccine. The microbe of small-pox, therefore, has obviously become so modified that, while it can no longer produce a virulent toxin, it still retains the power of elaborating a protective antitoxin, and also retains sufficient vitality to reproduce its like through many generations in the human body.

Evidence pointing in the same direction has been obtained with other pathogenic microbes. Pasteur found that the microbe of fowl cholera, when treated in a certain manner, can have its virulence greatly lessened, and if it be then injected into the tissues of fowls, only slight poisoning is produced. From fowls thus treated, microbes are obtained also capable of producing only slight poisoning, and inoculations can be carried through a successive series of fowls with a like result. Each of these fowls had by this inoculation with a weakened or attenuated microbe become protected against the original and virulent microbe.

In the case of the pathogenic micro-organism of anthrax, this great pioneer in the field of the microbial etiology of disease discovered similar facts. If grown outside of the body at a temperature of 42.5° C. for eight days, this microbe could no longer produce the disease in susceptible animals, but, notwithstanding, it endowed them with a certain degree of protection against the original virulent microbe. Similar results were obtained with the microbe of hog fever, and it is important to note that a duration of immunity exceeding that known to be produced by any toxin was obtained, for the protection following inoculation of the attenuated microbe lasted for at least one year.

These instances are sufficient to show that immunity equally with poisoning is dependent upon a soluble substance produced by the micro-organisms; that the duration of even a high degree of immunity resulting from the introduction into the body of the immunising substance as distinguished from the microbe is only of brief duration; and, accordingly, with the existing evidence, it is impossible to account for the prolonged immunity following upon the recovery from many infective diseases, or from inoculation with vaccine lymph, otherwise than by assuming that so long as immunity continues the microbial sources of infective disease continue to exist in an attenuated and otherwise modified form in the protected body.

Attenuation for the purposes of protection would therefore appear to be essentially a process in which the condition of life of the microbe is so altered that its capacity for manufacturing poisons is weakened or destroyed, while its disease-preventing properties are retained. Unless by education we can so tame and civilise a pathogenic microbe as to subdue its virulent and hostile disposition, while at the same time its beneficial and protective properties are left unimpaired, the hope of obtaining—as for plague, cholera, and tubercle—immunising vaccines equal in efficiency to the lymph of vaccinia will probably never be realised.

The theory which I have suggested implies that long-enduring protection from infective disease cannot be obtained by the introduction into the body of either the poisonous or the immunising products of microbes—the toxins or antitoxins—but only by inoculation of such microbes as are capable in the body of assuming a non-virulent form, or of microbes already converted into this form.

I would here point out that, however highly we may value the objects and success in some important directions of the experiments of Dr. Monckton Copeman and others on the effects of glycerine upon vaccine lymph, it must not be overlooked that the powerful microbicidal action of glycerine upon the contaminating organisms of this lymph may, in the course of time, weaken or even destroy the activity of the specific organism by which the long-lasting protection against small-pox is produced.

In the case of some diseases it is possible that the modification of the pathogenic power of the micro-organism necessary to convert it from a poison-producing to an antidote-producing agent cannot be accomplished in the body. Thus may be explained the failure of certain diseases to protect the body from subsequent attacks of the same disease, well recognised in the instances of pneu-

monia, influenza, diphtheria, rheumatic fever, erysipelas, and tubercle. On the other hand the microbes of other diseases may, in small numbers, and attenuated both in virulence and in power of conferring protection, persist in the body after convalescence has been established and actually rendered it not only more susceptible to fresh infection but also to a recurrence of the disease by auto-infection. Results obtained by experiments with toxin and venom support the former possibility, for owing to some as yet unexplained individual peculiarity, an animal which had received a number of successive doses of toxin or venom, each considerably below the minimum lethal, instead of having thereby acquired protection, may unexpectedly exhibit serious symptoms of poisoning, and may even die when it receives a dose considerably below that required to produce death in an animal which had not previously received any toxin or venom. The probability of the second event is supported by the well-known effects upon the life and pathogenic power of microbes of changes, even although slight, in the conditions to which they are subjected. A change in temperature, the addition to, or removal from the fluid, in which they are grown of a minute quantity of a chemical substance, may convert a non-virulent form of a pathogenic organism into a virulent form. Similar causes may, outside the body, also render moderately or intensely virulent a previously non-virulent microbe, and thus may be explained variations in the severity of epidemics, as well as the occurrence of outbreaks of infectious disease not originated by infection from any previously existing case.

The dependence of microbial existence upon the composition of nutrient media may also partly account for the age liability which forms so conspicuous a feature in the history of such infectious diseases as scarlet fever, measles, and whooping-cough. Further, pathogenic microbes, attenuated as to their virulence but not as to their protective power, may enter the body and render it, immune by a process of accidental vaccination; and thus may be explained, without recourse to such unsatisfactory phrases as individual or racial peculiarities, well-authenticated examples known to all of us, of repeated exposure to infection without the production of disease, and of the immunity enjoyed by the inhabitants of towns and districts daily subjected to the virus of typhoid fever, malaria, or yellow fever.

These are not mere hypotheses unsupported by experimental data. Describing the results of his experiments on anthrax, Pasteur states that when fowls are inoculated with the virulent microbes of this disease, they remain well until they have been cooled down to a subnormal temperature; and, in the earlier stages of the poisoning thus induced, if the temperature be again raised, the symptoms of anthrax disappear and the fowls recover. Anthrax microbes, as well as those of fowl cholera, if cultivated at a temperature between 42° and 43° C., acquire varied degrees of lethality according to the age of the culture, and the microbes of each variety of lethality can be almost indefinitely reproduced by maintaining certain conditions of cultivation. If microbes so grown as to be no longer able to produce anthrax in rabbits are first inoculated in a successive series of experiments in young, and, for that reason, extremely susceptible rabbits, and if the microbes obtained from the last of the series are then inoculated into somewhat older and finally into adult rabbits, the original virulence of the microbe is found to have been regained. "The work in my laboratories," he states, "has established that pathogenic microbes are not morbid entities. They can assume various forms of physiological activity, depending on the media in which they live and multiply. As a consequence, one can modify their virulence. It can be exalted or enfeebled, and each state can be fixed." Impressed by the far-reaching possibilities suggested by these and other fruits of his fertile imagination, it is not astonishing that the great discoverer, whose divining rod of science had thus thrown a clear light on the mysteries of centuries, should exclaim, "The hour has now arrived when we may enter the enchanted grotto full of priceless treasures."

Passing now to consider the origin of the protection-producing substances—antitoxins or antivenins—it is important to bear in mind that the symptoms of a pathogenic disease, the toxic phenomena by which it is characterised, are, with a few doubtful exceptions, directly caused by the poisons generated by micro-organisms, and not by the micro-organisms

themselves. The production of microbicidal agents does not, therefore, in connection with this question, require consideration, but it may be pointed out that there is evidence of the production, both by toxins and by micro-organisms, of substances specially unfavourable to the vitality of the micro-organisms themselves.

The production of antitoxin in the body, whether following the introduction of virulent microbes or of toxins entirely free from microbes, has generally been explained by a reaction occurring in the tissues of the body, whereby either a proliferation of leucocytes and the production by them of the protecting substances is excited, or the normal cells of the body are stimulated in such a way that they secrete the protective substance.

I have, to some extent, already discussed the question of phagocytosis, which is involved in the first explanation. To the objections that have been stated there are others which can be derived from the results of observation and experiment. In many instances, when immunity to a high degree has been produced by venom, no increase can be found in the number of leucocytes immediately, or at varying periods, after the subcutaneous injection of large, though, in the circumstances, easily tolerated doses of venom. Further, when one half more than the minimum-lethal dose of venom is mixed outside of the body with antivenin, and the mixture injected into an animal, the quantity of antivenin required to prevent this lethal dose from producing death is only the quarter of a cubic centimetre; whereas if the antivenin be administered half an hour before the same dose of venom, as much as 3 cubic centimetres are required. That is to say, in conditions which are the more favourable for the proliferation of leucocytes, or for the production by them of protecting substances, the antivenin is less efficient as a protecting agent than when the conditions are much less favourable.

As to the second theory, often termed the reaction theory, it is also opposed by the experiments I have last mentioned, but equally so by the fact that a high degree of immunity can be produced by an appropriate adjustment of doses without any observable reaction occurring. Even when a distinct reaction, such as an elevation of temperature, is produced during the process of immunisation, the production of the reaction is in itself of no other significance than that a dose of an active substance, sufficiently large to cause an observable effect, had been administered.

The subject, however, is surrounded by difficulties, not a few of which have arisen from the attempt to obtain an explanation without separating the influence of the microbe from that of the toxin, with the result that biological conceptions have perhaps been introduced unnecessarily into the consideration and discussion of the subject. As a contribution to the solution of the problem I would advance the following facts: Although searched for, no proteolytic or fermentative action has been discovered in the case of any toxin or venom; by subjection to certain external influences, such as elevation of temperature, and the influence of electric currents and of certain chemical reagents, toxins and venoms may have their poisonous action destroyed, while the immunising or protective action is retained; and toxins have been found actually to contain protective or remedial substances along with their toxic ingredients, as shown, for instance, by Hunter in the case of the toxin of tubercle.

These considerations suggest that the protecting substance originates directly from the toxin, or is indeed an ingredient in its complex composition. The suggestion is supported by experiments which show that the degree of protection artificially produced in an animal—for it is, perhaps, not unnecessary to state that protection and immunisation are only relative and not absolute—is proportional to the total quantity of toxin or venom introduced, rather than to the amount of reaction produced in the animal by any of the several administrations. The remarkable facts which have been described in connection with the stomach administration of venom, obtained also by Ehrlich and Kobert with the somewhat similar bodies abrin and ricin, and by Valli with the virus of hydrophobia, seem likewise to receive their most satisfactory solution on this supposition. A dose of venom, several hundred times greater than is requisite to produce death by subcutaneous injection, fails when introduced into the stomach to produce any poisonous symptom whatever, but

still so protects the animal that considerably more than the minimum-lethal dose may now be subcutaneously administered without producing death.

It is difficult to account for these facts otherwise than by assuming that the venom while in the alimentary canal had been subjected to a process of analysis, as the result of which its toxic constituents had been separated from those that are antitoxic or protective; and while the former had either been destroyed or had failed to be absorbed, the latter had passed into the blood in sufficient quantity to protect the animal against otherwise lethal administration of venom.

There are, undoubtedly, many facts still required before a convincing explanation can be formulated of the origin of the antitoxic substances that appear in the body after the reception of pathogenic or other similar toxins; but the facts already ascertained appear to indicate that the antitoxic or immunising substances originate not from vital reactions upon constituents of the body but from the toxins themselves, being produced by chemical changes in them, or being actually among their normal ingredients.

The question is not only of scientific interest but it has also a practical bearing. The manufacture of the immunising substance is attended with much difficulty. A satisfactory antitoxin can rarely be obtained until a tedious process, extending over several months, has been followed. Antipneumococcus serum requires as long a time as six months, the immunising serum of yellow fever from twelve to eighteen months, and the nearest approximation yet obtained to a satisfactory protecting serum for tubercle the almost impractical period of several years. Were it recognised that the antitoxin originates directly from the toxin, the preparation of it would be freed from existing difficulties and mysteries, and, after some necessary chemical research, it could be produced in the laboratory and thus brought into closer relationship with ordinary medicinal substances.

Any generalisation in medicine, while it may serve the useful purpose of emphasising advancement in knowledge, must remain barren of practical result unless it also supplies general principles as well as specific indications for treatment. It may with some confidence be stated that the doctrine of the toxic origin of disease does not fail in these respects.

In the case of ordinary poisons it has been well established that recovery is largely promoted by hastening the removal of the poison from the body, especially by means which it is the province of pharmacology to indicate; and the eliminative treatment which has long been followed in many diseases thus finds in their now definitely established toxic origin a sufficient explanation and justification. Clinical and experimental evidence, not restricted to ordinary poisons, but gained also from the study of the effects of toxins and venoms, has taught us that treatment should also include the adoption of measures for increasing the resistance afforded by the body to toxic and morbid processes. If a dose of venom below the minimum lethal be administered to an animal, and, after all obvious symptoms of poisoning have disappeared, this dose be followed by a second, also considerably below the minimum lethal, the animal may die, although each dose was in itself insufficiently large to cause death. If an animal has been inoculated by a non-lethal quantity of the virus of a recognised disease such as anthrax, and, after recovery has apparently been established, if a non-lethal dose of the virus of another disease be inoculated, death will follow the inoculation of the second dose, although that dose is quite insufficient of itself to produce death in an animal which has not previously been thus treated. In both cases the power of resistance has been so weakened by the first and apparently recovered from administration that a quantity of virus in itself insufficient to cause death now succeeds in doing so. From such examples the explanation is found of the widely prevalent employment of means to increase the strength or resistance of a patient, of the value of tonics and foods and of fresh air and light, not only in promoting recovery from illness, but also in actually preventing a fatal termination. Expressed in another form, they constitute means for slightly increasing for any given degree of disease the minimum quantity of the disease-producing influence or substance required to produce that degree of disease.

These as well as other methods of treatment that might be

referred to do not, however, directly affect the true cause of the malady. Hitherto this cause could be counteracted or opposed only in the instances of the well-known poisons which are dealt with by toxicology, and of a very few diseases such as ague and syphilis, in which the cause was surmised, without being proved, to be a poisonous substance; and in substances fitted to antagonise these poisons by chemical combination, or, though only to a limited extent, to counteract their effects by physiological processes, therapeutics has possessed satisfactory resources. By the demonstration of the production of many diseases by toxins generated by micro-organisms, the opportunities for the application of these principles has been greatly extended. Diseases whose treatment had previously rested on an uncertain basis have now been brought into the range of rational therapeutics; and it has been shown that morbid processes which had already become so definitely established as to display serious symptoms can be entirely arrested, and, above all, that illnesses which would otherwise inevitably terminate in death may be so perfectly controlled that the fatal termination can be prevented and recovery ensured.

A dose considerably above the minimum lethal of the toxin of tetanus is administered to an animal. Several hours after the administration, when symptoms of tetanus had manifested themselves, the antitoxin of tetanus, derived from an animal which had been immunised against the virus, is injected under the skin, and in a short time afterwards the symptoms of the disease disappear and the animal recovers.

A dose of cobra venom sufficient to cause death in two or three hours is administered to an animal; the venom illness is developed, and while it is quickly advancing to apparently an early death, a dose of antivenin—the blood serum of an animal highly immunised against this venom—is administered, and by-and-by the symptoms become mitigated, and in a few hours the animal, which otherwise would certainly have died, is restored to a perfectly normal condition.

By this antidotal treatment, further, not only is disease arrested and even death conquered, but the structural alterations in the muscle fibre and elsewhere that the tetanus toxin produces, and also the acute and rapid changes in the parenchyma of the kidney, characterising the poisonous action of serpent's venom, are altogether prevented from occurring.

How are these marvellous therapeutic or curative effects to be explained? The explanations that have been advanced are essentially the same as those applied to the production of immunity, and they have already been disposed of in the discussion of that subject. Specially bearing on the therapeutic aspect of the question are the further considerations that antitoxins are destitute of any distinct physiological action, and, founding on Declory's recent work on antivenin, antitetanin, and the antitoxin of diphtheria, they have even no influence on the processes of ultimate nutrition. Their curative action cannot therefore depend on physiological antagonism, and it is highly improbable that it has any biological basis whatever.

Referring again to experiments made with serpent's venom, when this venom in lethal quantity is mixed in a test tube with a small quantity of antivenin, the venom almost instantly loses its toxic power. Further, if the smallest quantity of antivenin required to produce this change after contact for a definite time with a lethal quantity of venom be determined, it will be found that if the time of contact is lessened this quantity of antivenin is no longer able to remove the toxicity of so large a quantity of venom. When, again, venom is injected under the skin of an animal at the same time as, but in a different position from, the antivenin, the quantity of the latter required to prevent death is for the same dose of venom about twelve times larger than when the two substances had been mixed together before they were injected. Such distinctions are difficult of explanation otherwise than by supposing that a combination, chemical or mechanical, is effected between the antivenin and the venom, for they indicate that when the conditions are the more favourable for ensuring contact between the antitoxin and the toxin, the antidotal action is more powerful than when the conditions are less favourable for this contact.

This view is also supported by the fact that if the antivenin be administered after the venom, the dose of the former required to prevent death is enormously larger than when the

two substances are simultaneously administered after they have been mixed together outside of the body. In the case of antivenin and venom the difference is as great as 1 to 1,200.

This experimental result, harmonising altogether with a physical as distinguished from a biological explanation of the antidotal action of antitoxins, emphasises the lesson, gradually receiving acceptance in practice, that for the effective treatment of an infectious disease the quantity of antitoxin must be a very large one, and at least 1,000 times greater than is indicated by the *in vitro* experiments by which their antidotal power has usually been determined and standardised.

For this reason the antitoxic serums frequently in use at the present time must be regarded as too dilute solutions. It is indeed probable that the process of immunisation, even when carried to its utmost limits, is incapable of producing antitoxic serums sufficiently powerful, in doses which can be administered, to cure a patient suffering from the effects of a large lethal quantity of toxin. Chemistry, however, has as yet left almost untouched the investigation of antitoxic serums, and it may confidently be expected that, when more knowledge has been obtained of their chemical composition, this difficulty will be overcome by the separation of the curative from the worthless ingredients.

By such results as are exemplified in the experiments that I have described a new era has been originated in practical medicine. Considering how limited were the means—if, indeed, they previously had existed—of actually preventing death when the fatal disease conditions were already present, a special fascination attaches itself to the subject of the antidotal treatment of disease, the newly created serumtherapeutics. It has merely entered the first stages of its development, and has had to contend in its applications to human beings with the difficulties presented by the presence of undiscoverable amounts of disease toxins, diffused by living generators, which are present in the body in unknown quantities and in varying toxic potentialities. The results already obtained are, however, of much value. Diphtheria has had its case mortality reduced from 70 per cent. to 26 per cent., or, according to another estimation, from 40 per cent. to 8 per cent.; hydrophobia has been so far brought under therapeutic control, by means which have not as yet been developed to their full efficiency, that its mortality has shrunk at least from 16 to 1 per cent.; the prognosis of tetanus has been deprived of much of its gloomy forebodings; the cure of pneumonia, of tubercle, of erysipelas, and of septicæmia is on the eve of being realised; a complete demonstration has been obtained of the power of antivenins to prevent the toxic and lethal effects of venoms; and the experimental data are being surely accumulated for completing the greatest triumph of preventive medicine by the discovery of an antitoxic serum for the cure of small-pox.

These, however, are to be regarded as merely the first fruits—in some cases requiring further maturing by the light of science—of the ample harvest which is ripening. Their acquisition, at the same time, has been sufficient to supply materials for constructing, in imperfect outline, the doctrine of the toxic origin of disease to which I have ventured to ask your attention. This doctrine has at least the merit of being able to bind together in one harmonious unity the conception of the actual nature or essence of a large number of diseases, including those which most urgently demand consideration. It supplies a simple and intelligible basis for treatment. Under its directing influence it may confidently be anticipated that Medicine will reach a position of definiteness previously unattainable; and, above all, that the healers of disease will have their resources in this beneficent function rendered more effective and valuable for mankind.

MEDICAL PRACTITIONERS IN GERMANY.—According to Eulenburg-Schwalbe's *Reichsmedizinical Kalender*, recently issued, the total number of medical practitioners in the German Empire in 1897 was 24,873, being an increase of 873 as compared with the previous year. They were distributed in the several kingdoms and States of the Empire as follows: Prussia, 14,957; Bavaria, 2,699; Saxony, 1,832; Würtemberg, 835; Baden, 949; Alsace-Lorraine, 731; Hesse, 655; and Hamburg, 519.

ADDRESS IN SURGERY.

BY

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*At the Annual Meeting of the British Medical Association at
Edinburgh, July, 1898.*

THE PRESENT POSITION OF SURGERY.

MR. PRESIDENT AND GENTLEMEN,—I desire to join my colleagues in offering you a most sincere welcome to Edinburgh, and I desire also to express the hope that you will all be able to look back upon your visit here as pleasant, interesting, healthy, and profitable both to mind and body.

When asked by a deputation of my colleagues in Edinburgh to give the Address in Surgery I felt that an honour had been very kindly and courteously shown me, but in accepting this offer I also felt that I had undertaken a responsibility—a responsibility which called upon me to speak to this distinguished audience as a representative of Scottish surgery. This responsibility was all the more serious to me, for my friends know well that I am more ready with the knife than with pen or speech, and as my daily life for many years has been to lecture and demonstrate to students as babes entering the profession, I had some fear that I might be offering to you as men and kings in the profession baby's food. My first difficulty was to select a text on which to address you. I might have offered you some of the results of nearly forty years of active hospital and private surgical practice, but I felt that an account of any such results was more fitted for the Departmental Sections. I also at one time thought I might have endeavoured to prove to you, and I think could have proved to you with success, how much Scottish surgeons and Scottish work have assisted in the development and improvement of surgical practice, but with this thought there suddenly came to my mind the old Scotch saying, "Ye'll hae a guid conceit o' yersel," and accordingly I at once dropped the idea of Scottish self-glorification.

After consideration it seemed best to me to take some more general text, and accordingly I decided to offer you a few remarks upon the present position of surgery. It must, I think, be universally acknowledged that the present position of surgery is of the highest. There are now few diseased conditions in which surgery does not play a very essential part in connection with treatment, and there is scarcely a single organ of the body, internal or external, which is not the subject of successful surgical procedure. The brain, the organs of the chest, abdomen, pelvis—many of which were so long looked upon as belonging solely to the province of the physician—are now shared, if not principally absorbed, by the surgeon as regards the relief or cure of their diseases.

It has sometimes occurred to me that on not a few occasions my esteemed colleagues, the physicians, have a strong longing to be surgeons for the time being, in order that they might be able to carry out some surgical procedure which their experience has taught them to be more efficacious than medicine.

For the sake of convenience, and partly also as is known to some here, that a discourse in this country is not considered complete unless delivered under from three to twelve heads, I propose to treat my subject under certain heads. In consideration for your feelings and time I propose to confine these heads to three, the minimum number allowed, and to speak of present surgery in:

- I.—Its Scientific Aspect.
- II.—Its Practical Aspect.
- III.—Its Moral Aspect.

I.—ITS SCIENTIFIC ASPECT.

It must at the outset be acknowledged—and acknowledged with gratitude—that the marvellous advances in connection with present surgical practice are largely indebted to those who have diligently, honestly, and successfully carried on experimental and other research in connection with the sciences of chemistry, physiology, bacteriology, anatomy, and pathology. We, as surgeons, look forward hopefully to receive