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ON POISONS AND DISEASE AND SOME EXPERIMENTS WITH THE TOXIN OF THE BACILLUS TETANI[1, 2]

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SECTION N of our association has, as you are aware, the very wide field of the medical sciences for its subject-matter, and it seems appropriate for a member of that section to address you on a subject which, while a primary concern of medicine and biology, is yet not without interest to scientists in general. I am therefore presenting to-night some considerations on poisons and disease.

Many of us who are not students of the medical sciences are but little interested in theories of disease. When illness overtakes us we wish to be cured "safely, quickly and pleasantly." There lived in the first century B.C. in Rome a Greek, a very successful and learned physician who was also a writer and philosopher, who promised his patients to cure their diseases according to that excellent and oft-quoted formula, *"Curare tuto, celeriter et jucunde."* We may be sure that this Greek scholar, the friend of the great writers and statesmen of his day, was a bit of a humbug as a physician, for only the God of healing himself could always make such a promise good. Nevertheless, the physicians of our day frequently succeed in curing certain diseases in accordance with this happy formula, but their greatest achievement in modern times is the prevention of disease.

1 Address of the president of the American Association for the Advancement of Science, Boston, December 27, 1933.

2 A grant from the Carnegie Corporation of New York enabled my coworkers and myself to carry out the experimental work described in the second part of this address.

Medicine in its cruder forms was no doubt, next to food, clothing and shelter, one of the earliest concerns of primitive man. He must soon have learned that certain bulbs, roots, seeds, berries, leaves and other parts of plants could not be eaten without fatal results; and he also soon learned that the bites of venomous serpents led to a more or less rapid death, and that there were numerous poisonous insects and grubs, poisonous fish, and other creatures on land and in the waters that had to be guarded against and many of which could not be eaten with impunity. We may be certain also that primitive man very early acquired a knowledge of how poisons that destroyed him could be utilized in the chase to bring down large and dangerous animals that were used by him for food and other purposes. The removal of venom from the poison sacs or the crushed head of a deadly snake and its application to the head of an arrow or a spear is an act that requires only the most elementary degree of mental acumen. As far as we know, every race of man in its early stages made use of arrow poisons, and the practise still prevails among uncivilized peoples to-day. The number of poisons that have been and are still used for this purpose, according to students of the subject, probably runs into the hundreds. We know that poisons suitable for this purpose are found in large number among plant products and in innumerable forms of animal life from the lowest to the highest. They range in fact from the most nauseating of odoriferous, volatile, but often only relatively harmful compounds to the most lethal of the fixed venoms and toxins. The invention of smearing arrows, spear heads and other weapons with poisons was certainly of the highest utility for primitive man in the chase, as it enabled him to kill the largest and most dangerous animals with the least amount of danger to himself. The antiquity of the invention can be traced back to a very early stage in man's history, and it is probably the first example of a physiological or pharmacological experiment made by him. The experimental pharmacology, the surgery and medicine of primitive man were early burdened with a belief in the supernatural causes of disease, and such rational experimentation as there was gave place to "a nightmare of evil spirits," magic and sorcery and a reliance on enchantments, as is still the custom in our day among backward peoples. Stinging insects and venomous serpents were no doubt the first among animal forms to invent hypodermic injection, a procedure which was introduced into medical practise only in the years 1845 to 1856. The venoms of stinging insects and deadly serpents are products of their own metabolism, formed in special glands, but it must not be thought that they have been developed in the long course of time solely for self-protection. It is well known to workers in institutes devoted to the preparation of antivenins that the venom is indispensable to the serpent for the maintenance of its health. The poison can not be expressed from the glands during the period of sloughing the skin or too soon after ingestion of food without fatal results to the reptiles. The venoms, therefore, play an essential rôle in the internal economy of these creatures, perhaps quite aside from the fact that they contain proteolytic ferments essential for digestion. Similarly, the poisons of bees and wasps appear to aid in the development of their eggs, after they have been fixed on them.

The mortality due to venomous snakes and stinging insects is a trifling matter compared with that due to the biting insects. These also introduce beneath the skin small amounts of irritating substances, that are of negligible importance in comparison with the extrinsic or adventitious agents that may be introduced into the bite at the same time. The biting insects, such as certain kinds of mosquitoes, fleas, the tsetse fly, the African horse fly, the body louse, or "cootie," and various ticks, are responsible for the great scourges that have decimated mankind and destroyed his domestic animals. Their responsibility is, however, of an indirect character, as they merely happen to be the carriers of deadly varieties of microorganisms. Among the serious diseases due to biting insects are malaria, yellow fever, black death, or bubonic plague, African sleeping sickness of man and the allied diseases of domestic animals, typhus fever and many more.

The elucidation of the causes of these and other infectious diseases, the development of specific curative agents for some of them and methods for their eradication and prevention are among the great achievements of the biological and medical sciences during the past sixty years. Only the most highly civilized and wealthy nations of the world are in a position to suppress more or less completely the dreaded insect-borne diseases of which I have been speaking. Malaria is one of them that can be completely eradicated, and yet Professor Bass writes of this disease as follows: "Unfortunately the outlook is not so favorable for the less civilized and less fortunately situated people of the world. The proportion of the people in many countries who have the disease varies from none in some countries to practically 100 per cent. in others. Even now millions, yes, more than a hundred million people throughout the world, suffer with it every year and more than a million die."

Among the remains in caves of the Madelenian epoch in the Vézère, the Dordogne and elsewhere in France are found the bones of human beings and those of many large animals, as the bear, the aurochs, mammoth, reindeer and others of that time. The man of this period fashioned for himself from bones spear points, harpoons, hooks, needles and other implements, and carved pictures, on bones, reindeer antlers and teeth, of many of the animals of his time, and there is at least one considerable work of his art that "depicts trees, horses and an aurochs, and a snake biting a man's leg." In this remote period of antiquity the serpent, as ever since, "bruised the heel of man." What is of especial interest to us is the fact that the spear heads and harpoons of the man of that epoch had a series of pits on them or a series of parallel grooves, which some archeologists believe were designed to hold deadly poisons. It is apparent that such poisoned weapons were also effective in warfare, and this use of poisoned spears and arrows by primitive man against his human enemies has never been forgotten. South American Indians invented "poison gas" long ago, according to Baron Nordenskiöld, who says: "The Indians of (South) America cultivate a spice plant, Spanish pepper (Cayenne pepper), which is of the greatest importance to them. They have discovered that by the burning of this pepper there is developed a sort of "poison gas" that proves effective in laying siege to villages fortified by palisades." The Romans in their wars with the Gauls and Germans and other peoples in the early centuries of our era lost many of their men from wounds made by poisoned arrows—wounds that were of no significance of themselves. L. Lewin, an investigator and historian in this field of study, has gathered references from the literature that prove that the French, Swiss and Spaniards continued to employ poisoned weapons in hunting deer and the wild boar down to the fourteenth and even to the latter part of the sixteenth century, particularly in Spain. Some historian has said that war has been the chief industry of man throughout the ages and promises to continue to be so for many a long day. Certainly in our day war and preparations for war must still be counted among the greatest of our industries. At the moment chemists in the employ of governments everywhere throughout the world are busier than ever in inventing lethal gases, fluids and even relatively insoluble toxic substances for the destruction of the enemy's forces and, unavoidably at times, of his civilians.

We have mentioned arrow poisons that are secreted by the poison glands of venomous serpents. Such poisons are generally spoken of as venoms and sometimes as toxins, but it will be seen later that the latter term is generally applied in our day to the deadly poisons elaborated by pathogenic microorganisms. It is interesting to note that our words *toxic, toxin,* in*tox*-icate, and the large number of combining forms and derivatives so widely employed in the biological sciences contain the root or stem of the Greek word for bow—τοξον—often used in the plural for arrows. The poison for smearing arrows was originally termed τοξικον φαρμακον, but in the course of time the noun of the phrase was dropped and the adjective form, τοξικον, "of, or pertaining to the bow," took on the significance, "poison for arrows," and then of poison in general. The literature of the ancients, as well as our own and that of other nations and their folk-lore, contain numerous figurative expressions based on this ancient use of poisoned weapons. Job mourns, "For the arrows of the Almighty are within me, the poison whereof drinketh up my spirit." Stockman, in writing of arrow poisons, after speaking of the widespread belief that malignant disease or pestilence is due to the invisible but deadly arrows of the offended gods, remarks "that even such an impalpable feeling as love was conveyed into the heart by means of Cupid's darts."

Many of you practise archery in your vacations, as a pastime or as an aid to health, and you may possibly know that the English scholar and man of letters, Roger Ascham, Latin secretary to Queens Mary and Elizabeth and the author of that well-known treatise entitled "The Scholemaster," wrote a book on archery in 1545, which he called, "Toxophilus," or Lover of the Bow. The treatise is in the form of a Socratic dialogue between Toxophilus, who defends the use of the bow as an indispensable national weapon and also as a means of dispelling the "grosse and colde humours" that "gather and vexe scholers," and Philologus, who has to be convinced of the advantages derived from "shoting." The little work is no longer read in our day, but is full of classical learning and reflections on a variety of subjects touching the physical and moral health of men and nations. Through it the word "toxopholite" was introduced into the language, to designate the devotee of archery, and in England there was even a "Toxopholite Society" in the eighteenth century.

We have been speaking of the silently operating and, to primitive man, mysterious and deadly agents that are found so widely distributed in nature and that are usually designated as poisons, and we may ask, What is poison?

WHAT IS POISON?

Let me say to begin with that no one has ever been able to give a concise and accurate definition of a poison that would apply to every one of the many thousands of known poisons. All attempts to do this have simply ended in offering definitions that do not define. The medical jurisprudence of this country and of England has never attempted to define the word *poison.*

The exponents of the medical and biological sciences are, however, no worse off in respect to the impossibility of defining in a satisfactory manner such terms as *living* or *life, disease* and *health,* than are the exponents of the other natural sciences in defining certain of their fundamental concepts.

Nature has not affixed a poison label to any particular substance or class of substances. The pharmacist does that. I have met intelligent people who actually believe that once a poison always a poison, and that it continues to exert its noxious power in some degree to the last molecule. If ten milligrams of nitrate of strychnine be dissolved in five hundred cubic centimeters of sterilized physiological saline solution, each cubic centimeter will contain 0.02 mg of the strychnine salt, but no one in the world could demonstrate either a harmful or a beneficial action after the injection of a half or one cubic centimeter of this solution underneath a person's skin or when so small a quantity as this is taken by mouth. We can, however, still detect the bitter taste of this highly diluted strychnine solution if we hold a cubic centimeter of it in the mouth for a few seconds, and if a wine-glassful were swallowed a mild stimulation of the digestive apparatus might or might not occur. The experience of physicians throughout the ages has convinced them that even the most deadly of poisons are entirely innocuous when given in certain minimal quantities. Scientists have arrived at the same conclusion on the basis of their experimental work. To be quite accurate, however, we can only say that neither a harmful nor a beneficial influence can be detected after such minimal doses by *any methods known to us at present.*

There is, however, another fact of fundamental importance for everything that is endowed with life, whether it be a plant or an animal or something that lies somewhere between the two. This fact may be expressed as follows: The harmful effects of a large dose of a drug or a poison do not fall off *pari passu* with the diminution in dose. The law of concomitant variation in respect to the two variables does not hold for the living cell. On the contrary, with the diminishing dose there may occur a turn-about in the action of the drug with the appearance of a highly beneficial action, one indeed that is indispensable for the continuance and maintenance of health, as is the case when we pass from the toxic dose of a hormone to its therapeutic dose. Examples of this beneficial action are seen daily in medical practise. Many powerfully acting drugs, to which the popular designation of poison is entirely applicable, such as strychnine, quinine, the digitalis glucosides, certain arsenicals, insulin, parathyroid extracts, the vitamins, and a long list of other drugs illustrate this principle when their dosage is restricted to a certain amount. This fact holds also for other agents of our environment that may be very harmful in their action when they come in contact with our tissues in too high a concentration. Sunlight and other forms of radiation are instances in point. In ordinary concentrations sunlight is beneficial, but it is deadly in its effect on many organisms when they are exposed to it for too long a time. Its scorching action on the skin of adults at high altitudes and in the tropics is well known, and it is also well known that very young children have died as a result of exposure for too long a time to the burning rays of the noonday sun without having been previously inured to its action.

POISONS IN OUR BODIES

An excellent illustration of our principle that toxic substances may be highly beneficial and even indispensable to life is furnished by certain poisons that are produced in our own bodies and circulate in our blood, at a concentration below the toxic level. Many will be surprised to learn that we ourselves are walking drug shops, and that an experienced chemist or pharmacologist would have no difficulty in preparing arrow poisons from some of our own organs that would have delighted the heart of primitive man. Let me name only a few of these autogenous poisons that serve not only to maintain our normal state of health but are also indispensable for the alleviation or removal of the symptoms of grave metabolic disorders—insulin, a hormone manufactured in certain cells of the pancreas, is one of them. It is known to all of you that when the concentration of this hormone in the blood falls below a certain level for any length of time, a serious disease known as diabetes mellitus inevitably appears. Our bodies probably require for the maintenance of health that the pancreas should produce and pass into the blood during each 24 hours about eight milligrams of this substance, and when, as I have just said, this amount is no longer furnished by the pancreas, diabetes results. You are also well aware of the fact that the subcutaneous administration of insulin as manufactured from the pancreas of beeves causes an immediate and spectacular improvement in the diabetic patient. As long as the deficiency of insulin persists, the patient must have his daily injections of the insulin from animal sources. During the first years of this so-called replacement therapy, it was occasionally observed that children fell into convulsions after the administration of an overdose of insulin. This extraordinary effect is daily seen in the laboratories in which insulin is being standardized for medical practise by testing it out on rabbits that have been previously kept without food for 24 hours. After a certain dose these animals fall into the most violent epileptiform convulsions, which generally end fatally if nothing is done, but which can be immediately and entirely dispelled by the intravenous injection of a little glucose. After the injection of this antidote the animal is immediately restored to perfect health. A similar treatment was applied to children that had been given too much of the drug. It is the function of this hormone to supervise and control, so to speak, the metabolism of carbohydrates in our tissues, and it is especially toxic in overdose for those animals or human beings the sugar content of whose blood happens to be low at the time of its administration for curative purposes. No experimentalist can doubt that an intravenous injection of 20 or 30 mgm of this hormone would suffice to kill a person of average weight who has gone without food for a couple of days. It is well known to physicians that under certain circumstances, as when a tumerous growth invades the hormone-producing organ, or even without this cause, an excessive amount of the hormone is produced and distributed in the body. In such instances serious impairment of health and death may occur. Fortunately, indeed, we are not often poisoned in this manner. In one recently reported instance a year-old child had repeated epileptiform convulsions, with retarded mental development and only about half of the normal amount of sugar in the blood, in consequence of an overproduction of insulin in its pancreas. Removal of a large part of the overactive pancreas caused the child's condition to return to the normal state. Cases of this nature have also been seen in adults, and here also an operative procedure was followed in some instances by an improvement in health. Conditions of this type, in which the causative agent is produced in insufficient amount or in excess in our own bodies, are spoken of as diseases of endogenous origin. Another, and one of the most striking instances of overproduction of a hormone, is seen when the very small parathyroid glands, four or more in number, which lie close to the thyroid gland in the neck or are embedded in it, are stimulated for one reason or another to produce their hormone in excessive amounts. Calcium is then removed from the bones to such a degree that they can no longer bear the weight of the body. The individual becomes bedridden, his muscles atrophy, other consequences follow, and he dies unless he can be rescued by the removal of one or more of these very small but diseased glands. There are still other toxic hormones, some of which circulate in the body in much smaller concentration than insulin. Among them is adrenalin, or the epinephrin of our pharmacopœia. An intravenous injection of this much used and therapeutically valuable drug is fatal to animals and human beings in doses that are not so very large and furnish definite proof of its inherent toxicity. Unfortunately, also, a number of deaths have occurred from its unwise use or from overdosage. Such accidents appear to be inevitable now and then in the use of drugs in general. As I have said, this is one of the hormones, as distinguished from insulin, of which the body appears to need under normal conditions only a very small amount in each unit of time. Its concentration in the blood, which, by the way, is sufficient for the body's ordinary needs, is minute and is represented by the astonishingly small number of 10^{-8}. It is endowed with extraordinary ability to constrict tiny blood vessels and is of the greatest service in medicine for this reason. And those who suffer from bronchial asthma obtain almost instantaneous relief from their spasmodic labored breathing after subcutaneous administration of a small amount of the hormone. But even in these patients toxic effects have been noted after a very prolonged use of the drug in too large a dose. Death has occurred from too rapid intravenous injection of one or more milligrams in the case of persons suffering from one of the thyroid diseases, and it is estimated that 10 mgm, or about one sixth of a grain, when intravenously injected, would kill a human being of average weight. I need not multiply instances of the deadly effects of excessive amounts of these peculiar principles that are so indispensable to the maintenance of health when they circulate in the body in an appropriate concentration.

It is not otherwise with the vitamins, which may be called hormones of plant origin and which are equally indispensable to the maintenance of health. One of these, irradiated ergosterol, or vitamin D, has been shown to induce very marked pathological and chemical alterations in the tissues of experimental animals, which finally lead to the death of the animals after too prolonged a medication with this principle, and there is already a considerable literature on the harmful effects of overdosage or of too prolonged an administration of this vitamin D to very young children. Fortunately, in most of these instances, the harmful symptoms disappeared after the vitamin was withdrawn. It would appear that with this drug what is called in medicine, the *dosis therapeutica* soon passes into the *dosis toxica.* Very recently a pathological state called *hypervitaminosis A* has been described as occurring in young rats that have received excessive doses of vitamin A. The disease is characterized by a faulty nutrition of the skin, inflammation of the eyes, spastic contractures of the extremities and cessation of growth, all of which pathological alterations may lead to the death of the animal. Early discontinuance of the overdosage is followed by disappearance of these symptoms and resumption of growth. It is thought that this disease is not likely to occur in human beings, as they would probably not receive such very large doses of the vitamins as were given to rats.

I have spoken to you of hormones and vitamins to show how difficult it is to define the word "poison." From the wider biological view we should not think of poisons as being inherently more malevolent than any of the other agents or influences of our environment to which we are constantly exposed. I incline to the belief that no living cell exists whose contents or metabolites are not toxic to some other living cell; in other words, all cells are in reality cryptotoxic systems.

WHAT IS DISEASE?

Death hath a thousand doors to let out life, . . .—*Massinger: A Very Woman.*

The late Sir Clifford Allbutt, the distinguished regius professor of medicine of the University of Cambridge, has said, "Disease is the correlative of health and is incapable of a more penetrating definition." So also we find it difficult to define health in a concise sentence or two. People speak of one as being in good health, or in bad health, or that he enjoys only a moderate degree of health. Statistical determinations are not available, as far as I know, that would furnish us with a statement of what might be called a "normal state of health" for various periods of life. It is evident that there must be degrees of disease, that vary from one that is not determinable by any of our present methods of diagnosis to one that is plainly recognizable as such a departure from the normal that we can characterize it as disease. The great Claude Bernard pithily remarked: "The healthy are really invalids unaware of their illness."—(Garrison). Disease and health, then, are correlatives not clearly distinguishable from each other at certain stages. Everything that lives is constantly menaced by one external agent or another and is therefore subject to disease in varying degree, according to circumstances. The botanist, zoologist and other biologists here present will bear me out in this statement. Plant pathologists and immunologists have shown how great is the number of bacterial, virus, fungoid, algal and other infections of plants, and that in their reaction to disease plants behave in a manner not fundamentally distinct from that seen in animals. There is an essential unity in living things in all their innumerable and varied forms. The potentialities of life are illimitable in kind and degree in respect to its chemical, physical and architectural capacities.

Striking examples of the manner in which the protozoa and other lower forms of animal and plant life react to invasion by bacteria and other injurious agents are found in scientific writings before the middle of the last century. Metchnikoff, who was himself a student of the infectious diseases of the protozoa, as well as those of man, has expressed the opinion that the causes of infectious diseases might have been disclosed before the 70's and 80's of the last century, if students in that field of science had paid more attention to the comparative physiology and pathology of the 1830's.

We may now take up the main thesis of this address, namely, that innumerable chemical substances in our environment and, to a lesser extent, abnormal products in our own bodies are the direct inciting causes of a very large number of diseases. Without attempting to give an estimate of the number of such chemical agents, we may say that many of the derivatives of the constituents of the earth's crust, a great number of chemical principles of plant and animal origin, a large percentage of the hundred thousand and more synthetic products of the chemist's skill, such as the so-called "war gases" and those that are employed in our industries, are all capable of inducing serious diseases in man and his domestic animals and, within limitations, in the various forms of plant life on which he depends for his existence. The number of such active chemical agents, to which we must add all our drugs, is very large and runs far up into the thousands.

Man has never given up the search for substances that would either cure or alleviate his ailments, and this belief has been fully justified in the course of the ages. By trial and error and by planned experimentation in more recent times valuable remedies of preventive or curative character have been discovered. From early times also and in every corner of the globe man has sought for and found so-called "stimulants"—hypnotics, inebriants, mental sedatives and hallucinating substances—that affect his psychical states. Some of these, as opium, the coca leaf, the seeds and other parts of the Solanaceae, for example, have given us sedative and other principles of the highest value in medicine. Among western nations we find beer, wines and other alcoholics, coffee, tea and tobacco in daily use as "stimulants," and people in general do not speak of them as poisons, and very properly so, when they are used in moderation, with due regard to age, state of health and other factors.

For more than a century medical scientists and biologists have occupied themselves with the action of chemical substances, to use a most inclusive term, on man and other forms of animal life and also on various kinds of plant life. The effects produced in living cells vary from barely perceptible functional or physiological and micro-structural alterations to structural alterations of such character and degree that life can no longer persist. I have long held the opinion that every reversible functional change in a cell or cell state is accompanied by a reversible, if only microphysical, alteration of structure which, in many instances, as in the autonomic nervous system, for example, can not be detected by present-day methods.

The word *reversible* is not here used in the sense of the physicist when he speaks of a *reversible process*, but only to designate a departure from the normal state of an organ where *restitutio ad integrum* finally occurs. But even in physiological and structural restitutions a price has to be paid, but this can be done because of the peculiarly favorable mechanisms involved and because the energy needed for the restitution can be supplied as needed by other structures of the body. Extreme departures from the normal can not be too often induced at short intervals without final damage to the system in which they occur.

Scientists place great emphasis on the fact that living mechanisms are endowed with the capacity to *retard* the degradation of energy that occurs in other natural processes. This retardation, as is well known, is seen at its best in the plant world. We should not, however, regard the storage of potential energy by plants and the delayed increase in entropy during their span of life as something that sharply and uniquely differentiates them from non-living systems. The physicist, C. E. Guye, of Geneva, has pointed out in his philosophical essays on physico-chemical evolution that in the system, ocean-water-vapor-atmosphere-mountain-ocean, we have, at the expense of solar energy, an arrangement in which there also occurs a retardation in the increase of entropy. The water evaporated from the ocean rises in the air, descends to mountain tops, gives rise to water courses that do mechanical work in eroding their beds and in other ways, and in due time the cycle is completed with a marked retardation of the degradation of energy. "In this way evaporation struggles against an immediate degradation of energy just like plant organisms . . . it would be wrong to attribute to the vital processes an exclusive monopoly of the struggle, if it is desired to speak of the striving against the degradation of energy."

Two great lines of investigation are always to be borne in mind in these studies of the interaction, or interplay of actions, between the agent studied and living cells. What changes have taken place in the chemical structure of the agent during its sojourn in the living thing? A very large number of substances have been studied from this point of view, and such studies come under the heading "fate of the substance in the organism." The ability of living systems of all kinds to effect the most varied and profound chemical alterations in substances that are not found in their own cells—substances that are new and strange to them, so to speak—is most extraordinary. The discoveries in this branch of pharmacology to which many specialists have devoted years of research have greatly enlarged our knowledge of the chemical mechanisms here concerned. Many agents penetrate deeply into the citadel of life, and what life does to them in a chemical way is all in the day's work and differs, as a rule, in quantitative fashion only from the usual routine of metabolism. However, there are many instances when the living organism forms, in response to the appropriate agent, an apparently entirely new substance, which it has never before produced. Substances of this class have become of the greatest theoretical and therapeutical importance within the lifetime of the seniors among us, and are named antitoxins or immune bodies. I regret that I have not time to discuss this interesting subject further in this brief address.

The other great field of research in the interplay of actions referred to is far more difficult and more complicated than is the study of the fate of a chemical substance in the organism. It occupies itself with the functional and structural alterations induced by chemical agents taken in from the environment or formed in various cells of the organism itself. It would take me too far afield to say anything in respect to these numerous and varied functional alterations, but I shall, however, permit myself to say a few words in regard to the structural changes produced by certain doses of our chemical agents acting over a shorter or a longer period of time. Here I shall not take into consideration highly corrosive agents, such as strong acids, alkalis and other substances of inorganic nature, but will confine my remarks solely to those agents that belong to organic chemistry. Substances of this class, as I said earlier in this lecture, are the direct or proximate cause of many diseases.

A few examples only of diseases of chemical origin that may cause profound structural alterations in various tissues of the body can be cited here. Among these are the gangrenous and convulsive types of ergot poisoning, which, from the early middle ages to our own time, have destroyed thousands of lives or have permanently maimed an even larger number of people; the many forms of forage disease that so often destroy cattle, horses and sheep, and the infectious diseases of these and other domestic animals, in so far as the causative agent of these diseases is a definite chemical principle. Other examples of chemically induced disease are found among those produced in man by the numerous varieties of pathogenic microorganisms. Of the many diseases due to this large class of agents I can take into account here only such diseases of man as are caused by the bacillary forms. Many bacteriologists and pathologists now incline to the belief that, in the greater number of such infections, chemical agents play the dominant rôle in the observed symptoms and in the cellular lesions that finally occur. They believe that there are excellent reasons, based on both experimental and clinical observations, for believing that toxins are elaborated during the course of all bacterial infections, even though the exact origin and nature of these toxins is not always known. It has been demonstrated, however, that in some of the infectious diseases of this class, such as tetanus, diphtheria and botulism, the bacillus in each instance serves only to produce a toxin which is responsible for the chain of events. I shall give presently a brief account of some of our experiments with the toxin of tetanus; but I wish particularly to impress upon your minds the fact that when the pathologist studies the lesions that occur in human beings and animals as the result of the above-named and many other forms of chemically induced disease, he is confronted with the same evidences of direct injury to cells, particularly those of highly specialized function, as are encountered in diseases whose etiology is less definitely established.

It was remarked in a preceding part of my address that everything that lives is constantly menaced by one external agent or another and is therefore subject to disease. It was also shown that there are autogenous sources of disease whose primarily inciting causes or etiology are not always known. Disease in its reversible early stages can not be more clearly defined until we are better informed in respect to the many chemical and physical processes and the composition and function of the many microphysical structures that are concerned with the maintenance of the ever-varying "normal state" of cells or cell states. When disease reaches that stage where, in one or more organs of the body, inclusive of the entire nervous system, functional or structural deviations from the condition called health are recognizable by the clinician and the pathologist, and especially when death ensues, we are all too ready to regard disease from our human point of view as something that a kinder nature might have ordered otherwise. In the wider biological conception disease is no more and no less malevolent or purposeful than any other of the fundamental processes or characteristics of life. Whether it has a "survival value" in the philosophy of evolution I can not say. Old age is our last disease.

I have attempted to give you in a very general but inadequate way some conception of the very large number of poisons of organic and inorganic origin that are capable of inducing disease. Only a very few of the many diseases whose cause is definitely assignable to agents of this character could be named in our brief summary. I am far from asserting that all the departures from the normal state that are due to poisons can always be differentiated from each other in all their stages as separate clinical entities. In the early stages of poisoning, as also in the later chronic period and especially when the patients are entirely unaware of the inciting cause of their illness, the physician is limited to the study of the complexes of symptoms, called syndromes, that may vary from the organic or physical to the psychopathic, or a combination of these types, and he may be quite unable to say from the evidence at hand what poison has caused the illness or, in fact, that it is due to any poison. When, however, the symptom-complexes include one or more elements either of a functional or structural type, or a combination of the two, that are uniquely characteristic of the action of a well-known poison a more complete diagnosis can be made. In the great majority of instances of chemically induced disease the fact is easily established that one or more poisons are involved. We have also seen that, in many of the clearly recognizable infectious diseases, the efficient agent that produces the morbid state is a poison generated by the infective microorganism. We have furthermore gone so far as to believe that there exists in organized nature not a single living cell whose contents or metabolites are not toxic for some other living thing, or may not on occasion be injurious to the cell itself. I can not but believe that the subject-matter of my address, with whose central thought many of you are entirely familiar, has become, in our day, of great significance for every department of medicine as well as for many aspects of biological research.

(To be concluded)

OBITUARY

ALFRED FABIAN HESS[1]

THE Harvey Society learns with profound regret of the death of the distinguished president of the society, Alfred Fabian Hess. In the lengthening list of its presidents, none has been more devoted to its interests, none has sought more earnestly to maintain its fame, none has devoted more energy to the realization of its purposes. He exhibited his sympathetic attitude by consenting to return to a former custom of the society to occupy his office for two successive terms. In the second of these, unexpectedly and in the full tide of his powers, his grievous loss is sustained. He has been a member since 1911 and has himself been one of its lecturers (January 15, 1921).

Dr. Hess has numerous claims to the high regard of his professional colleagues. Beyond the custom of most men, his life was given solely to the interests of his calling. He knew no divided allegiance; the whole of his thought and energy exhibited extraordinary singleness of purpose. A life of contented leisure, so easily within his choice, he exchanged by

[1] Minutes adopted by the Harvey Society at a meeting held on December 14. The committee appointed to draw up the minutes consisted of James W. Jobling, William H. Park and Alfred E. Cohn.