THE WISDOM OF THE BODY:

The Harveian Oration,

DELIVERED BEFORE

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BY

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"Who hath put wisdom in the inward parts? or who hath given understanding to the heart?"

MR. PRESIDENT AND FELLOWS OF THE COLLEGE,—We are met here to-day to celebrate our annual feast, founded by the immortal Harvey with the twofold purpose of promoting mutual love and affection among ourselves and of commemorating the famous men who, by their works, have benefited the College. This is our day of All Saints, when we canonize in our memory and record our indebtedness to not only those who have assisted our work by material gifts, not only those Fellows of the College who have been teachers and leaders of successive generations in the science and art of medicine, but also all those of any race or profession on whom the mantle of Harvey has fallen and who, following his injunction to our Fellows and Members, to "study out the secrets of nature by way of experiment," have enlarged the bounds of science and increased the powers of our art.

It is customary and right in this our annual oration to begin by calling to mind the work of the Founder himself, and especially the great discovery of the circulation of the blood, which represents the beginning and the foundation of all that we know in physiology and medicine. Harvey's treatise on the Motion of the Heart is throughout so modern in spirit, so akin in conception and treatment to records of research of the present day, that we may easily fail to appreciate the stupendous advance in human physiology that it embodies, and to wonder that we have had to wait so long for the full fruition of Harvey's discovery. But it must be remembered that the ordered knowledge of the world around us, whether living or dead, which we call science, forms a connected whole, and though, as its line advances, a brilliant discovery may push one part of the line in advance of the rest, such an outpost must remain more or less in the air and incapable of further advance until the whole line has moved up to its support. We now know that many of the problems raised by Harvey, with the promise to himself and his readers of further consideration at a later date, depended for their solution on the progress of other branches of human knowledge. And that is why to-day in our minds and memories we are reckoning among our saints not only the distinguished line of Fellows of the College, but also men such as Boyle, Mayow, Hales, Cavendish, Lavoisier, Bernard, Pasteur, and a host of others, who were only in spirit our colleagues and most of whom were not even students of medicine. Indeed we might say that, during the two hundred years succeeding Harvey's work, the whole scientific world has been travailing in order that medicine might be born, and thus it is that our science has had to wait until our own days for the attainment of those ends which Harvey had in mind in his dream of the results of his discovery.

> "Finally, reflecting on every part of medicine, physiology, pathology, semeiotics, therapeutics, when I see how many questions can be answered, how many doubts resolved, how much obscurity illustrated, by the truth we have declared, the light we have made to shine, I see a field of such vast extent in which I might proceed so far, and expatiate so widely, that this my tractate would not only swell out into a volume, which was beyond my purpose, but my whole life, perchance, would not suffice for its completion."

In the new light shed by his great discovery he probably failed to appreciate the extent of the dark shadows cast by the great clouds of ignorance which had still to be dispersed. But the advance of knowledge, though slow at first, has progressed with ever-accelerating speed. When I compare our present knowledge of the workings of the body, and our powers of interfering with and of controlling those workings for the benefit of humanity, with the ignorance and despairing impotence of my student days, I feel that I have had the good fortune to see the sun rise on a darkened world, and that the life of my contemporaries has coincided not with a renaissance but with a new birth of man's powers over his environment and his destinies unparalleled in the whole history of mankind.

Not but there is still much to be learned; the ocean of the unknown still stretches far and wide in front of us. But for its exploration we have the light of day to guide us; we know the directions in which we would sail, and every day, by the co-operation of all branches of science, our means of conveyance are becoming more swift and sure. Only labour is required to extend almost without limit our understanding of the human body and our control of its fate.

HARVEY'S GREATEST GIFT TO THE WORLD.

The great gift which Harvey gave to us was, indeed, not his discovery of the circulation of the blood, but his method of formulating and solving a problem. For countless ages man had learned slowly and painfully by experience. The more observant among them had from time to time noticed certain recurring sequences in the infinity of fortuitous phenomena continually presented to them, and as a result mankind had by slow degrees improved his lot and his powers over the forces of Nature. But how slow was the rate of progress! There is no evidence that the age-long duration of the period during which man had sticks and stones to defend himself and to procure his food, the long delay in the discovery of the working of bronze and later of iron, are to be ascribed to any mental inferiority of those men as compared with those of the present day. What was lacking was the method. Mankind had advanced by fits and starts as the result of discoveries which were probably accidental, and these discoveries spread gradually along the lines of commerce and culture by imitation and the implicit copying of ritual. But with the realization of the possibilities of the method of experiment—that is, the creation and repetition of a chosen experience under controlled conditions, such as we find in its full development in Harvey's treatise—man came almost at a bound into the full use of the brain capacities which he had evolved during a long struggle for existence against the warring forces of an inclement nature.

It is true that the ultimate goal and the biological justification of science is the improvement of human conditions; but for the full and untrammelled exploitation of the advantages of the experimental method it is essential that mere material advance shall not be the target of our ambition. This great secret of success in science was fully realized by Harvey, when he enjoined us to search out by experiment not the causes and cure of disease, but the secrets of Nature. This implies that we are to give free scope to the spirit of curiosity, with some measure of which every man, at any rate in his youth, is endowed. We ourselves are but part of the order of Nature, and all knowledge therefore is contributory to the science of medicine.

THE WORK OF THE HEART.

Since this was the spirit that actuated Harvey, it is evident that his whole life would not have sufficed for the completion of the work opened up to him by his great discovery. Under its light he could see many summits to be attained and the beginning of paths which must be followed. But long and arduous search was necessary before these paths could be traced out in their entirety. Thus the determination of the output of blood from the heart and the cause of its variations evidently seemed to Harvey a problem whose solution was ready to hand. He says:

> "The actual quantity of blood expelled at each stroke of the heart, and the circumstances under which it is either greater or less than ordinary, I leave for particular determination afterwards from

numerous observations which I have made on the subject. Meantime, this much I know, and would here proclaim to all, that the blood is transfused at one time in larger, at another in smaller quantity; and that the circuit of the blood is accomplished now more rapidly, now more slowly, according to the temperament, age, etc., of the individual, to external and internal circumstances, to naturals and non-naturals—sleep, rest, food, exercise, affections of the mind, and the like."

But many years had to elapse before we could give a quantitative expression both to the amount of blood under normal conditions and to its variations, and explain the manner in which these variations are brought about. The Rev. Stephen Hales, second only to Harvey as an experimental physiologist, has only calculations based on measurement of the dead organ. The determination of the output in the living animal was first made in our own times, and it is only within the last ten years that methods have become available which reveal in man himself the quantity of blood leaving the heart in each unit of time, and therewith enable us to estimate the total work of this organ. Such methods have been devised by Krogh and by Haldane. If we accept the results of the former, we may say that in a normal man at rest each cavity of the heart expels about 4 litres a minute. During violent exercise, when, as we know, the requirements of the body for oxygen may be increased tenfold, this quantity rises to 24 or even to over 30 litres a minute. These figures convey only imperfectly the enormous rush of blood which is being effected by the heart under these conditions. An ordinary laboratory tap will deliver nothing like 30 litres a minute; to obtain this amount it is necessary to have recourse to a large tap such as that which is supplied to a bath. It means that the whole blood must pass through the heart and round the body every ten seconds and complete the circulation of the body six times in every minute. And it must be remembered that the heart is putting out this colossal amount of blood against an arterial pressure which is higher than normal and which may amount to 150 to 180 mm. Hg, as against the 100 to 110 mm. which is the ordinary systolic pressure in the arteries of a resting individual.

We see, therefore, that the heart has a marvellous power of adapting its work and its performance in accordance with the needs of the body as a whole, and is fully deserving of the feeling of respectful admiration which inspires Harvey to speak of it as "the sun of the microcosm," "the household divinity," "the foundation of life," "the source of all action."

Its Power of Adaptation.

To search out the intimate character of this power of adaptation is a problem almost as enthralling in interest as the demonstration of the circulation itself. It is easy to show that the increased output of blood from the heart during exercise is simply an expression of an increased inflow into this organ, the heart being so constituted that under normal conditions it will send on into the arteries all the blood that flows into it from the veins. Harvey probably had some inkling of this power when, in speaking of the action of the auricles, he ascribes to them the property of exciting a stronger contraction on the part of the ventricles, comparing the latter to the tennis player who can strike more forcibly and further if he takes the ball on the rebound.

In the intact animal a large number of processes, nervous as well as chemical, are involved in the increased action of the heart during muscular exercise. By the action of the central nervous system and of other physiological processes involved, the strain thrown on the heart is minimized, so that it can effect the increased work with the greatest possible economy of effort. But the intimate character of this power of adaptation is only fully displayed when we cut away these protective mechanisms which are normally shielding the last citadel of life, and study the reaction of this organ when it is entirely isolated from the central nervous system and is reduced to the condition of a muscular pump with valves, working rhythmically and steadily in virtue of its own automatic powers.

We can make a "heart-lung preparation" in which, the lungs being retained in connexion with the heart, the blood passing through this organ is kept properly aerated. The systemic circulation is, however, replaced by a system of elastic tubes passing to a venous reservoir, in which we can vary at will the inflow of blood into the heart, the arterial pressure (and therewith the resistance to the expulsion of blood from the left ventricle), and the temperature of the blood supplying the heart, while we can measure the pressures at any moment of time in all the cavities of the heart as well as the changes in volume of this organ. In such a preparation we find that, within very wide limits, the output of blood corresponds exactly to the inflow. Whatever is supplied to the heart on the venous side is expelled by it on the arterial side. And again, within very wide limits, whatever is the resistance to be overcome in the arteries, so long as we keep the inflow of blood constant, the output of blood by the left ventricle remains unaltered whether the pressure in the aorta be 40 or 200 mm. Hg.

We know now that the energy for all vital movements is derived immediately from the food, and in each tissue from the oxidation of the constituents of the tissue or of the blood circulating through it. It is possible in such an isolated heart to measure its respiratory exchanges and therewith the extent of the oxidative processes responsible for the energy of the heart's contraction. We then find that the amount of oxygen taken in by the heart and converted for the most part into carbonic acid is proportional to the amount of work that the heart is set to do. The isolated heart is like the whole man—the harder he works the greater are his respiratory exchanges. I am accustomed to compare the heart with an ideal motor car which, without action on the part of the driver, would automatically admit more petrol and air when the resistance to the movement of the car increases—as, for instance, in going uphill.

The Law of the Heart.

The heart has thus the power of automatically increasing the chemical changes and the energy evolved at each contraction in proportion to the mechanical demands made upon it, behaving in this way almost like a sentient and intelligent creature. But the cause of this power must lie in the muscular walls of the heart itself, and a study of the conditions under which it occurs and the concomitant changes in the heart has revealed the secret of its wonderful power. The solution is simple. We find that, in the isolated heart, every increased resistance to its contraction is associated with an increased diastolic volume of the cavity or cavities, which have to overcome the resistance. Putting the matter in another way, we may say that the larger the diastolic volume of a given heart, the greater is the force of the contraction which immediately ensues. The energy of contraction is therefore a function of the diastolic volume of the heart. Dilatation of this organ is not merely a pathological phenomenon, but is the means by which the heart achieves its purpose, and maintains an activity which varies with the needs of the organism for more or less blood.

In this relation we find also the secret of the power of compensation, such as occurs in cases of valvular disease and has been always a puzzle to pathologists. Injury, for instance, to an aortic valve, with the production of regurgitation, causes increased filling of the left ventricle at the following diastole, since this receives blood not only in the ordinary way from the pulmonary veins and left auricle but also by a reflux through the damaged valve. The dilatation invokes an immediate increase in the force of the contraction, so that within a few beats the left ventricle sends on into the aorta the total amount of blood flowing into it during the preceding diastole, and the aorta receives sufficient blood not only to supply the body, but to make up for the amount leaking back through the damaged valve. The same reasoning applies to the compensation which occurs for any valve lesion, whether it be of the nature of a leak or of a stenosis, increased filling or increased resistance; and in an otherwise healthy individual constant increase in work has as a secondary result increased growth and hypertrophy of the cardiac muscle, so as to make it fit to meet the abnormally increased demands throughout the life of the individual.

You will remember that Harvey insists on the essentially muscular nature of the heart. "It was not without good grounds," he says, "that Hippocrates in his book *De Corde* entitles it a muscle; as its action is the same, so is its function, namely, to contract and move something else." Increasing dilatation of the heart means increased length of its muscular fibres, so that we can express the law of the heart as a relation between length and energy—the longer the muscle fibre the greater the energy of its contraction. In this form we find that the law of the heart is that of all muscular tissue, whether voluntary or involuntary. The Swedish physiologist Blix showed many years ago that the energy evolved in the contraction of a frog's muscle was proportional to its initial length, and A. V. Hill has proved that this holds good for the heat production during activity, and therefore for the total chemical changes which are responsible for the contraction and recovery of the muscle. So that in searching after the cause of the heart's power of adaptation we are brought into the region of final causes, in which we associate function with structure, and see in muscular contraction the expression of molecular changes occurring at the surface of longitudinal fibrillae. Thus we bring together in one formula the sum total of our experiences with regard to the nature of excitation itself, development of mechanical energy, and the chemical, electrical, and heat changes which accompany muscular contraction. We are still far from a complete understanding of these matters, and still farther from any possibility of reconstructing a muscle fibre. But the path, so far as we can see along it, seems to lead to no impassable barrier, and to promise a complete description of the acts of excitation and contraction as molecular events occurring at surfaces.

The Limits of Adaptation.

Is there any limit to this power of adaptation? In skeletal muscle an increase in the length of the muscle fibres leads to an augmentation of the energy changes of contraction, succeeded later by a diminution as the muscle becomes overstretched. In the healthy mammalian heart the limits are set by the strength of the muscle fibres themselves. Freed from the pericardium, we find the heart goes on increasing the strength of its contraction with increasing dilatation until the muscle fibres are actually ruptured; and when the heart finally fails we find its substance beset with haemorrhages. In the body this overstrain of the heart is prevented by the tough fibrous sac of the pericardium. When the demand on the heart is so great that the heart dilates to the limits of the pericardium, any further dilatation and therefore increased strength of beat becomes impossible; the output therefore falls off, and in the whole animal this diminished output results in defective supply of blood to the muscles and brain, giving rise often to fainting and at any rate enforcing complete rest. Further activity of the animal becomes impossible, and the heart is automatically given less work to do, so that it can recover, unless the increased activity of the animal and of the heart is a necessary condition of the animal's continued survival, as in a fight to the death. In this case when the heart comes up against the pericardium the fight is finished and the animal succumbs. We find the same story in the terminal changes of heart disease, where the process of compensation which I have described above becomes insufficient. Here again enforced rest may give time and opportunity for re-establishment of a sufficient circulation; but with advance of the fundamental morbid condition, even complete rest becomes powerless to relieve the heart: the output falls off, the circulation is insufficient for the needs of the tissues, and we get all the secondary results of failure of compensation—suppression of urinary secretion, waterlogging of the body, and malnutrition of all its organs which usher in the fatal termination.

During the last few years great advances have been made in our knowledge of the causation of many of these morbid conditions, and this increased knowledge has, as always, enhanced our powers of dealing with such cases, of staying the course of the disease or delaying its fatal issue. It is interesting to note that these advances are the direct outcome of researches made with the sole object of elucidating the intimate nature of muscular contraction. In his book Harvey remarks: "Of these things we shall speak more opportunely when we come to speculate upon the final cause of this motion of the heart." Such speculation at that time would have been in vain. It seems probable that he anticipated finding the solution in the study of the generation of animals, but we know now that to penetrate more deeply into the final cause of the action either of skeletal muscles or of the heart requires a physical and chemical knowledge which even now we are only beginning to attain. I would remind you that the string galvanometer, the employment of which has thrown so much light on the essential nature of disturbances in the heart rhythm, was invented by Einthoven with a view to studying the electrical changes accompanying activity in any kind of tissue.

The Inherent Contractile Power of the Heart.

In dealing with the origin of the rhythmic power of the heart Harvey rightly ascribes it to the heart muscle itself, and brushes aside any suggestion that it is dependent on the nervous system, or the liver, or any other organ. His assurance on this point was due to his observation of the developing chick, in which the first sign of life was the pulsating spot of blood in the region where the heart was being formed. It is interesting to note that it is the same method—namely, the investigation of development—which has settled the question of the seat of the rhythmic power of the heart and has revealed to us the origin and course of the rhythmically recurring wave of contraction in the heart of man. By means of a technique, first devised by Harrison in the United States, it is possible to cultivate living tissues outside the body, in much the same way as we have learned to grow micro-organisms. Using great care to exclude infection, we are able to transfer to plasma or salt solution on a glass slide fragments of tissue which, being kept warm, live and multiply. From such a preparation further generations can be brought up, and in one such case a preparation of the muscle cells of the heart of a chick has been kept alive, growing and dividing, for twelve years, a time far beyond the natural span of the life of the fowl. Such a result proves that mortality is but an accident of the complexity of our living machine and not a necessary quality and fate of the tissues of which the body is composed. But during these twelve years the muscle cells have not ceased to contract rhythmically, showing that in their peculiar properties must be sought the origin of the rhythmic beat of the heart, thus finally disposing of the various views which have been held, according to which the origin of the heart beat was to be sought in the nervous ganglion cells and fibres present in different parts of this organ.

And it is by the embryological method—that is, by observing the processes of generation—that Keith and Flack were able to lay the anatomic foundations of our present knowledge of the origin and course of the contractile processes in the heart of the higher animals. In the developing heart, as in the lower vertebrates, the beat originates in that part of the contractile tube which later will form the sinus venosus. In the course of the changes undergone during development, Keith showed that this sinus tissue persisted at definite parts of the mature heart and could be distinguished under the microscope from the surrounding parts of the heart. This special sinus tissue was given the name of the sino-auricular node and the auriculo-ventricular node.

The Cardiac Cycle.

The brilliant experiments by our distinguished Fellow, Sir Thomas Lewis, have resulted in a complete knowledge of the part played by these nodes in the cycle of the heart's contraction. He has shown how the sino-auricular node is the pace-maker of the heart, how the contractile process originating here spreads through the auricular muscle to the auriculo-ventricular node, and then passes rapidly through the bundle of specialized muscular tissue, known as the A-V bundle, to all parts of both ventricles. We have in this bundle an interesting example of a muscular tissue differentiated to serve the propagation of excitation rather than for contraction, so that it closely resembles nerve in the manner of its function. To the same fine and careful experimenter we owe the explanation of one of the commonest conditions of the diseased heart —namely, auricular fibrillation or delirium, which is responsible for the irregular ventricular contractions, often leading rapidly to exhaustion and failure of the heart. It is remarkable that the clue to the explanation of this condition was first given by the observations of Romanes on the contractile tissue of jellyfish, which by its rhythmic pulsation propels these graceful animals through the sea-water. It was shown by Mayer for the jellyfish and by Mines for the frog's heart that it was possible to obtain a ring of contractile tissue in which a wave of contraction passed continuously round the ring, and the merit of Lewis's observations is the proof that delirium is of the same nature as this circus movement, so that the contractile wave continually progresses over the muscular tissue, exciting each part in turn but in a completely inco-ordinate fashion. It was long ago shown by Marey that the rhythmicity of the heart was bound up with the prolonged refractory period affecting the heart muscle after its contraction, during which period it was insusceptible to any form of excitation. Lewis has shown that the circus movements which are responsible for fibrillation are due to a disturbance in the normal relation between the rate of conduction of the excitatory process and the refractory period in the heart muscle. Thus instead of an orderly progression of impulses from one node to the next and so to the auriculo-ventricular bundle and ventricles, every individual fibre is contracting rhythmically but independently of what is happening in its surroundings.

The Central Nervous System and the Heart.

Time will not allow me to deal with the manner in which the heart, already so perfect as it would seem in its power of adaptation, is controlled by the central nervous system, so that the adaptation to changes in the environment and to the needs of the most distant parts of the body can be carried out with greater perfection and with the least possible drain on the energies of the heart muscle. Among such adaptations must be included those attendant on the emotions—"every affection of the mind that is attended by either pain or pleasure is the cause of an agitation whose influence extends to the heart." But indeed, Harvey's treatise, being the foundation of modern physiology, might serve as a text to a commentary, from which but little of our present-day knowledge of the organs of the body could properly be omitted.

I should like, however, to be permitted to allude to another chapter in modern physiology, which can be said to have grown out of Harvey's discovery of the circulation of the blood, and which is becoming every day of increasing importance.

HORMONES.

In the dedication to his work Harvey compares the heart to the sovereign king, and throughout he continually recurs to what we should now describe as the "integrative function" of this organ. In virtue of the circulation which it maintains, all parts of the body are bathed in a common medium from which each cell can pick up whatever it requires for its needs, while giving off in return the products of its activity. In this way each cell works for all others—the lungs supply every part with oxygen and turn out the carbon dioxide which they produce, the alimentary canal digests and absorbs for all, while the kidneys are the common means of excretion of the soluble waste products of the body. Changes in any one organ may therefore affect the nutrition and function of all other organs, which are thus all members one of another. But, in addition to enabling this community of goods, the circulation affords opportunity for a more private intercourse between two or at any rate a limited number of distant organs.

It is now eighteen years since I drew the attention of this College to the chemical messengers or hormones which are employed by the body for this purpose. As an illustration of the method by which they work, I adduced the example of carbonic acid gas, which is the product of all cellular activity and at the same time has a specific excitatory effect on the respiratory centre, so that the respiratory movements keep pace with the needs of the whole body for oxygen. The typical hormone, however, is a drug-like body of definite chemical composition, which in a few cases is actually known, so that the substance has been synthesized outside the body. It is more or less diffusible and may even withstand without alteration the temperature of boiling water. It is generally easily oxidizable in a neutral or alkaline medium, so that after its production it does not remain long in the blood; it delivers its message and is then destroyed. Each specific hormone is manufactured by a group of cells and turned into the blood, in which it travels to all parts of the body, but excites definite reactions in one or a limited number of distant organs. The production and action of these substances are continually going on in the normal animal. They are necessary to health and their production in excess or in deficit give rise to disease and maybe to death. Typical of these substances is secretin, a substance produced in the epithelial cells lining the upper part of the small intestine when these come in contact with weak acid, so that it is produced in normal circumstances by the passage of the acid chyme from the stomach into the duodenum. Directly it is produced it is absorbed into the blood and travels round to the pancreas, to the liver, and to the intestinal glands, in all of which it excites secretion. By means of this chemical reflex the arrival of the products of gastric digestion in the small intestine evokes within a couple of minutes the secretion of the three juices whose co-operation is necessary for completing the work of digestion and solution of the food already begun in the stomach. It is probable that this mechanism is but one of a whole chain of chemical reflexes responsible for the orderly progression of the various stages in the digestion of food.

These hormones may apparently be formed by any kind of tissue. In many cases a gland which has, in the evolutionary history of the race, poured its secretion by a duct into the alimentary canal or on to the exterior, loses its duct and becomes a ductless gland, the secretion being now transferred either immediately or through the lymphatics into the blood stream. In either case these chemical messengers may be formed from masses of cells which have at no time had a glandular structure and may be modified nervous tissue, germinal tissue, or some part of the mesoblast.

The Thyroid.

As a type of the ductless gland derived from one with an external secretion the most familiar example is the thyroid. The physiological action of its internal secretion and the morbid results of its excess or deficiency, affecting tissue growth and development, metabolism and mentality, are familiar to all. In recent years the active substance has been actually isolated, and its constitution determined, by Kendal, who has shown that it is an iodine derivative of an amino-acid, tryptophane. It seems almost a fairy tale that such widespread results, affecting every aspect of a man's life, should be conditioned by the presence or absence in the body of infinitesimal quantities of a substance which by its formula does not seem to stand out from the thousands of other substances with which organic chemistry has made us familiar.

The Sexual Hormones.

But although we do not yet know their constitution, the chemical messengers associated with the reproductive organs are possibly even more marvellous in the influence they exert on the different parts and functions of the body. The effects of castration have been the subject of observation almost from the beginnings of civilization, but it is only during the last few years that definite proof has been brought forward showing that these effects are due to the removal of chemical messengers normally produced in the testes. The whole differentiation of sex, and the formation of secondary sexual characters, are determined by the circulation in the blood of chemical substances produced either in the germ cells themselves or, as seems more probable, in the interstitial cells of the testis and ovary, which themselves are probably derived from the germ cells of the embryo. Thus it is possible by operating at an early age to transfer male into female and vice versa. Removal of the ovaries from a hen causes the assumption of male plumage; the removal from a young cock of the testes and their replacement by the implantation of ovaries cause a disappearance of the comb and the assumption of the plumage of the hen. Each animal as concerns its general build and colour has a neutral form which, as has been shown by Pézard, results from the extirpation of either testes or ovaries. In fowls the neutral form, as judged by the plumage, approximates the male, whereas in sheep the neutral form resembles the female. There is no question that, by the implantation of ovaries or testes into the foetus at a sufficiently early age, one could produce the whole development of the internal and external genitalia corresponding to the sex of the gland implanted. It is worthy of note that these sex characters affect also the mentality and the reactions of the animal, although they are quite independent of any nervous connexions. Here, as in the case of the thyroid, the functions of the central nervous system in their highest manifestations depend on the circulation in the blood of chemical substances or hormones. The wonderful development that takes place in the female after conception to fit her to nourish the foetus as well as the young child, is also due to hormones, produced in some cases perhaps in the ovaries, in other cases in the product of conception itself.

The Hormone of the Adrenal Medulla.

We owe to Schafer the knowledge of the internal secretion of the medulla of the suprarenal bodies. As Cannon has pointed out, this secretion is poured into the blood during conditions of stress, anger, or fear, and acts as a potent reinforcement to the energies of the body. It increases the tone of the blood vessels, as well as the power of the heart's contraction, while it mobilizes the sugar bound up in the liver, so that the muscles may be supplied with the most readily available source of energy in the struggle to which these emotional states are the essential precursors or concomitants.

The Pituitary Hormones.

Wonderful, too, is the influence exerted by the secretions of the pituitary body. This tiny organ, which was formerly imagined to furnish the mucus to the nasal cavities, consists of two lobes which have different internal secretions. That produced by the anterior lobe seems to influence growth, excess producing gigantism or acromegaly, while deficiency leads to retarded growth and infantilism. The posterior lobe, which in aspect would seem but a small collection of neuroglia, nevertheless forms one or more substances which, circulating in the blood, have the most diverse influences on various parts of the body. They cause contraction of the uterus and of the blood vessels (these are possibly two distinct substances); they may increase or diminish the flow of urine; they affect the excretion of chlorides by the kidney; and, according to Krogh, their constant presence in the blood is essential for maintaining the normal tone of the capillaries. In the frog the post-pituitary hormone is responsible for the protective adaptation of the colour of the skin to the environment, an adaptation which is effected by retraction or expansion of the pigment cells or chromatophores of the skin; and if we may accept Kammerer's conclusions, the pituitary hormone which is poured into the blood for this purpose affects the germ cells themselves, so that individuals born of parents that have lived in light or dark surroundings are correspondingly light or dark—a real transmission of acquired peculiarities, effected not by the gemmules of Darwin, but by the influence of a soluble diffusible hormone on the germ plasm.

Integration of Functions.

In the multiplicity and diversity of the physiological effects produced by these various chemical messengers one is apt to lose sight of the fact that we are here investigating one of the fundamental means for the integration of the functions of the body. These are not merely interesting facts which form a pretty story, but they are pregnant of possibilities for our control of the processes of the body and therewith for our mastery of disease. Already medical science can boast of notable achievements in this direction. The conversion of a stunted, pot-bellied, slavering cretin into a pretty attractive child by the administration of thyroid, and the restoration of normal health and personality to a sufferer from Graves's disease by the removal of the excess of thyroid gland, must always impress us as almost miraculous. In the same way we may cure or control for the time being diabetes insipidus by the injection of the watery extract of the posterior lobe of the pituitary body. The latest achievement in this direction is the preparation by Banting and Best in Canada of the active principle normally formed in the islets of the pancreas, and the proof that the diabetic condition in its severest forms can be relieved by its subcutaneous administration.

The Therapeutics of Hormones.

In my Croonian Lectures I asserted that if a mutual control of the different functions of the body be largely determined by the production of definite chemical substances in the body, the discovery of the nature of these substances will enable us to interpose at any desired phase in these functions, and so to acquire an absolute control over the workings of the human body. I think I may claim that, in the eighteen years that have since elapsed, we have made considerable progress towards the realization of this power of control which is the goal of medical science. But there still remains much to be done and many difficulties to be unravelled, and it may be worth our while to consider along what lines researches to this end must be directed. There are no doubt many hormonic relationships of which at present we are unaware, since every year research adds to their number. But assuming we know that such and such an organ produces an internal secretion which is necessary for the normal carrying on of a given function or functions, we may desire to diminish or enhance its effects in a patient or to replace it when it seems to be entirely lacking. There seem to be three possible methods by which we medical men can interpose our art in the hormonic workings of the body.

I.

In the first place we may find what is the effective stimulus to the production of the hormone, and, by supplying this, increase its production by the responsible cells. For instance, we know that by the administration of acid, or at any rate by increasing the passage of weak acid from the stomach to the duodenum, we can enhance the production of secretin and so of pancreatic juice and the other juices. Probably, therefore, when we give dilute acids to assist gastric digestion, we are setting into motion the whole chain of reflex processes in the alimentary canal, and the chief value of our administration may be its effect on the pancreas. But in a large number of cases we do not yet know what is the effective stimulus to the production of these internal secretions. In the case of the adrenals we know the secretion can be augmented through the central nervous system and the splanchnic nerve under the influence of emotions or of lack of oxygen, but we have no knowledge of the factors determining the production of the pituitary hormones or of insulin by the islets of Langerhans, and this condition of ignorance extends to most of the other ductless glands.

In some cases deficient production of a hormone may be due to the absence from the food and drink of some necessary constituent. Thus iodine is essential to the formation of the specific secretion of the thyroid gland (iodothyrin).

If iodine be entirely absent from the drinking water and the soil, so that it is not contained even in minute quantities in the vegetable food grown in the district, the thyroid undergoes hyperplasia—in a vain endeavour to make bricks without straw, to produce its proper hormone without iodine. This seems to be the cause of the great prevalence of simple goitre in certain districts—especially in Switzerland and in parts of the United States. It has been shown that goitre can be practically eliminated from these districts by the occasional administration of small doses of iodine or iodides (Marine, Lenhart, Kimbull and Rogoff). These results were communicated in 1917 to Dr. Klinger of Zürich, and as a result of his experience the Swiss Goitre Commission has recommended the adoption of this method of goitre prevention as a public health measure throughout the entire State. Already great progress has been made in the abolition of this disease from the country. Thus the incidence of goitre among all the school children of the canton of St. Gallen has been reduced from 87.6 per cent. in January, 1919, to 13.1 per cent. in January, 1922.

II.

Where a disordered condition is due to diminished production of some specific hormone we may extract the hormone from the corresponding gland or tissue in animals. It is characteristic of these hormones that, so far as we know, they are identical throughout all the classes of vertebrates, and it is possible that they may be found far back in the invertebrate world. This method is easy when, as in the case of the thyroid, the active principle is stored up in the gland and is unaltered by the processes of digestion, so that we can obtain all the curative effects of the hormone if we administer dried thyroid by the mouth. We have no evidence that any other of the hormones with which we are acquainted partake of this resistance to digestion, so that to produce their specific effects they have to be introduced by subcutaneous injection—a great drawback when the administration has to provide for the constant presence of a small concentration of the hormone in the blood and tissues. In the case of insulin, for instance, it seems necessary to repeat the injection every twelve hours to obtain any continuity of action, and the same thing probably applies to the pituitary extract, while in the case of the genital hormones no reliable effect has been obtained except by the actual implantation of the organ from an animal of the same family.* We may, however, look forward to the day when the chemical constitution of all these hormones will be known, and when it may be possible to synthesize them in any desired quantity. We may then be able to overcome the inconvenience of subcutaneous injection by giving relatively colossal doses by the mouth, or we may be able to modify their constitution to a slight extent so as to render them immune to the action of digesting fluids without affecting their specific action on the functions of the body.

III.

The ideal, but not, I venture to assert, the unattainable, method will be to control, by promotion or suppression, the growth of the cells themselves whose function it is to form these specific hormones. Though this method seems at present far from realization the first steps in this direction have already been taken. It must be remembered that the power of controlling growth of cells involves the solution of the problem of cancer. Here the experiments on the growth of normal cells outside the body have shown that they can be stimulated to vie with cancer cells in the rate of their growth, or can be inhibited altogether according to the nature of the chemical substances with which they are supplied. And we know that the growth of certain cells, such as those of the mammary gland or of the uterus, is excited by specific chemical substances produced in the ovary or foetus; and we may be able to find specific substances or conditions for any tissue of the body which may excite growth which is retarded, or diminish growth when this is in excess. It may be that in some cases purely mechanical interference will suffice. Thus in experiments by Steinach and others it has been found that ligature of the vas deferens close to the testis, while causing atrophy of the seminiferous cells, brings about overgrowth of the interstitial cells, which, as we have seen, are chiefly responsible for the hormones determining the secondary sexual characters. Among these secondary sexual characters must be classed the whole of a man's energies. Virility does not mean simply the power of propagation, but connotes the whole part played by a man in his work within the community. As a result of this hypertrophy these authors claim to have produced an actual rejuvenation in man, and thus to have warded off for a time senility with its mental and corporeal manifestations. Further experiments and a longer period of observation are necessary before we can accept these results without reserve, but it must be owned that they are perfectly reasonable and follow, as a logical sequence, many years' observations and experiments in this field.

It would indeed be an advantage if we could postpone the slowly increasing incapacity which affects us all after a certain age has been passed. Pleasant as it would be to ourselves, it would be still more valuable to an old community such as ours, where the arrival of men in places of rule and responsibility coincides as a rule with the epoch at which their powers are beginning to diminish. The ideal condition would be one in which the senile changes affected all parts of the body simultaneously, so that the individual died apparently in the height of his powers. For it must not be thought that in any such way we could prolong life indefinitely. Pearl has pointed out that if all the ordinary causes of premature death were eliminated, this would increase the average duration of life by not more than thirteen years. On the other hand, he shows that the children of long-lived parents have an expectation of life which is twenty years greater than that of the average individual.

It is evident, then, that if longevity is our goal it is not medical science we must look to but eugenics, and I doubt whether the question is one with which we are concerned. The sorrow of life is not the eternal sleep that comes to everyone at the end of his allotted span of years, when man rests from his labours. It is the pain, mental and physical, associated with sickness and disability, or the cutting off of a man by disease in the prime of life, when he should have had many years of work before him. To us falls the task of alleviating and preventing this sorrow. In our childhood most of us learnt that suffering and death came into the world through sin. Now, when as physicians we stand on the other side of good and evil, we know that the sin for which man is continuously paying the penalty is not necessarily failure to comply with some one or other of the rough tribal adjustments to the environment, which we call morality, but is always and in every case ignorance or disregard of the immutable working of the forces of Nature which is being continually revealed to us by scientific investigation. In spite of the marvellous increase in knowledge, to some aspects of which I have drawn your attention, suffering is still widespread amongst us. Only by following out the injunction of our great predecessor—to search out and study the secrets of Nature by way of experiment—can we hope to attain to a comprehension of "the wisdom of the body and of the understanding of the heart," and thereby to the mastery of disease and pain which will enable us to relieve the burden of mankind.

*In my Croonian Lectures in 1905 I reported some experiments made in conjunction with Dr. Lane-Claypon, in which I had produced hypertrophy of the mammary glands in virgin rabbits, and in some cases actual milk production, by the daily subcutaneous injection of the filtered watery extract of young rabbit foetuses. Similar results were obtained by Foà. But a weak point in these experiments was that the ovaries had not been previously extirpated. Ancel and Bouin have shown that in the rabbit the mere rupture and discharge of a Graafian follicle, with the subsequent growth of a corpus luteum, are sufficient to cause hypertrophy of the mammary glands (the effective hormone presumably having its seat of manufacture in the luteal cells). It seems possible, therefore, that the effect of our injections may have been on the ovaries, and that the growth of the mammary glands was only a secondary and indirect result. I do not therefore now regard our experiments as conclusive.