THE WISDOM OF THE BODY

THE HARVEIAN ORATION

DELIVERED BEFORE
THE ROYAL COLLEGE OF PHYSICIANS OF LONDON,
ON ST. LUKE'S DAY, 1923

BY

ERNEST H. STARLING
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M.D.HON. (BRESLAU), DOCT. HON. STRASBOURG, F.R.S.
FOULERTON RESEARCH PROFESSOR OF THE ROYAL SOCIETY
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*"Who hath put wisdom in the inward parts?
or who hath given understanding to the heart?"*

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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 two-fold 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 canonise in our memory and acknowledge our indebtedness, not only to those who have assisted our work by material gifts and whose names are recorded in the Roll of the College, or to those Fellows of the College who have been teachers and leaders of successive generations in the science and art of medicine, but also to 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 our Science and increased the powers of our Art.

On this occasion it is my pleasant duty to make special mention of two recent gifts to the College, and to exhort others to imitate the benefactors. Sir Thomas Barlow, who had already richly earned our gratitude by his devoted service in the various offices of the College, including that of President, as well as by his contributions to the science and art of medicine, has in this year presented the College with one thousand pounds.

Dr. R. W. Innes Smith has given to the College a portrait in oils of Sir Charles Scarburgh. It will doubtless be remembered that the subject of this portrait was specially mentioned in his will by Harvey, who left his velvet gown and his little silver instruments of surgery "to my loving friend Mr. Dr. Scarburgh."

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 may 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. 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.

Great as was the gift which Harvey gave to us in his discovery of the circulation of the blood, greater still was the method he taught us of formulating and solving the problems which we continually encounter in our endeavours to control disease. For countless ages mankind had learned slowly and painfully by experience. The more observant had from time to time noticed certain recurring sequences in the infinity of fortuitous phenomena continually presented to them, and as a result man 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 only 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 realisation of the possibilities of the method of experiment, *i.e.* 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 realised by Harvey when he enjoined us to search out, not the causes and cure of disease, but "the secrets of Nature, by experiment." 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.

If 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 beginnings 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 expelled 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 measurements 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 four litres per 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 (3 gallons) per 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 per 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 he body every ten seconds, and complete the circulation of the body six times in every minute. And it must be emembered that the heart is putting out this colossal mount 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 ndividual.

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 contraction 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 minimised, 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 fully displayed only when we cut away the 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 connection with the heart, the blood passing through this organ is kept properly aërated. 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 ultimately from the food, and in each tissue rom the oxidation of the constituents either of the tissue r of the blood circulating through it. It is possible in uch an isolated heart to measure its respiratory exchanges, nd so determine the extent of the oxidative processes esponsible for the energy of the heart's contraction. We hen find that the amount of oxygen, taken in by the heart nd converted for the most part into carbonic acid, is roportional to the amount of work that the heart is set to o. The isolated heart is like the whole man—the harder e works, the greater are his respiratory exchanges. I am ccustomed to compare the heart with an ideal motor car which, without action on the part of the driver, would utomatically admit more petrol and air when the resisance to the movement of the car increases—as, for instance, n going up hill.

The Law of the Heart.

The heart has thus the power of automatically increasing he chemical changes and the energy evolved at each conraction, in proportion to the mechanical demands made pon it, behaving in this way almost like a sentient and ntelligent creature. But the cause of this power must ie 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 there-

fore a function of the diastolic volume of the hea
Dilatation of this organ is not merely a pathologic
phenomenon, but is the means by which the heart achiev
its purpose, and maintains an activity which varies wi
the needs of the organism for more or less blood.

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

You will remember that Harvey insists on the essential
muscular nature of the heart. "It was not without goo
grounds," he says, "that Hippocrates in his book *D*
Corde entitles it a muscle; as its action is the same, so
its function, namely, to contract and move somethin
else." Increasing dilatation of the heart means greate
length of its muscular fibres, so that we can express th

.w of the heart as a relation between length and energy: ie longer the muscle fibre, the greater the energy of its ɔntraction. In this form we find that the law of the eart is that of all muscular tissue, whether voluntary or ıvoluntary. The Swedish physiologist Blix showed ıany years ago that the energy evolved in the contraction f a frog's muscle was proportional to its initial length, ıd A. V. Hill has proved that this holds good for the heat roduction during activity, and therefore for the total ıemical changes which are responsible for the contrac-on and recovery of the muscle. So that in searching fter the cause of the heart's power of adaptation, we are rought into the region of final causes, in which we ssociate function with structure, and see in muscular ɔntraction the expression of molecular changes occurring t the surface of longitudinal fibrillæ. Thus we bring ɔgether in one formula the sum total of our experiences ith regard to the nature of excitation itself, development f mechanical energy, and the chemical, electrical and eat changes which accompany muscular contraction. Ve are still far from a complete understanding of these ıatters, and still farther from any possibility of recon-ructing a muscle fibre. But the path, so far as we can e along it, seems to lead to no impassable barrier, and promise a complete description of the acts of excitation ıd contraction as molecular events occurring at surfaces.

THE LIMITS OF ADAPTATION.

Is there any limit to this power of adaptation? In eletal muscle, increasing the length of the muscle fibres ads to an augmentation of the energy changes of ɔntraction, succeeded later by a diminution as the uscle becomes overstretched. In the healthy mammalian heart the limits are set by the strength of the musc fibres themselves. Freed from the pericardium the hea goes on increasing the strength of its contraction wi increasing dilatation until the muscle fibres are actual ruptured, and when the heart finally fails we find its su stance beset with hæmorrhages. In the body this ove strain of the heart is prevented by the tough fibrous s of the pericardium. When the demand on the heart so great that the heart dilates to the limits of the pe cardium, any further dilatation and resultant increas strength of beat becomes impossible; the output ther fore falls off, and in the whole animal this diminish output results in defective supply of blood to the muscl and brain, giving rise often to fainting, and at any ra enforcing complete rest. Further activity of the anim becomes impossible and the heart is automatically give less work to do, so that it can recover, unless the increase activity of the animal and of the heart is a necessa condition of the animal's continued survival, as in a fig to the death. In this case, when the heart comes u against the pericardium, the fight is finished and th animal succumbs. We find the same story in th terminal changes of heart disease, where the process c compensation which I have described above becom insufficient. Here again enforced rest may give time an opportunity for re-establishment of a sufficient circulatio but with advance of the fundamental morbid conditio even complete rest becomes powerless to relieve the heart the output falls off, the circulation is insufficient for th needs of the tissues, and we get all the secondary result of failure of compensation—suppression of urinary secre tion, water-logging of the body and malnutrition of all it organs, which usher in the fatal termination.

During the last few years great advances have bee 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 study the electrical changes accompanying activity in any kind of tissue.

The Inherent Rhythmic 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 powe of the heart, and has revealed to us the origin and cours of the rhythmically recurring wave of contraction in th heart of man. By means of a technique, first devised b Harrison in the United States, it is possible to cultivat living tissues outside the body in much the same way a we have learned to grow micro-organisms. Using grea care to exclude infection we are able to transfer to plasm or salt solution on a glass slide fragments of tissue which being kept warm, live and multiply. From such a prepara tion further generations can be brought up, and in on such case a preparation of the muscle cells of the heart o a chick has been kept alive, growing and dividing, fo twelve years—a time far beyond the natural span of the lif of the fowl. Such a result proves that mortality is but a accident of the complexity of our living machine, and no a necessary quality and fate of the tissues of which th body is composed. But during these twelve years th muscle cells have not ceased to contract rhythmically showing that in their peculiar properties must be sough 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 b sought in the nervous ganglion cells and fibres present i different parts of this organ.

And it is by the embryological method, *i. e.* by observin the processes of generation, that Keith and Flack wer able to lay the anatomic foundations of our presen knowledge of the origin and course of the contractil processes in the heart of the higher animals. In th developing heart, as in the lower vertebrates, the bea originates in that part of the contractile tube which late will form the sinus venosus. In the course of the change undergone during development, Keith found that this nus tissue persisted at definite parts of the mature heart, nd could be distinguished under the microscope from the irrounding parts of the heart. This special sinus tissue as given the name of the sino-auricular node and the iriculo-ventricular node.

The brilliant experiments by our distinguished Fellow, ir Thomas Lewis, have resulted in a complete knowledge f the part played by these nodes in the cycle of the eart's contraction. He has shown how the sino-auricular ode is the pace-maker of the heart, how the contractile rocess originating here spreads through the auricular uscle to the auriculo-ventricular node, and then passes pidly through the bundle of specialised muscular tissue iown as the A-V bundle to all parts of both ventricles. Ve have in this bundle an interesting example of a uscular tissue differentiated to serve the propagation of citation rather than for contraction, so that it closely sembles nerve in the manner of its function. To the me fine and careful experimenter we owe the explanation one of the commonest conditions in the diseased heart, mely, auricular fibrillation or delirium, which is respon-ble for the irregular ventricular contractions, often ading rapidly to exhaustion and failure of the heart. is remarkable that the clue to the explanation of this ndition was first given by the observations of Romanes the contractile tissue of jelly-fish, which by its rhythmic ilsation propels these graceful animals through the sea-ater. It was shown by Mayer for the jelly-fish and by ines for the frog's heart that it was possible to obtain a ng of contractile tissue in which a wave of contraction ssed continuously round the ring, and the merit of ewis's observations is the proof that delirium is of the me nature as this circus movement, so that the ntractile wave continually progresses over the muscular tissue, exciting each part in turn but in a complete inco-ordinate fashion. Marey long ago pointed out th the rhythmicity of the heart was bound up with th prolonged refractory period affecting the heart musc after its contraction, during which period it was insu ceptible to any form of excitation. According to Lew the circus movements which are responsible for fibrillatio are due to a disturbance in the normal relation betwee the rate of conduction of the excitatory process and th refractory period in the heart muscle. Thus instead an orderly procession of impulses from one node to th next and so to the A-V bundle and ventricles, eve individual fibre is contracting rhythmically but ind pendently of what is happening in its surroundings.

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

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

THE CHEMICAL INTEGRATION OF THE BODY.

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, 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 synthesised outside the body. It is more or less diffusible, and may even withstand without alteration the temperature of boiling wate It is generally easily oxidisable in a neutral or alkalir medium, so that after its production it does not rema long in the blood; it delivers its message and is the destroyed. Each specific hormone is manufactured b a group of cells and turned into the blood, in which travels to all parts of the body, but excites defini reactions in one or a limited number of distant organ The production and action of these substances a continually going on in the normal animal. They a necessary to health, and their production in excess or i deficit gives rise to disease and maybe to death. Typical c these substances is secretin, a substance which is generate in the epithelial cells lining the upper part of the sma intestine when these come in contact with weak acid, an therefore under normal circumstances at the moment c the passage of the acid chyme from the stomach into th duodenum. Directly it is produced it is absorbed int the blood and travels round to the pancreas, to the live and to the intestinal glands, in all of which it excite secretion. By means of this chemical reflex the arriva of the products of gastric digestion in the small intestin evokes within a couple of minutes the secretion of th three juices whose co-operation is necessary for complet ing the work of digestion and solution of the food alread begun in the stomach. It is probable that this mechanisn is but one of a whole chain of chemical reflexes responsibl for the orderly progression of the various stages in th digestion of food.

These hormones may apparently be formed by an kind of tissue. In many cases a gland which has, i the evolutionary history of the race, poured its secretio by a duct into the alimentary canal or on to th 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. 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 wide-spread 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.

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 civilisation, 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 testes 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 versâ.* 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 an implantation of ovaries causes a disappearance of the comb and the assumption of the plumage of a 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 fœtus 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 connections. 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 fœtus 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.

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 otent reinforcement to the energies of the body. It ncreases the tone of the blood vessels, as well as the ower of the heart's contraction, while it mobilises the ugar bound up in the liver, so that the muscles may be upplied with the most readily available source of energy n the struggle to which these emotional states are the ssential precursors or concomitants.

Wonderful too is the influence exerted by the secreions of the pituitary body. This tiny organ, which was ormerly imagined to furnish the mucus to the nasal avities, consists of two lobes which have different internal ecretions. That produced by the anterior lobe seems to nfluence growth, excess producing gigantism or acroegaly, while deficiency leads to a retarded growth and nfantilism. The posterior lobe, which in aspect would eem but a small collection of neuroglia, nevertheless orms one or more substances which, circulating in the lood, have the most diverse influences on various parts f the body. They cause contraction of the uterus and f the blood vessels (these are possibly two distinct ubstances), they may increase or diminish the flow of rine, they affect the excretion of chlorides by the kidney, nd, according to Krogh, their constant presence in the lood is essential for maintaining the normal tone of the apillaries. In the frog the post-pituitary hormone is esponsible for the protective adaptation of the colour of he skin to the environment—an adaptation which is ffected by retraction or expansion of the pigment cells or hromatophores of the skin; and, if we may accept Kammerer's conclusions, the pituitary hormone which is oured into the blood for this purpose alters the germ ells themselves, so that individuals born of parents that ave lived in light or dark surroundings are correspondingly ight or dark—a real transmission of acquired peculiarities

effected, not by the gemmules of Darwin, but by tl
influence of a soluble diffusible hormone on the germ plasn

The Therapeutics of Hormones.

In the multiplicity and diversity of the physiologic: effects produced by these various chemical messenger one is apt to lose sight of the fact that we are hei investigating one of the fundamental means for tl integration of the functions of the body. These are n merely interesting facts which form a pretty story, bı they are pregnant of possibilities for our control of tl processes of the body and therewith for our mastery (disease. Already medical science can boast of notab achievements in this direction. The conversion of stunted, pot-bellied, slavering cretin into a pretty, attra tive child by the administration of thyroid, and tl restoration of normal health and personality to a suffer from Graves' disease by the removal of the excess (thyroid gland, must always impress us as miraculous. I the same way we may cure or control for the time bein diabetes insipidus by the injection of the watery extra of the posterior lobe of the pituitary body. The late achievement in this direction is the preparation, b Banting and Best of Canada, of the active princip normally formed in the islets of the pancreas, and th proof that the diabetic condition in its severest forms ca be relieved by its subcutaneous administration.

In my Croonian Lectures I suggested that, if a mutu control of the different functions of the body be large determined by the production of definite chemical sul stances in the body, the discovery of the nature of thes substances would enable us to interpose at any desire phase in these functions, and so to acquire an absolut 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 realisation 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:

(1) 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 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, b
we have no knowledge of the factors determining tl
production of the pituitary hormones or of insulin by tl
islets of Langerhans, and this condition of ignoran
extends to most of the other ductless glands.

In some cases deficient production of a hormone ma
be due to the absence in the food and drink of son
necessary constituent. Thus iodine is essential to tl
formation of the specific secretion of the thyroid glar
(iodothyrin). If iodine be entirely absent from tl
drinking water and the soil, so that it is not containe
even in minute quantities in the vegetable food grown i
the district, the thyroid undergoes hyperplasia—in a vai
endeavour to make bricks without straw, to produce i
proper hormone without iodine. This seems to be tl
cause of the great prevalence of simple goitre in certai
districts, especially in Switzerland and in parts of tl
United States. It has been shown by Marine and othe
that goitre can be practically eliminated from these distric
by the occasional administration of small doses of iodir
or iodides. These results were communicated in 1917 t
Dr. Klinger, of Zurich, and as a result of his experienc
the Swiss Goitre Commission has recommended the adoj
tion of this method of goitre prevention as a public healt
measure throughout the entire state. Already great pro
gress has been made in the abolition of this disease fro
the country. Thus the incidence of goitre among a
the school-children of the canton of St. Gallen has bee
reduced from 87·6 per cent. in January, 1919, to 13·1 pe
cent. in January, 1922.

(2) Where a disordered condition is due to diminishe
production of some specific hormone, we may extract th
hormone from the corresponding gland or tissue i
animals. It is characteristic of these hormones that, s

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.[1] We may however look forward to the day when the chemical constitution of all these hormones will be

[1] 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 secretion of milk by the daily subcutaneous injection of the filtered watery extract of young rabbit fœtuses. Similar results were obtained by Foa. 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.

known, and when it may be possible to synthesise the in any desired quantity. We may then be able to ove come the inconvenience of subcutaneous injection b giving relatively colossal doses by the mouth, or we ma be able to modify their constitution to a slight extent s as to render them immune to the action of the digesti juices without affecting their specific action on th functions of the body.

(3) The ideal but not, I venture to assert, the unattair able method will be to control, by promotion or suppres sion, the growth of the cells themselves, whose functio it is to form these specific hormones. Though this metho seems at present far from realisation, the first steps in th direction have already been taken. It must be remembere that the power of controlling growth of cells involves th solution of the problem of cancer. Experiments on th growth of normal cells outside the body have shown tha they can be stimulated to vie with cancer cells in the rat of their growth, or can be inhibited altogether accordin to the nature of the chemical substances with which the are supplied. And we know that the growth of certai cells, such as those of the mammary gland or of the uterus is excited by specific chemical substances produced in th ovary or fœtus, and we may be able to find specific sub stances or conditions for any tissue of the body, whic may excite growth when this is retarded or diminis growth when this is in excess. It may be that in som cases purely mechanical interference will suffice. Thus in experiments by Steinach and others, it has been foun that ligature of the vas deferens close to the testis, whil causing atrophy of the seminiferous cells, brings abou overgrowth of the interstitial cells which, as we hav seen, are chiefly responsible for the hormones determinin the secondary sexual characters. Among these secondar

xual characters must be classed the whole of a man's ergies. Virility does not mean simply the power of opagation, but connotes the whole part played by a man his work within the community. As a result of this pertrophy, these authors claim to have produced an tual rejuvenation in man, and thus to have warded off r a time senility with its mental and corporeal anfestations. Further experiments and a longer period observation are necessary before we can accept these sults without reserve, but it must be owned that they e 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 e slowly increasing incapacity which affects us all after certain age has been passed. Pleasant as it would be ourselves, it would be still more valuable to an old mmunity such as ours, where the arrival of men in aces of rule and responsibility coincides frequently th the epoch at which their powers are beginning diminish. The ideal condition would be one in which e senile changes affected all parts of the body suddenly d simultaneously, so that the individual died apparently the height of his powers. For it must not be thought at in any such way we could prolong life indefinitely. earl has pointed out that if all the ordinary causes of emature death were eliminated, this would increase e average duration of life by not more than thirteen ars. On the other hand, he shows that the children long-lived parents have an expectation of life which is enty years greater than that of the average individual. longevity is our goal it is not medical science we must ok to, but eugenics.

I doubt whether this question is one with which we e concerned. The Sorrow of the World is not the eternal sleep that comes to everyone at the end of l allotted span of years, when man rests from his labou It is the pain, mental and physical, associated wi sickness and disability, or the cutting off of a man by disea in the prime of life, when he should have had many yea of work before him. To us falls the task of alleviati and preventing this sorrow. In our childhood most of learnt that suffering and death came into the wor through sin. Now, when, as physicians, we stand the other side of good and evil, we know that the sin, f which man is continuously paying the penalty, is n necessarily failure to comply with some one or other the rough tribal adjustments to the environment, whi we call morality, but is always and in every case ignoran or disregard of the immutable working of the forces Nature, which is being continually revealed to us scientific investigation. In spite of the marvellous increa in knowledge, to some aspects of which I have draw your attention, suffering is still wide-spread amongst u Only by following out the injunction of our great pr decessor, to search out and study the secrets of Natu by way of experiment, can we hope to attain to a con prehension of "the wisdom of the body and the unde standing of the heart," and thereby to the mastery disease and pain, which will enable us to relieve t burden of mankind.

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