Hormones.[1]

By Prof. E. H. STARLING, C.M.G., F.R.S.

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 it produces, 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 directed attention 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 synthesised outside the body. It is more or less diffusible, and may even withstand without alteration the temperature of boiling water. It is generally easily oxidisable 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 gives rise to disease and maybe to death.

Typical of all hormones 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 set free 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 the co-operation of which 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.

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.

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 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

[1] From the Harveian Oration, entitled "The Wisdom of the Body," delivered before the Royal College of Physicians of London on St. Luke's Day, October 18.

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 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 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 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 mobilises 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.

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.

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.

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 realisation of this power of control which is the goal of medical science. But there still remain 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 example, 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 vain an 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.

(2) 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 example, 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 trustworthy effect has been obtained except by the actual implantation of the organ from an animal of the same family.[2]

[2] 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 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.

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 synthesise 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.

(3) The ideal, but not, I venture to assert, the unattainable, method will be to control, by promotion or suppression, the growth of those cells, the function of which is to form these specific hormones. Though this method seems at present far from realisation, 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. 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 fœtus ; 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 frequently with the epoch at which their powers are beginning to decline. 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 the world is not the eternal sleep that comes to every one 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 directed 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.

The Equation of Van der Waals.[1]

By J. H. JEANS, Sec. R.S.

VAN DER WAALS' equation

$$\left(p+\frac{a}{v^2}\right)(v-b)=aT$$

expresses the result of supposing a molecule to be endowed with two distinct physical properties—finite size, giving rise to the term b, and cohesive force, giving rise to the term a/v^2. The physical meaning of the equation is best exhibited by drawing diagrams of isothermals of the familiar type. Representing different gases there will be different diagrams corresponding to different values of a and b. It is, however, readily shown that one diagram of this type can be made to represent all values of a and b, and so the isothermals of all gases, by suitable expansions and contractions of its horizontal and vertical scales. On removing the scale from any single diagram we have a universal diagram which represents the p, v, T relation for all gases, but without specifying the scale. The circumstance that such a diagram is possible is equivalent to the so-called "Law of Corresponding States"; this is now seen to be a mathematical consequence of Van der Waals having confined himself to a two-constant specification of molecular structure.

Thus the accuracy, or the reverse, of the law of corresponding states provides a test of the sufficiency of Van der Waals' two-constant specification of a molecule. In actual fact the law is not very closely obeyed; the deviations show distinct correlation with atomicity, and so suggest that the two-constant specification is not altogether adequate—a full treatment must take account of differences of atomicity (or physical shape) as well as of differences of size and cohesive power.

Van der Waals explained his cohesive power by the supposition that all matter possesses inherent powers of attraction for all other matter. Gravitational attraction is numerically far too small to come into the question at all, so that it is to the electrical structure of matter that we must look for the origin of this supposed universal attraction.

If molecules were electrically charged structures, similar molecules would repel one another; as they are electrically neutral, they will repel in some orientations and attract in others, but two molecules meeting at random are as likely to repel as to attract. It is only when the *duration* of molecular encounters is studied that we find an explanation of the preponderance of attraction over repulsion—attractive encounters draw the molecules farther and farther into each other's sphere of influence, and so last longer than repulsive encounters. Comparing the two types of encounters, the "birth rate" is the same for each, but the "expectation of life" is longer for attractive encounters, so that for the encounters in being at a specified instant, there is a preponderance of attractive encounters, and hence a resultant attractive force. This attractive force, however, originates far more in an abstruse theorem of statistical mechanics and far less in an inherent property of matter, than Van der Waals supposed.

If this interpretation is right, the cohesive forces must disappear at very high temperatures and must steadily increase with decreasing temperatures, so that a must be a function of the temperature and not, as Van der Waals supposed, a constant. In point of fact, all attempts to bring Van der Waals' equation into closer agreement with observation begin by making a a function of the temperature. Moreover, a is found to vanish at infinite temperatures in conformity with the suggested explanation.

The second constant b was supposed by Van der Waals to have its origin in the finite sizes of the molecules. If, for example, the hydrogen molecule is regarded as a sphere, its radius as calculated from the observed value of b is found to be $0{\cdot}64\times10^{-8}$ cm. The same radius can be calculated independently in other ways; the coefficients of viscosity, of conduction of heat and of self-diffusion all agree in yielding the value $0{\cdot}68\times10^{-8}$ cm. The average of these, $0{\cdot}66\times10^{-8}$ cm.,

[1] Synopsis of part of the Van der Waals Memorial Lecture delivered before the Chemical Society on November 8.