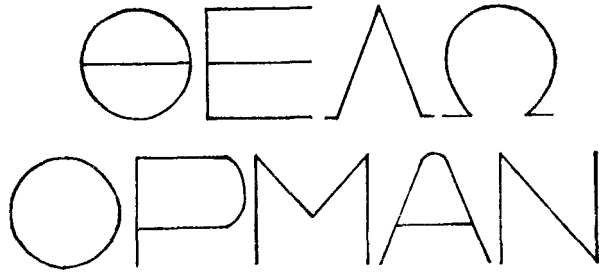
THE ROLE OF THE HORMONES IN LIVING CONTROL SYSTEMS

An Inaugural Lecture

GIVEN IN THE UNIVERSITY COLLEGE OF RHODESIA

Professor J. J. Jones
Faculty of Medicine

UNIVERSITY COLLEGE OF RHODESIA



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An Inaugural Lecture
given in the
University College of Rhodesia
on 23rd July, 1970

by

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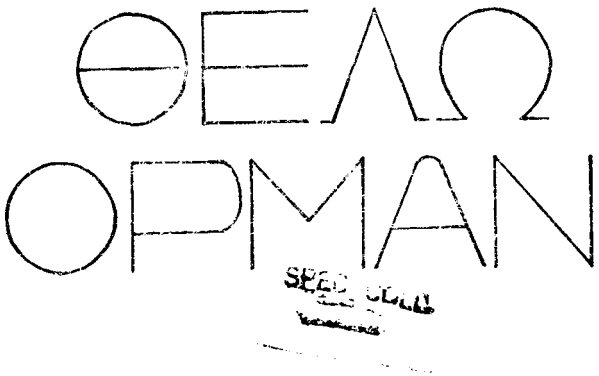

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It is always difficult to know what to say at an inaugural lecture, not that I have given one before; on the last suitable occasion the audience was excused: its knowledge of English was not at all good. I am told that the main purpose of such a lecture is to allow the newly appointed and autocratic professor to speak about his department. He can explain in public how he expects its research and work to go forward, possibly for the rest of his professional life. I am delighted to say that on this occasion the position is entirely the reverse.

One attraction for me in coming to Rhodesia is the opportunity to follow a line of research using a new technique: the radio-immune assay.[1] This type of research had already been started in our Medical Faculty. It was started, and started most ably, by Dr. Symington with Mr. Ellison and Mr. Hale in Anatomy and by Miss Kritzinger in Physiology. The radio-immune assay is for measuring the hormones in the body; most of this lecture will be about the hormones and their importance in medical research.

I must explain what I mean by a hormone: it is a word that first appears in the Hippocratic Corpus;[2] the Hippocratic Corpus is a collection of medical writings attributed to the medical school at Cos. It dates from around four hundred years B.C. and formed the basis of medicine for the next two thousand years. The hormones were the vital principles that stirred the body into a state of activity. Hormone means arouse, stir up, urge on; it can also mean stimulate or excite. The title of my lecture, ΘΕΛΩ ΟΡΜΑΝ expresses my wish to stir up, my wish to stimulate; this, I believe, must be the first aim of any teacher.

Hormone has become confused with humour; we often say humoral when we mean hormonal. This is wrong: in the Hippocratic Corpus the hormones are entirely separate from the humours. The four humours of the body were the four primary fluids, each one formed from an element of the Pythagoran system[3] (Fig. 1)

The black bile also known as atrabilia was found in the spleen and in the adrenal gland[4] above the kidney. I shall have more to say of the adrenal when I come to the hormones.

The yellow bile or chole was stored in the gall bladder; it had at least the colour of its parent element: fire.

The cold, wet humour was thought to act as a cooling system for the brain, to prevent it becoming overheated. It was secreted by the pituitary body which sits in the Turkish saddle on the floor of the skull. The overflow from this cooling system escaped as phlegm through holes in the roof of the nose and appeared at the nostrils as the nasal mucus or slime. We still use the word phlegm for the mucus that is coughed from the throat.

The last humour was blood; according to Hippocratic ideas, air passed from the lungs to the heart, where it was changed into blood and distributed to the remainder of the body through the veins.

A system of disease based on the humours was popular in medicine for hundreds, even thousands of years. According to this humoral pathology, all illness was caused

by a lack of balance between the humours, an excess of any one humour being the cause of ill health. This appears to have been the rationale for blood-letting or venesection which, for very many years, was the treatment of choice for almost any illness. It was a crude attempt to redress the balance between the humours by removing the plethora of blood. Apart from a physical wellbeing, the humours were also implicated in the control of the mind and personality; indeed, this idea persists in our everyday language: we still use the word "humour" to describe a person's mood, his state of mind; we have taken the names of the four cardinal humours to define the various types of personality. We speak of a cheerful, sanguine view of life, sanguine implying a preponderance of blood. The choleric man has fire in his belly, he is angry, irritable, even bilious. A cold, damp personality is called phlegmatic; there is too much phlegm, too much of the cold, wet humour in his make-up. Most interesting of all is melancholy: melancholy means nothing more than black bile, black bile in the spleen and adrenal.

In the Hippocratic Corpus the hormones were entirely separate from the humours. Unlike the idea of a humour, the hormones made little or no impression on early medical thinking; the idea was lost and the word was not used again until 1905. Hormone was coined de novo by Sir William Bate Hardy,[5] at that time a physiology tutor at Cambridge University. It was used to describe the internal secretions that control and regulate the activity of the body; the idea of an internal secretion wasn't new: it is one of the many important ideas in physiology that we owe to Claude Bernard.[6] I regard Bernard as the founder of modern physiology. The internal secretions are those secretions that pass directly into the bloodstream from a particular group of glands; these glands have no ducts, no openings to the surface of the body; they are the endocrine glands, the glands of internal secretion. The internal secretions that control the body were to be known as the hormones. The paradigm of this group had been dis-

covered some three years earlier by Sir William Bayliss and by Ernest Starling.[7] It is secretin, the internal secretion from the intestine, which controls digestion. There was considerable opposition to the use of the word "hormone" to describe these regulating secretions; opposition came, in particular, from Sir Edward Sharpey-Schafer; he was the immediate predecessor of both Starling and Bayliss as professor of physiology at University College in London. Schafer was the leading endocrinologist and an authority on internal secretions, particularly the secretions of the pituitary body and adrenal gland.

May I digress for a moment to tell my favourite story about the discovery of the secretions in these glands? It is a story that I heard from Sir Henry Dale [8] at his Sharpey-Schafer memorial lecture. Dale told us that the first experiments on the adrenal were made by a London general practitioner, a Dr. George Oliver. Oliver took an interest in physiology and, like all good physiologists, he had a flair for invention. He designed a caliper, an instrument for measuring the size of the arteries at the wrist. With this instrument he carried out some extremely dangerous experiments on his own family; he injected his own wife and children with a variety of gland extracts just to see what happened to their arteries. Fortunately most of the extracts were inactive: nothing happened, but when he tried a solution of a calf's adrenal on his own son there was a definite spasm, a definite narrowing of the arteries. Oliver was very excited; he took his extract to Professor Schafer, then at University College, and urged him to try it on a dog. Schafer was reluctant to make the experiment, but allowed himself to be persuaded. The dog was injected and there was an enormous rise in arterial pressure, so great it almost forced the mercury from the manometer.[9] In the following year, in 1895, they obtained a similar rise in pressure with an extract of the pituitary.[10] The increased pressure is due to a narrowing of the blood vessels, so the active principle is called vasopressin. I find it curious that these two organs, the adrenal and the pituitary, chosen

for humour production in the Hippocratic system, turned out in reality to be the most important of the body's endocrine glands.

Schafer objected to the word hormone; he pointed out that it was quite unsuitable for those secretions that slow down the activity of the body. He suggested that the whole group of controlling secretions should be known as the autacoids, meaning self-regulators; those secretions that had an inhibiting or depressing effect were to be called chalones, meaning relaxants, or colyones, meaning hindrances.[11] His suggestions have not been accepted: chalone is now seldom used, except very specifically to describe the particular group of internal secretions that regulate the growth and division of cells.[12] I shall have more to say of the chalones when I come to cancer and the malignant diseases. Hormone is now used indiscriminately for all types of controlling secretions, irrespective of whether their main action is to stimulate or depress.

Sir Julian Huxley [13] has given us the best definition of a hormone: they are the chemical agents that carry information from one part of the body to another. Information is also transmitted by the nerve fibres, but even this system relies on nerve-hormones to transfer the information between the fibres where they come together at the synapses. I should like to illustrate the way in which hormones carry information by considering one particular hormone, vasopressin, and how its information is used to control the kidney.

All the fundamental information in our bodies is present from the moment of conception; it is present in the very first cell, the fertilised egg cell. This is the inherited or genetic information that each one of us receives from our parents. It takes the form of a chemical code that can be found in every cell in the body. The code is chemically an acid, the information acid (Fig. 2). Each information acid consists of two strands wound around one another to form a double spiral, a double helix. The backbone of the acids is identical; all the

information that they carry depends on the attached groups called bases. The genetic code can be likened to a rather elaborate Morse code. As you must know, in the Morse code there are two symbols, a dot and a dash. They can be arranged in various ways to represent the twenty-six letters of the alphabet. In the genetic code there are not two but four symbols: the four kinds of base. Again, they can be arranged, but always in groups of three, to represent the letters of the genetic code.[14] Each letter denotes one of the twenty-three amino-acids; the amino-acids are the building blocks from which all living tissues are made. The message encoded on the information acid is copied on to a messenger which carries it to the part of the cell where proteins are made, the ribosome. Here the information is used to control the formation of the hormone, vasopressin, by joining together nine amino-acids. Although every cell in the body contains the necessary information to make vasopressin, in practice the hormone is produced only in a few nerve cells in a small part of the brain that lies below the central chamber or cavity. This part of the brain is called the hypothalamus (Fig. 3). The hormone is attached to a carrier and flows from the brain through the nerve fibre to be stored in the pituitary body.[15, 16]

When the nerve cells in the hypothalamus become active (and I will leave, for a moment, the cause of this activity) a minute quantity of electricity passes into the nerve cell and very rapidly spreads from the brain to the pituitary body. The electric current carries calcium into the nerve endings where it displaces vasopressin from the pituitary to enter the blood.[17, 18] Vasopressin is carried by the blood to the kidneys. This is an essential feature of a hormone: they always carry their information through the blood stream. At the kidney, vasopressin becomes attached to the very last part of the kidney tubule which is carrying urine on its way to the bladder. This is as far as vasopressin goes; it transfers its information to the second messenger, to its deputy hormone.[19] The deputy

hormone is released inside the kidney cell by vasopressin which remains outside the cell. The membrane of the cell nearest to the blood stream contains an enzyme or catalyst; when vasopressin combines with this enzyme its shape is altered so that it can no longer hold on to the deputy hormone; the deputy becomes free to cross the cell to the opposite wall in contact with the urine. Here the deputy enlarges pores in the cell membrane so that water can pass back from the urine and into the blood.

A few unhappy people cannot make vasopressin; either they lack the genetic information or the pituitary is destroyed by disease. They are unable to absorb water from the urine and are obliged to pass half or even one litre of urine every hour, night and day.[20] This is the disease called diabetes. Diabetes is a very apt name—it means a syphon; water seems to be syphoned through these people, in at the mouth and almost at once out in the urine. This particular form of diabetes was first recognised by Johann Frank[21] in 1794. He distinguished it from the more common form of diabetes by tasting the urine. In one case the urine is as sweet as honey, in the other it is insipid, virtually tasteless, like water.

This is how information is carried from the brain to the kidney. I would like to consider next how it is used to control the amount of water in the body. I must emphasise that this control is essential for a normal, healthy existence.[22] The amount of water in our bodies is a delicate balance between the quantity that we drink and the amount that evaporates from the skin or is lost in the urine. Should this balance be disturbed, water accumulates and enters the cells, which become swollen. This swelling is particularly dangerous in the brain; the patient becomes mentally confused, he appears to be drunk, he is in a state of intoxication, a state of water intoxication. On the other hand, a disturbance of the balance may lead to the loss of water from the body; the cells shrink, and again the brain is the first to suffer. The unfortunate patient becomes unconscious; he may eventually die in a fit of

convulsions.

The amount of water in our bodies is controlled by a typical regulating system (Fig. 4). The first requirement is to measure how much water is present; this measurement is made in two ways: the volume of water in the blood stream is monitored by the heart,[23] and the information is conveyed along nerve fibres to the brain. The second measurement is the size of the brain cells; this is recorded in the hypothalamus itself.[24] If, for example, there is not enough water in the body so that the heart is underfilled, so that the brain is beginning to shrink, the hypothalamus becomes active and releases vasopressin from the pituitary gland to be carried by the blood to the kidneys, where it increases the re-absorption of water from the urine and prevents any further loss from the body. At the same time, activity in the hypothalamus engenders a sensation of thirst and a drive to increase the water by drinking. In the other direction, should there be too much water in the body so that the heart is overdistended and the brain is beginning to swell, under these conditions the secretion of vasopressin stops, the hormone rapidly disappears from the blood and the kidney can excrete the surplus of water as a large volume of dilute urine.

In this control system information first passes from the brain to the kidney, information carried by vasopressin, and then information returns from the kidney to the brain, information about the blood volume, information about the size of the nerve cells. This return of information to the brain is called feedback. A control system based on feedback is said to use stabilising refection.[25] All the control systems in the body employ feedback; information always goes back to the controller, usually in the brain, to show that the required change has taken place and to prevent any further change. The main disadvantage of a system based on feedback is its delay. By delay I mean the time taken for information to go around the "loop" from brain to kidney and back from kidney to brain. The effect of the delay is that compensation for

a disturbance of water balance cannot be instantaneous; inevitably an appreciable time must elapse between an alteration of the water content of the body and its correction by the kidney. As a result, the amount of water in the body cannot be maintained at an exactly steady level; it tends to fluctuate, it tends to rise and fall.

This defect in a control system is called oscillation or hunting. It can be overcome by what I would like to call anticipation; the correct technical term is input feedforward.[26] It is not sufficient to measure misalignment; it is not sufficient to compare the actual quantity of water in the body with the ideal or required amount. For accurate control it is also necessary to detect and recognise disturbances coming from outside the body, disturbances that are likely to upset the water balance. It is only by measuring the disturbance and by estimating its effect that compensations can be set in motion to prevent the change before it occurs.[27]

The control system for water in the body shows two good examples of anticipation—two good examples of controls that rely on the measurement of outside disturbances. When water is drunk it is absorbed from the intestine and passes through the portal vein to the liver. Nerve endings in the liver detect the water as soon as it is absorbed; they send information to the brain to stop vasopressin secretion so that the kidney can excrete the water almost as fast as it enters the blood stream and before there is any appreciable change in the total water content of the body.[28] Anticipation also occurs when a man is exposed to heat. To prevent a rise in body temperature that might otherwise prove fatal, water is poured on to the surface of the skin by the sweat glands; the water evaporates to carry away the heat. A rise in temperature stimulates nerve endings in the skin and hypothalamus, vasopressin is released and the kidney re-absorbs water from the urine. In this way the kidney can anticipate the need of the sweat glands to use water, to lose heat.[29]

This is but one of the multitude of control systems that

make up the subject of physiology. They are all designed to serve one general purpose: they produce stability, they prevent change. This is the most important concept in physiology. It is another idea that we owe to Claude Bernard;[30] he expressed his idea in the following words: "la fixité du milieu interieur est la condition de la vie libre." Homeostasis means standing still. Walter Cannon, the American physiologist, gave this name to the control processes in the body that achieve stability. He made an exhaustive study of homeostasis and concluded that: "in our bodies, if a state remains steady, it does so because any tendency towards change is automatically met by increased effectiveness of the factors that resist change."[31] This concern with control and regulation is the essence of physiology; it separates the subject from biophysics and biochemistry. Physiology is the study of the overall control of the body as opposed to the detail of the chemical and physical changes that occur in and around the living cell. The physiologist has been very aptly defined as the control system analyst of biology. We may say physiology is living kybernetics.[25]

Since all the control systems in the body depend on the carriage of information by hormones or nerve hormones, it is clear that the accurate measurement of the hormones is essential for the proper understanding of physiology. The main difficulty in measuring the hormones is the minute quantities involved. For the peptid hormones that interest me, this amounts to one part in one million-million in the blood stream—far too small for a straightforward chemical analysis. Until recently the only available method for measuring these hormones was to try their effect on an isolated piece of muscle or to inject them into a small experimental animal such as a rat. This type of analysis that uses living tissue is called a biological assay; it is quite suitable for measuring large amounts of the hormones in the blood stream; it is totally inadequate to detect the resting basal level.

The new and far more sensitive technique is the radio-

immune assay.[1] As the name indicates, two processes are involved: radiation and immunity. The first is remarkably simple: it is quite easy to make radioactive hormone by attaching radioactive iodine to the hormone. Immunity is quite another matter. Immunity depends on an animal, such as a rabbit, making antibodies; the primary purpose of the antibody is to destroy parasitic microbes, to prevent disease. If hormone is injected into the rabbit its defence system may mistake the hormone for a microbe; it may manufacture antibody to destroy the hormone (Fig. 5). When the hormone is attached to particles of Indian ink the rabbit's defence system mistakes them for microbes.[32] Scavenger cells in the lymph tissue eat the particles and copy the chemical structure of the hormone on to a peptid.[33] The peptid passes through a tube to a lymph cell; the lymph cell divides to form a colony of identical cells; some of these cells are stimulated by hormone attached to their surface to enlarge and manufacture antibody which is released into the blood stream.[34, 35, 36] The basis of the assay is to mix the rabbit's blood serum, containing the antibody, with radioactive hormone so that they combine together. If a patient's blood containing the natural hormone is added to the reaction mixture it competes with the radioactive hormone for antibody. The change in the amount of radioactivity attached to the antibody is a very delicate measure of how much natural hormone is present. The radio-immune assay can be made extremely sensitive; it can detect as little as one million millionth part of a gram. This is certainly a small amount, but I must remind you that, even so, it represents around six hundred million individual molecules.

Apart from physiological control systems, hormone research is also a great help in the diagnosis of disease. Most of the illnesses that afflict us produce some alteration in physiological control; indeed, many diseases represent a primary breakdown in the hormonal control system itself. Diabetes mellitus is an excellent example; it is a disease in which the blood sugar goes out of control.

Many illnesses are the result of an invasion of our bodies by parasitic micro-organisms: by bacteria, viruses, protozoa and the like. These germs commonly show their presence in the body by destroying part of a control system. Addison's disease is a case in point: the tubercle bacillus destroys the adrenal gland; the patient eventually dies because he can no longer control the salt in his body.

I would like to turn now to cancer and the malignant diseases. Cancer is a disease that is the direct result of a breakdown in physiological control.[37] You may remember from the beginning of this lecture that the chalones are a particular group of hormones that control the growth and multiplication of the cells in the body. The essential change that turns a normal cell into a destructive parasitic malignant mass must involve an escape from these hormones:[38] an escape which allows the cell to grow and spread without further regard to the requirements of the surrounding tissue; without further regard to the welfare of the body as a whole. Not content with escaping from its regulating hormones, the cancer may go on to make its own hormones. Cancers of the endocrine glands commonly continue to secrete their characteristic hormones; it is much more of a surprise to find that a cancer developing in some other part of the body may also take up hormone production. This story begins with the American physicians, William Schwartz and Frederic Bartter.[39] They noticed that one of their patients with a cancer of the lung became mentally unbalanced and showed signs of water intoxication. Schwartz and Bartter realised that this intoxication might be due to an increased secretion of vasopressin; they suggested that the cancer, by growing in the chest, had interrupted the nerves carrying information from the heart to the brain and caused an overproduction of vasopressin by the pituitary (Fig. 4). At this time in London we had a very good biological assay for vasopressin, an assay that used the anaesthetised rat. It gave us the opportunity of testing their idea.[40, 41] When I left London we had studied twenty-six patients with water

retention and cancer of the lung. All these patients had the same type of cancer; to be exact, a cancer that develops in the lining of the bronchus, a cancer composed of small oval cells. This is the cancer that is almost always associated with tobacco smoke or some similar form of air pollution.[42] We found that the Americans were correct—all these patients had very high levels of vasopressin in their blood and urine; there could be no doubt that the water retention and intoxication were due to an overproduction of the hormone. We went on to examine samples of the cancer taken from the lung at operation or post-mortem. To our surprise we found that the cancer itself contained the hormone. This means that the water intoxication was not due to vasopressin from the pituitary gland; the lung cancer had begun to make the hormone.

I must point out that vasopressin is not the only hormone secreted by lung cancers; many other hormones are produced, including corticotrophin, thyrotrophin, erythropoietin, parathormone, oxytocin, gonadotrophin, melanotrophin, gastrin, glucagon and insulin.[43, 44] It has been calculated that as many as 2 per cent. of these cancers produce hormones; in England alone this represents over six hundred new patients every year, so it is not a particularly rare disease. Although the lung is the most usual site for a cancer that secretes hormones, they can also be found in other parts of the body. A particularly rare example has recently been described by Mr. Simon Wapnick in our Department of Surgery.[45] It is a cancer of the prostate gland at the neck of the bladder; this cancer was making vasopressin.

It is a curious fact that all the hormones secreted by cancers have the same chemical structure: like vasopressin, they are all peptids. Daniel Rudman[46] is an American pathologist. He claims that the formation of new and unusual proteins and peptids is a characteristic of all cancer cells and not a property confined to a small proportion of lung cancers. Rudman believes that some of these novel peptids simply happen to act as hormones to

produce such changes as water retention. If Rudman is correct and all cancers produce new and unusual proteins, it is probably due to some change in the genetic message, some alteration of the information acid[47, 48, 49] (Fig. 2).

Each time a cell divides, the double strand of information acid unwinds; each single strand makes a copy of itself for the new cell. It has been estimated that once in every hundred million cell divisions a mistake occurs—an exact replica is not produced. This may seem an extraordinarily small risk, but I must remind you that in our body there are one thousand million million cells.[50] Some of these cells divide many times every day; a minute risk in a single cell is enormously magnified when the whole body is considered. The information acid can be damaged by poisons, particularly the poisons in tobacco smoke or the poisons added to food to change its taste or colour. Radiation can damage the information acid; in this country sunlight is the main cause of skin cancer.[51] A virus can foist its own strand of information (or messenger) acid on to the cell;[52, 53] the acid directs the cell to make new viruses; in the process the cell may turn malignant. The alteration in protein synthesis may occur at the ribosome; a likely cause here is a chemical change in the transfer acid[54] so that the wrong aminoacids are carried into the ribosome to be attached to the developing peptid chain.

If abnormal proteins are a characteristic of all malignant cells, it may explain why cancer is not more common, particularly in young people.[55, 56] The cancer proteins, being foreign to the body, would stimulate the formation of antibodies to destroy them.[50, 57, 58] This idea is not entirely speculative; evidence points in this direction from the field of organ transplants, particularly transplants of the heart and kidneys. These grafts or transplants are rejected by this very mechanism; indeed, it is not possible to make a successful transplant without first suppressing the antibody-forming cells.[59] Such treatment carries a risk: it may allow cancer to develop in the body.[60] A recent survey suggests that as many as 2 per cent. of patients

with kidney transplants die from cancer every year.[61, 62, 63] They die presumably because they can no longer make antibodies to destroy the cancer cells.

May I conclude this lecture by pointing out that my chosen field of research, research that is concerned with the interaction between the hormones and the antibodies, is certain to prove fruitful, both in medicine and in physiology. The more accurate measurement of the hormones will give us a better understanding of the control systems that make up the body's physiology. The accurate measurement of the hormones is also essential for the correct diagnosis and proper treatment of a great variety of diseases—diseases which are essentially due to a failure of communication, a failure in the carriage of information and the consequent failure in control.

We can also hope that a study of the hormone-antibody reaction will give us a new insight into the nature of the malignant cancerous change. It may even prove possible to develop a radio-immune assay for cancer proteins.[33] Such an assay would have immense clinical value, not only for the early diagnosis of cancer, but also as a guide to the treatment of malignant disease.

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