Physiology the Basis of Treatment.¹

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THE ultimate aim of medicine is the prevention or cure of disease: this practical aspect so far dominates all others that it is often referred to as the healing art; indeed, it is difficult to think of medicine apart from treatment.

The term 'physiology' is usually used to designate the science of function, whether it is studied in broad outline and dealing with the mechanism of action or as the physico-chemical mechanisms leading up to this action. Disease means the unusual functioning of tissues which may be the result of accident, hereditary weakness, or parasitic organisms. Generally it is wrong to speak of this as malfunctioning: the unusual functioning is physiological and perhaps the best for the organism under the unusual conditions. The science of medicine, then, is nothing more than trained and organised common sense based on physiology. It is still usual to speak of it as an inexact science; this is obviously wrong, since medicine uses the same methods as every other science and the results of observation are as definite as those of the chemist or physicist, although it is true that in the complexity of the problem with which the physician may have to deal all the conditions of importance may not be known and the results of an investigation, though correct for the conditions under which it is undertaken, may be misleading.

It is not to medicine as a whole that I wish to direct attention here, but only to that part of physiology which forms the basis of treatment.

When the sciences of physiology and pathology a century ago passed from the realms of natural history to deduction and experiment, they naturally attracted the more original and eager minds in medicine, and the text of the writings of the nineteenth century deals with changes in structure and function. Treatment became neglected, the old shibboleths and rituals of treatment which had held sway for centuries were discarded, and there was nothing with which to replace them. Diagnosis was then and is now far ahead of treatment; diagnosis is often accurate where there is no satisfactory treatment, and yet diagnosis is only a means to the end.

The science of treatment or pharmacology is therefore relatively new; it includes knowledge of all kinds dealing with the treatment of disease or alleviation of suffering. It is the climax of physiology and pathology, devised to subserve a practical end, and forms an important part of the great biological topic of the influence of conditions on the living organism. Few drugs now exist the mode of action of which is not understood, and the goal is not so far distant when it will be possible to introduce into the animal economy a factor which will exaggerate or retard the function of any tissue or collection of cells in the body, leaving the others unaffected; and most of these results have been

obtained by the methods used in experimental physiology.

The first object of science is to ascertain facts. Certain facts in physiology are relatively easily ascertained—those, for example, which involve the behaviour of ferments of isolated cells or of tissues, and require well-known chemical or physical methods. Other facts involving the physiology of the whole organism are more difficult to interpret, though they are the basis of the therapeutic side of medicine. More and more is physiology being regarded as the application of physics and chemistry to the phenomena of life. I might go beyond this and say that physiology is getting further and further from practical medicine, and this is the more regrettable as most of the chairs in physiology are connected with the medical schools and because the science of treatment is largely dependent on experimental physiology.

No branch of experimental biology has received less consideration in Great Britain than that of pharmacology: it is also the most neglected branch of medicine, and although the object of medicine is the healing of the sick, it is amazing that medical schools in Britain, often equipped with all other modern laboratories, lack departments of therapeutics. But the advent of institutions for experimental therapeutics is upon us, though Britain has taken little part in the movement. In this connexion we welcome the magnificent buildings of the University of Cape Town, and when the new hospital with its medical school is completed I confidently anticipate that adequate accommodation will be provided for that important branch of applied physiology, pharmacology, and that this will include laboratories of physiology and organic chemistry, which must be in close and direct association with the wards. The enormous importance of one branch of treatment to Africa, chemo-therapy, I will refer to later.

It is not surprising that British pharmacology should be so much behind that of other countries in the production of new curative remedies; practically all come from abroad; I may mention ephedrine for spasmodic asthma, liver extract for pernicious anaemia, insulin, the organic arsenicals, the dyes such as 205, the new anaesthetics local and general, hypnotics, and many others.

It has often been stated that the action of remedies may be best determined by experimenting with them on healthy men. This is not true; quinine is used to treat malaria, yet not one of the subjective symptoms induced in man has the remotest connexion with its curative properties. The same is true of the use of the iodides in syphilis and salicylates in rheumatism. The experiments of Joig and his pupils in 1825 with camphor, digitalis, and other drugs on healthy men added nothing of value to pharmacology. Subjective sensations are, it is true, produced, which are erroneously attributed to the drug which has been taken. Few,

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if any, experiments made on man without the most careful controls are of any real value. Properly controlled experiments have been made, however, with many substances. Precise experiments, for example, have been made both in Germany and America with bromides in epilepsy. In these experiments half the epileptics were given potassium chloride and the other half sodium bromide; after several weeks' use the bromide had decreased the number of attacks, whilst the chloride had no distinct action.

CHEMO-THERAPY.

At one time hopes ran high that the chemical structure of the molecule might indicate pharmacological action. During the last fifty years, many laborious researches have been conducted with this object: to modify the molecule that it may conform to some required action. But the mystery remains as mighty as ever. It is most probable that subtle energy factors binding the molecule—factors not displayed in a formula—control the action; certain it is that drug action is not determined directly by chemical combination with body constituents, but rather by delicate physical processes such as those of adsorption, solution, and surface tension.

Chemists have as yet not even determined the requirements of the molecule for the production of colour sensation. On the other hand, slight alteration of a molecule already complicated and with a known action has led to the production of many useful compounds, and not infrequently we may foresee the type of action which will occur under such special conditions. Considerations of this nature have led to the synthesis of the new local anaesthetics, antiseptics, antipyretics, diuretics, tropaneines, and other useful substances.

Parasites causing disease in man may be crudely divided into worms, protozoa, and bacteria. Chemo-therapy, that is, specific therapy of infectious disease, has had marked success in curing disease due to parasites in the first and second of these groups; these diseases are found mainly in the tropics. It has obtained much less success in the third group.

Diseases due to protozoa have an especial significance in Africa, and reference must be made to that area of tropical Africa occupying more than a million square miles in which one form of these, namely, trypanosomes, produce their ravages. Trypanosomiasis is one of the most serious of all tropical diseases and affects both man and beast; it is a scourge which renders vast tracts of land practically uninhabitable and takes its death-toll often in thousands and occasionally even in hundreds of thousands, and yet it is a disease which I believe should be curable if not preventable. The problem is one of wide interest and importance—scientific, humanitarian, and economic.

The members of two groups of chemical substances excel all others in their curative value in trypanosomiasis and spirochaetosis; these are the organic arsenical compounds and the dyes. The most satisfactory arsenical compound yet discovered

for the cure of trypanosomiasis is tryparsamide. It is less toxic than atoxyl and has a slightly higher therapeutic index; it has a most marked trypanocidal action in animals and has been used with some success in cases of sleeping sickness from *T. Gambiense*. One injection causes the disappearance of the parasite from the blood of man, and if the injections are repeated in courses, the cure may be complete.

DYES.

Many dye substances have been used in medicine. Trypan red and trypan blue belong to this group. Trypan blue was employed by my colleague, Prof. Nuttall, in piroplasma infections in animals, with results that most South Africans are well acquainted with. Afridol violet, a derivative of diamino diphenyl urea, and some allied dyes have also a powerful action on piroplasma.

How these substances act is not known, for like the organic arsenicals they do not kill the parasite *in vitro*. They have the property, however, of being adsorbed to the blepharoplast of the trypanosome; this adsorption is associated with diminished virulence of the parasite in infected animals, and after successive inoculations through several animals the organ may disappear. This direct action of a drug on a tissue, causing ultimately the complete disappearance of that tissue, is so remarkable that it is worthy of notice, as it represents the first known action of the kind.

The most valuable member of the afridol violet group so far produced was first made in the Bayer laboratory, but its composition was kept secret. It was, however, afterwards synthesised and its formula published by Fournneau, but only after long trials and infinite patience. The chemo-therapeutic index of this substance has the remarkable figure of 200 to 300; and so little as 1/32 mgm. will sometimes cure mice infected with trypanosomes. Fournneau has made many allied substances and derivatives of "205", he has modified the wings of the molecule by the addition of various side-chains, sometimes keeping the wings identical and sometimes changing them by joining two different complexes through the agency of phosgene. The number of such derivatives is obviously legion, and this makes it the more remarkable that he should have succeeded in synthesising "307", which at the present time is superior as a therapeutic agent to all other dyes in trypanosomiasis.

This "307" has a remarkable action on trypanosomes in laboratory animals, being three hundred times more effective than atoxyl. Its discovery has also opened a new era in therapeutics, since it represents the first chemical substance which when administered to man or animals in an infected trypanosome district gives a complete immunity to the disease for several months: it does not necessarily prevent trypanosome infection, but it prevents the effects of the disease. There is much in these experiments that suggests that we are on the fringe of a new pathology, and that our present crude methods of preparing anti-bodies in the future will be replaced by those of the organic and colloid chemist.

BACTERIAL INFECTIONS.

Tuberculosis is another problem of vast importance in South Africa, not only on account of its prevalence amongst susceptible individuals in both the European and native populations, but also because of its association with certain industrial diseases.

Much the most important industrial disease in South Africa is the silicosis produced in the extraction of gold from the conglomerate, both the pebbles and the matrix consisting of quartz. The gravity of pneumoconiosis depends largely on super-added tuberculous infection to which the workers have a predisposition, and in this respect crystalline silica is much more harmful than either amorphous silica or carbon. It may act by direct irritation, by its poisonous properties after solution, by colloidal action, or because it forms locally a nidus suitable for the growth of the tubercle bacillus.

Drugs are employed in tuberculosis either with the object of attacking and preventing the growth of the tubercle bacillus or other organisms with which the disease may be associated, of neutralising poisonous toxins, or of removing or relieving symptoms. It is with the first group that I am now concerned. Two groups of organic compounds are especially remarkable for their chemo-therapeutic action on bacteria. The first group has the quinine complex; quinine is the methyl-ester of cupreine and it can be reduced by nascent hydrogen to form hydrocupreine. The following table shows the effect of two derivatives of hydrocupreine in arresting the growth of certain micro-organisms:

	Ethyl hydrocupreine (optoquin).	Iso-octyl hydrocupreine (vuzin).
Diphtheria bacillus . . .	1 in 100,000	1 in 750,000
Pneumococcus . . .	1 in 400,000	Negligible
Staphylococcus . . .	1 in 500	1 in 16,000
Streptococcus . . .	1 in 1,000	1 in 80,000

The action of optoquin on the pneumococcus and of vuzin on bacillus diphtheriæ is highly specific; the higher and lower homologues have a greatly diminished effect. Many substances destroy bacteria in the test tube, but these drugs act in the animal body as well as in the test tube, and enough can be given by medicinal doses to animals and men to render the blood of these animals bactericidal.

The second group of drugs which exert a marked action on bacteria are certain derivatives of acridine. Trypaflavin was used during the War for infected wounds: unlike most antiseptics, it acts better in the presence of protein, but is not sufficiently selective or specific on micro-organisms in the presence of body tissues to be of any real value; it is easily absorbed and readily causes oedema. Rivanol is a more recent derivative of acridine. Morgenroth cured streptococcal infections by injections of rivanol under the skin. The injections to be efficient must be made soon after the infection and in the neighbourhood of the inoculated zone; rivanol will not cure a blood infection. The destruction of the tubercle bacillus presents two special difficulties: first in the fatty and protective

envelope surrounding the bacillus, and second in the small blood supply to the tuberculous lesion.

Hoyle and I have recently investigated two new types of gold compounds in tuberculosis. One of these is a complex aurous salt of ethylenethiocarbamide with the formula $(Au_2\text{etu})H_2O$, where 'etu' represents ethylenethiocarbamide.

This compound, prepared by G. T. Morgan, is stable, crystalline, and colourless at ordinary temperatures. It is soluble in distilled water, forming a solution neutral to litmus and with a pH value of about 6.2. It was tested for therapeutic effects on both human and bovine types of infection. For the former, inoculations were made subcutaneously into guinea-pigs with 1 mgm. doses of a virulent human strain. All the animals, control and experimental groups, died within a few weeks of one another, and all showed characteristic progressive lesions of similar extent.

It was found that treatment with the gold compound in bovine disease in rabbits prolonged life about 50 per cent when compared with controls. We adopted the arbitrary standard that treated animals should survive at least two or three times longer than the average length of life of the controls before clinical trial should be proceeded with. In view of the wide variations in individual susceptibility, and the difficulty that this entails in drawing sound positive conclusions from a small series of animals, it is absolutely necessary to exercise the utmost caution before arousing clinical expectations.

The second compound tested by us was a complex gold derivative of succinimide, prepared by my colleague, Sir William Pope. This compound is non-ionised and the gold is associated in chemical combination in an internal organic ring. It is a white, crystalline, stable compound at ordinary temperatures, readily soluble in water to a neutral solution.

This substance was tested for therapeutic effect in experimental bovine infections in rabbits. In some animals this treatment was supplemented by injections of potassium iodide subcutaneously; in no case has any therapeutic benefit been observed. There has been no increase in the lengths of life of the treated animals, and the type and extent of disease at post-mortem examination in treated and control animals has in every case up to the present been similar.

These compounds are interesting because one delays death and the other is entirely without action. They may afford a hint as to the lines on which organic chemists should proceed, and perhaps show that gold in the ionic form is desirable.

THE INTERNAL SECRETIONS.

In the last twenty years much evidence has accumulated to show that the glands of internal secretion are responsible for the regulation of growth, of metabolism, and often for our appearance if not for our very character. Exaggeration or diminution in the secretion of one or other of the tissues may induce conditions so decided as to be obvious to everybody, though the effects produced by minor alterations in the co-ordination of the several

secretions may not be so evident. Giants and dwarfs, unusual pigmentation and anæmia, disproportion in the growth of the skeleton, such as enlarged hands and face, bulging deer-like eyes or oriental eyes and beards in women are noticeable to everyone; excessive fatness or emaciation, a choleric or bucolic temperament cause no comment, yet may equally arise in the victim from a want of co-ordination in the internal secretion.

The gonads present the clearest evidence of the influence which a tissue may exert on metabolism. I will refer only to the ovary. The ovary differs from other organs of internal secretion in that it functions in a cyclic manner, and it is obvious that extracts made from ovarian tissue may exert a different action according to the period of the cycle when they are made. Numerous extracts have been prepared from the ovary which are reputed to exert one or other type of action. 'Oestrin' is the name given to one such substance: it can be made from many sources, both animal and vegetable, besides the ovary. Oestrin exerts a very definite action in lower animals, but its use in man is so variable and disappointing as to make it valueless in practical medicine. When it is injected subcutaneously into spayed rats and mice it produces typical oestrus with normal sex instincts, and when injected into immature animals it induces puberty; regular injections at fixed intervals will keep animals sterile.

Many experimental observations show that the corpus luteum is concerned with the rhythm of the oestrus cycle and with the prevention of ovulation. A persistent corpus luteum, both in the case of animals and women, produces sterility, a condition which is cured by its removal.

A third active substance distinct from oestrin and corpus luteum is elaborated by the ovary and was described by Marshall and myself. This substance is water-soluble and thermo-stable, and can be prepared from the ovary at one stage of its cycle only, by maceration with warm saline followed by boiling and filtering. The injection of this substance into animals causes a secretion of pituitrin, and this in turn renders the uterus supersensitive and highly responsive to other forms of stimulation.

Our experiments showed that at one stage only of the ovarian cycle was this hormone elaborated, namely, at the stage when the corpora lutea are degenerating. So long as the corpora are functioning they control the metabolism of the ovary, but when they degenerate control is lost and the ovary liberates the specific substance which excites the pituitary gland to secrete. This means that extracts of the ovary made between the heat periods or during pregnancy are without effect on the pituitary gland, but extracts made just before the heat period or just before parturition induce secretion of the gland. As the significant action of pituitary extract is to sensitise the uterus it is difficult, if not impossible, to avoid the conclusion that these two phenomena are closely associated.

It is not suggested that the ovario-pituitary endocrine mechanism is the sole factor in producing labour pains. No doubt the foetus itself acts as a

direct stimulus, and without the foetus the intense muscular contractions would not occur, but it is also clear that the onset of labour cannot easily be accounted for without postulating some further exciting cause apart from the foetus and the uterus.

In conclusion, no romance can be more remarkable than the fact that doctors, by using pituitary extract to stimulate the uterus in pregnancy, should have adopted the method which Nature herself employs and that physiological function is after all a pharmacological action.

MEDICINE AND PHYSIOLOGY.

Civilisation has been responsible for many new diseases. Our food-stuffs in great cities are often preserved and important constituents of fresh foods may be lacking. The science of dietetics has assumed an enhanced importance lately, which is partly due to the artificial preparation of many of our foods. Many experiments have been made in my laboratory to show that certain foods given in excess to animals fed on a synthetic diet, but containing an ample supply of the recognised vitamins, suffer from poisoning sometimes of the most profound and fatal kind. The same experiments made on animals living on an ordinary diet show that the excess of the 'poisonous' food is harmless. For example, certain preparations of irradiated ergosterol given to rats which are being fed on a synthetic diet act as a poison, but if the rats are fed on bread and milk the effect of the ergosterol is negligible. In real life we do not live on a completely synthetic diet; nearly everyone takes some if not an abundance of fresh food, so the practical value of this type of experiment may be over-estimated, though it is of considerable academical interest.

Civilisation has brought bad sanitation in houses, and even our windows may be depriving us of fresh air and filtering out certain rays of light, bringing its attendant tuberculosis—for tuberculosis is a disease of houses. Science is now engaged in endeavouring to remedy the evil effects which it has produced.

I have endeavoured to show that all precise knowledge in therapeutics is based upon controlled experiments on animals or man, and that the elucidation of the action of medicaments by the methods and data of experimental physiology is one of the most important steps taken to place medicine on a scientific basis. How important this is may be gauged from the fact that all fundamental advances in treatment in the last thirty years have originated directly or indirectly from experiments on animals. There can be no doubt that the future of therapeutics, and therefore of medicine as a whole, is intimately connected with physiology.

Britain for fifty years has every reason to be proud of her progress and achievements in physiology; it is acknowledged that she can show records second to none and that her savants have included some of the world's greatest investigators. It remains for us to hope that in the future she may attain equal success in the associated sciences directly concerned with the relief of suffering and cure of disease.