CORTISONE AND ACTH: THE PRESENT POSITION IN AMERICA

BY

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I have recently spent three months in the United States, during which time I had particularly good opportunities of watching most of the clinical and experimental work with "cortisone" and ACTH that is being carried out in the selected medical centres to which these hormones have been allotted for trial.

At the Editor's request, I shall attempt to provide for British physicians a *general and quite simple* account of the work accomplished in America up to the end of November, 1949. This is not easy, for many of the things seen or heard, both clinical and experimental, are as yet unpublished; and it would manifestly be wrong to describe them in detail or even to refer to some of them at all. Nevertheless a general account may be welcome, since knowledge of what is going on is still fragmentary in Britain.

The first part of my visit, so far as cortisone and ACTH are concerned, was mainly devoted to clinical observation of many patients in hospital under short-term treatment with one or other of the two substances. The patients seen included not only sufferers from the rheumatic diseases, on which Hench's original and dramatic discovery was made at Rochester (Mayo Clinic), but also sufferers from a wide variety of other diseases, both acute and chronic. During later weeks I took greater interest in the work going on feverishly at the selected centres on the important problem of how these hormones act, and how they (or other related compounds) may ultimately be harnessed for use in practical therapeutics.

The immediate effects of cortisone in rheumatoid arthritis were so dramatic that almost all the tremendous publicity, especially in the lay press, has been devoted to the hope that a cure has at last been found for this one serious and chronic disease. This position is no longer correct, for as soon as cortisone (or ACTH, which acts indirectly but similarly) had been tried out in a wide variety of other diseases, acute and chronic, immediate and astonishing results were seen to occur in a number of them.

It was then realized that something quite new and fundamental in medicine and therapeutics had been discovered, with far wider possibilities and implications than had at first been conceived. It is not too much to say that the problems of cortisone and its action in the body now extend far beyond the boundaries of the chronic rheumatic diseases, in which its remarkable effects were first demonstrated.

The Two Hormones—Cortisone and ACTH

Cortisone is, so far as we know at present, the essential substance involved in this new discovery, and it is necessary to explain how ACTH comes into the picture at all.

Cortisone is one of the steroid compounds, now accepted as a hormone, which had been shown to exist in the suprarenal cortex, and its structural chemical formula had been established. It is present, however, in such small amount that a supply sufficient to test its physiological actions completely was never obtainable from the suprarenal cortex. The cortisone now used clinically and experimentally is entirely a laboratory product, identical in chemical structure with the natural suprarenal secretion, and built up by

Kendall in 1938 by a long and difficult synthetic technique using bile acids as his starting-point or source. Kendall named his synthetic substance "compound E," and for ten years it lay simply as a chemical triumph until his colleague Hench, on good theoretical grounds which he has well described, first tried it in a patient suffering from rheumatoid arthritis. All the cortisone (compound E) now available in the United States is made by Merck and Co., Inc., essentially by Kendall's process, using bile acids from ox bile as the source.

ACTH, or pituitary adrenocorticotrophic hormone, is a natural product obtained from the pituitary glands of animals, chiefly pigs, and has not been made synthetically. Its preparation is not unduly troublesome for the expert chemist, but it seems difficult to ensure an end-product which is both active and pure. ACTH first became available in adequate amount for clinical investigation in 1948, in the autumn of which Hench actually began his work with cortisone in rheumatoid arthritis. It is now evident that the physiological function of ACTH is to stimulate the secretory activity of the suprarenal cortex, and the hormone was first used to advantage by Thorn and his colleagues in Boston as a test of suprarenal function in Addison's disease.

It is now clear that stimulation of the suprarenal cortex by ACTH induces an increased secretion of cortical steroids, including the all-important cortisone. So long as the suprarenal cortex is functionally intact, therefore, administration of ACTH merely excites an increased production of cortisone, and the clinical results are, theoretically at least, essentially the same.

The chief but not the sole supplies of ACTH used in America have come from the laboratories of Armour and Co., Chicago, the well-known meat-packing firm, to whom abundant hogs' pituitary glands are available.

To reiterate, for clearness. An increased amount of cortisone in the body, capable of inducing the clinical effects observed, can be brought about in two ways: (1) directly, by parenteral injection of synthetic cortisone, and (2) indirectly, by parenteral injection of ACTH, which stimulates the suprarenal cortex to secrete more cortisone.

One interesting point that may be of great importance in connexion with what are termed "side-effects" should be mentioned here. Injections of synthetic cortisone do not stimulate the suprarenal cortex—on the contrary, it has been suggested that they may "put it to sleep," at least for a time. ACTH, on the other hand, increases the natural production of cortisone and other steroids by the suprarenal cortex, and its continued use might lead to hypertrophy and uncontrolled hypersecretion.

Before leaving the description of the two hormones it should be stated that the American supplies of cortisone and ACTH, from Messrs. Merck and Co. and Armour and Co., respectively, have all been given free of charge to the carefully selected experimental centres; but it is clear that this arrangement cannot continue indefinitely, and may indeed very soon terminate.

Clinical Effects of Cortisone and ACTH

As just explained, the administration of each hormone gives rise to an immediate increase of cortisone in the body—in one case directly, in the other indirectly. The result is essentially the same; and since far more ACTH has been available, owing to its easier production, many more patients have been tested and treated with this hormone than with synthetic cortisone.

The rapid and intensely dramatic effects with each hormone in rheumatoid arthritis, first discovered by Hench and his colleagues, have already been adequately described in British journals. To me the most extraordinary thing was the speed of the improvement, with relief both of pain and of stiffness, and also, alas, the pathetic rapidity of relapse when treatment was stopped and replaced by injections of inert colloidal cholesterol in identical containers. The almost immediate euphoria and mental stimulation in the patients is equally remarkable, and there are now good reasons for believing that this is not just an ordinary psychological effect but if kept going by continual treatment may in rare cases end in acute psychosis.

The whole effect of this treatment in rheumatoid arthritis was aptly described by an American friend as "like suddenly turning off the tap and then (when hormone treatment is stopped) suddenly turning it on fully again." I saw no case of rheumatoid arthritis completely or permanently cured with cortisone or ACTH. Short courses of treatment, given at intervals, have, however, led to considerable lasting improvement over a number of months. It should be noted that scarcity of the two active hormones was not the only cause of the short periods of treatment, but also the undesirable "side-effects," which are described separately below.

I have seen the effects of cortisone and ACTH in a wide variety of diseases, chiefly medical but a few surgical. I observed immediate or rapid beneficial effects—probably as great but not so visibly dramatic as in a crippling disease of locomotion such as rheumatoid arthritis—in acute rheumatic fever, chorea, gout, chronic ulcerative colitis, lupus erythematosus diffusa, scleroderma (with oesophageal involvement), asthma, lymphadenopathies (including lymphosarcoma and Hodgkin's disease). I have heard of, but did not see, other diseases in which great improvement was obtained. Unfortunately, except on a second visit to Boston after an interval of several weeks, I was unable to follow the progress of many patients for an adequate time. I am therefore unable to state how many of the patients seen in the early stages of treatment subsequently relapsed, or if any were permanently cured as a result of the hormone therapy. I have no doubt that in one patient, suffering from acute lupus erythematosus and obviously at death's door, the effect of cortisone was absolutely life-saving. I cannot say, however, whether this patient has remained well or has subsequently relapsed.

One fact concerning the clinical action of cortisone (and ACTH) has already been touched on in American publications and may be mentioned here as of interest to surgeons as well as physicians. Wounds show no sign of healing and abscesses no signs of granulation-tissue formation in patients (or animals) to whom the hormone is being administered. The possible fundamental implications of this important observation are discussed below, but it seems obvious that this effect might be good (for example, in inflammatory diseases of joints, etc.) or disastrous (for example, on the granulation-tissue barrier round an active tuberculous lesion).

Side-effects of Cortisone and ACTH

I saw undesirable side-effects in a considerable number of patients treated with cortisone or ACTH, but none was severe and most of them seemed in process of passing off after treatment had ceased. I heard of serious side-effects, including persistent hypertension, glycosuria and even true diabetes, acute spread of tuberculosis, and violent mental disturbance. I can say nothing about these except to express a hope that, if true, accounts of them will soon be published.

By far the commonest side-effect seen by me with both hormones was a very modified Cushing's syndrome, characterized by "moon-face," acne, rapid gain in weight, hirsuties in females (seldom more than trivial), and striae of the skin. This side-effect was not to be wondered at, and indeed was almost to be expected in view of the well-known association of hyperactivity of the adrenal cortex with Cushing's syndrome. While relatively benign and unimportant, following *short* courses of treatment, it seems evident that the early development of this syndrome may preclude, until our knowledge increases, administration of cortisone or ACTH over long periods of time.

A few side-effects described may be due to other pituitary hormones being present in some samples of ACTH, but these should be avoidable in future.

How do Cortisone and ACTH Act in the Body?

It is far too early to attempt any real answer, and the most active and energetic research work, both in patients and in animals, is being pursued at a number of centres in the United States.

A few positive indications have already emerged, the most important suggestion being that cortisone has some governing or controlling action on the so-called collagen tissues (including connective tissues and scar tissue) and lymphoid tissues of the body. The full evidence in favour of this view has not yet been published; but what has already been said here about the clinical effects on the fibrous tissues in rheumatoid arthritis, on the prevention of wound-healing, and on the remarkable results in lupus erythematosus diffusa (a so-called collagen disease) is sufficient to indicate a promising line of research, which also lends itself to animal experiments.

Many complete and elaborate metabolic investigations have already been carried out on patients under treatment, some of which have been published. Nothing, however, indicating any constant and important chemical change in body metabolism has been discovered, but only some fresh knowledge of various side-effects—for example, glycosuria.

Quite a different line of research, which has already attracted great attention, arises from the work of Hans Selye and his colleagues in Montreal, Canada. Selye's recent paper in this *Journal* (November 19, 1949, p. 1129) on the "Participation of the Adrenal Cortex in the Pathogenesis of Arthritis" gives details of one part only of his researches. Selye's main hypothesis or generalization has been gradually shaping itself over a period of years as his "general-adaptation syndrome." He suggests that following exposure to a great number of "stresses" (emotional tension, infections, intoxications, etc.) the body may respond with increased production of adrenal cortical hormones, which help to raise general resistance. This general-adaptation mechanism may, however, go wrong and, on Selye's hypothesis, of itself become a principal cause of disease, including the rheumatic and the so-called collagen diseases. It is interesting to hear physicians in America already talking of "stress diseases," but it must be remembered that Selye's work simply puts forward a hypothesis, the proof of which must, as always, depend on how it fits all the facts.

Some Conclusions

1. The discovery of the clinical effects of cortisone (and ACTH) is something of quite fundamental importance in medicine, the ultimate implications of which, in the prevention or treatment of disease, cannot yet be foreseen.

2. No one knows how cortisone works. All we can say is that, thanks to the work of Hench and Kendall, we have been provided with a new and powerful weapon for medical research, the results of which may take a long time to gather fully.

3. The effects in the chronic rheumatic diseases are dramatic; and Hench, in a public lecture in Boston, described the discovery of cortisone as the "end of the beginning" of hope for sufferers from rheumatoid arthritis. This is true, but is as far as we should go at present, and uninformed but understandable publicity is to be deplored.

4. A number of other diseases, mostly chronic but some acute, show almost as striking immediate improvement when cortisone or ACTH is administered.

5. It is clear that both cortisone and ACTH are at present a long way removed from ordinary therapeutics, for they have unavoidable dangers as well as beneficial effects. Their practical application must await the results of intensive research.

6. Bile acids are at present the only source from which cortisone can be made commercially, and so long as this is so the hormone will always be very scarce and very expensive. It is well known that search for cheap and abundant vegetable "sources" is now going on in many parts of the world.

Meanwhile the chemists are not idle; and in conversation with some of the steroid chemists in the United States I gained the impression that they are not excited by these expeditions, but are confident that some simpler substance will be found having the same effects as compound E.

I wish to thank many medical friends in the United States who so willingly showed me their patients and discussed their problems, especially Drs. Bauer, Keefer, Thorn (Boston); Baehr, Loeb (New York); Hench, Kendall (Rochester, Minn.); Harvey, Marshall, Rich (Baltimore); Carlisle (Merck and Co.); Mote (Armour and Co.); and Sevringhaus (Hoffmann-LaRoche, Inc.).

MEDICAL NEW YEAR HONOURS

The names of the following members of the medical profession were included in a New Year Honours List published in the *London Gazette* on January 2.

Baron

LESLIE HADEN GUEST, M.C., M.R.C.S., L.R.C.P., M.P. Member of Parliament for Southwark North from 1923 to 1927, and for Islington North since 1937. For political and public services.

K.C.V.O.

HAROLD KINGSTON GRAHAM HODGSON, C.V.O., M.B., B.S., F.R.C.P., D.M.R.E., F.F.R., Director of the X-ray Department, Middlesex Hospital.

K.B.E. (Civil Division)

THOMAS ERNEST VICTOR HURLEY, C.B., C.M.G., V.D., M.D., F.R.C.S., F.R.A.C.S., Melbourne, Victoria, Australia. For public services.

Knighthood

HAROLD ESMOND ARNISON BOLDERO, D.M., F.R.C.P. Dean of Middlesex Hospital Medical School and Registrar of the Royal College of Physicians of London.

JOHN ALEXANDER CHARLES, M.D., F.R.C.P., D.P.H., at present Deputy Chief Medical Officer, Ministry of Health. Will succeed Sir Wilson Jameson as Chief Medical Officer of the Ministry of Health and of the Ministry of Education on May 11.

FRANK ARNOLD GUNESKARA, C.B.E., E.D., M.R.C.S., L.R.C.P., Senator, Ceylon.

WILLIAM WILLIS DALZIEL THOMSON, M.D., F.R.C.P. Professor of Medicine in Queen's University, Belfast.

THOMAS GEORGE WILSON, C.M.G., M.D., F.R.C.S.Ed., F.A.C.S., F.R.A.C.S., F.R.C.O.G. Director of Obstetrics and Gynaecology, University of Adelaide, South Australia. For public and philanthropic services.

C.B. (Military Division)

JOSEPH ARCHIBALD MAXWELL, C.V.O., C.B.E., F.R.C.S.Ed., Surgeon Rear-Admiral, R.N.

FRANCIS ROBERT HENRY MOLLAN, O.B.E., M.C., L.R.C.P.&S.I., Major-General, late R.A.M.C.

TERENCE CHARLES ST. CLESSIE MORTON, O.B.E., M.D., F.R.C.P., D.P.H., D.P.M., D.T.M.&H., Air Vice-Marshal, R.A.F., Honorary Physician to the King.

C.M.G.

ERIC HOWARD MANLEY LUKE, M.B., Ch.B. A surgeon at Wellington Public Hospital, New Zealand, for over 25 years and Chairman of the Council of the New Zealand Branch of the British Medical Association.

C.B.E. (Military Division)

THOMAS NORMAN D'ARCY, L.R.C.P.&S.I., D.O.M.S., Surgeon Captain, R.N.

ANDREW HARVEY, M.B., B.Ch., D.P.H., Group Captain, R.A.F.

C.B.E. (Civil Division)

JANET KERR AITKEN, M.D., F.R.C.P., Consulting Physician, Elizabeth Garrett Anderson Hospital. Member of the Council of the Royal College of Physicians of London.

ROBERT VIVIAN BRADLAW, F.R.C.S., M.D.S., F.D.S.R.C.S., Dean of the Faculty of Dental Surgery, Royal College of Surgeons of England; Professor of Oral Pathology in the University of Durham.

CLIFFORD VINEY BRAIMBRIDGE, M.V.O., M.B., B.Chir., F.R.C.S.Ed., Colonial Medical Service. Senior Surgical Specialist, Kenya.

IDA CAROLINE MANN, D.Sc., M.B., B.S., F.R.C.S., D.O.M.S., Senior Surgeon, Royal London Ophthalmic Hospital.

ERNEST ALEXANDER NICOLL, M.D., F.R.C.S.Ed., Surgeon-in-charge, Berry Hill Hall Miners' Rehabilitation Centre, and Consulting Surgeon to the Miners' Welfare Commission.

FREDERICK TAVINOR REES, M.C., T.D., M.R.C.S., L.R.C.P., Director-General of Medical Services, Ministry of Pensions.

O.B.E. (Military Division)

ALFRED EDWARD FLANNERY, L.R.C.P.&S.I., Surgeon Commander, R.N.

O.B.E. (Civil Division)

OKUNADE AJIBADE, L.R.C.P.&S.Ed. For public services in Nigeria. EDGAR SCOTT BOWES, M.R.C.S., L.R.C.P., Chairman, Poole Centre, St. John Ambulance Association.

THOMAS GREGORY BURNETT, M.B., Ch.B., Chairman, Bulawayo Hospital Advisory Committee, Southern Rhodesia.

ERNEST THOMAS CONYBEARE, M.D., F.R.C.P., Medical Officer, Ministry of Health.

PANAGODAGE BERTRAM FERNANDO, M.B., B.S., M.R.C.P., Professor of Medicine in the University of Ceylon.

ROBERT SEARSON RODNEY FRANCIS, M.B., Ch.B., of Hastings, New Zealand. For services to the community in connexion with the treatment of tuberculosis.

MINNIE GOSDEN, M.B., B.S., Colonial Medical Service. Senior Pathologist, Sierra Leone.

GEORGE VERT THOMSON McMICHAEL, M.B., Ch.B., D.P.H., Medical Officer of Health for the Burgh of Paisley.

DAVID GWILYM MORGAN, M.R.C.S., L.R.C.P., Administrative Medical Officer, United Cardiff (Teaching) Hospitals.

ARTHUR HAROLD MORLEY, M.B., Ch.B., F.R.C.S.Ed., Colonial Medical Service. Surgical Specialist, Tanganyika.

CHARLES ELIAS REINDORF, M.D. For public services in the Gold Coast.

ALFRED EATON SPAAR, F.R.C.S.Ed., Medical Practitioner, Kandy, Ceylon.

JOHN HARGREAVES HARLEY WILLIAMS, M.D., D.P.H., Secretary-General, National Association for the Prevention of Tuberculosis.

M.B.E. (Military Division)

MOHANDIRANGE DON SIMON JAYAWARDENA, E.D., L.R.C.P.&S.Ed., Major, Ceylon Medical Corps (Reserve).

Sir William Scott Douglas, K.C.B., K.B.E., Secretary of the Ministry of Health, has been promoted to G.C.B.

The King intends to confer the honour of Knighthood on Mr. Arthur Sims "for services to medicine and education in the British Commonwealth." In 1946 Mr. Sims made a gift of 10,000 £1 Ordinary Shares of Cooper, Triffitt and Co., Ltd., to the Royal College of Surgeons of England for the endowment of a Commonwealth Travelling Professorship, providing an income of £2,000 a year. In 1948 Sir Hugh Cairns was appointed the first Travelling Professor and was followed by Professor G. W. Pickering (1949) and Sir Reginald Watson-Jones (1950).