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SOME RECENT ADVANCES IN ENDOCRINOLOGY*

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Although recent advances largely depend on biochemical research and animal experiments, it would be a great mistake to ignore the importance of clinical observations and the interpretation of older clinical observations in the light of new knowledge. We have perhaps been rather dazzled by the influence of new hormones on the symptomatology of disease processes, and it might be argued by the pragmatic physician, or humanitarian, that successful therapy is the end-object of all medical research, but this conception certainly cannot replace the need for a deeper understanding of the causation of disease and its course. We must also not forget that Nature herself is a most prolific experimentalist, and if I may quote from my 1951 lecture at the New York Academy of Medicine: "Let us not be unduly obsessed by the laboratory so that our clinical senses and judgment become blurred, but, at the same time, let the clinician maintain a sensitive awareness of the experimentalist and biochemist, so that their penetrating shafts of revelation may not be shut out by obtuseness."

Growth Hormone—Its Multiple Manifestations

Thirty years ago Evans and Long produced giant rats by a saline suspension of pituitary glands of cattle. In 1939 Mirsky produced evidence that the nitrogen-retaining action of anterior pituitary extracts is mediated in part by the islets of Langerhans of the pancreas. Young (1941, 1951) and colleagues have studied the problem over a number of years from several angles. They observed that in rats (and also in young puppies) pituitary diabetogenic extracts did not produce diabetes but produced nitrogen retention, somatic growth, and an increased catabolism of fat, and histologically the pancreas of animals so treated showed hypertrophy of the islets of Langerhans accompanied by an increase in insulin content (Marks and Young, 1940). It was therefore concluded that the growth activity of a pituitary extract was closely related to its diabetogenic activity, and that the mechanism of "growth hormone activity" included the induction of hyperfunction of the pancreatic islets and hypersecretion of insulin.

In 1945 Li, Evans, and Simpson prepared from the anterior lobe of ox pituitary a purified protein having the biological characteristics of growth hormone. Its molecular weight was 44,250 and it contained tyrosine, tryptophan, and glutamic acid. The isolation of a crystalline growth hormone was announced by Fishman, Wilhelmi, and Russell (1947) and by Li, Evans, and Simpson (1948). In 1949 Cotes, Reid, and Young, using purified growth hormone in rats to measure growth-promoting activity and in cats for diabetogenic potency, formulated that the diabetogenic and growth-

promoting activities are due to the same pituitary substance. The diabetogenic action of pure growth hormone was confirmed by Campbell, Davidson, Snair, and Lei (1950), who also contrasted it with the relatively slight diabetogenic action of adrenocorticotrophic hormone (A.C.T.H.).

Szego and White (1949) showed that a purified growth hormone preparation, in fasting intact and adrenalectomized mice, spared nitrogen metabolism and accelerated fat metabolism, as evidenced by intense fatty infiltration of the liver of the fasting animals.

Becks *et al.* (1944) have demonstrated an antagonism between A.C.T.H. and growth hormone; and A.C.T.H. alone will inhibit growth in normal or adrenalectomized animals. In the hypophysectomized rat, A.C.T.H. does not influence the inactive condition of the epiphyseal cartilage, whereas growth hormone restores proliferative activity. This latter activity is prevented by the simultaneous injection of A.C.T.H. Growth hormone in the hypophysectomized rat caused an increase in protein of the carcass, whereas A.C.T.H. caused a decrease in protein and an increase in fat. The histological work was confirmed by Baker and Ingle (1948). Another interesting finding was that purified pituitary growth hormone has a marked galactopoietic activity (Cotes, Crichton, Folley, and Young, 1949).

Clinical Significance

What clinical significance have these observations? The occurrence of diabetes in the course of acromegaly is easier to understand, and also the fact that it is usually of greater severity than the diabetes of Cushing's syndrome. The finding of Coggeshall and Root (1940) that a substantial proportion of diabetic children are initially above average in height and physical development takes on added significance, as does the observation that mothers with large babies at birth are more prone to diabetes if they have not the condition already (Miller, Hurwitz, and Kuder, 1944). Acromegalics may be very large at birth. Cushing (1912) described the case of a Hungarian acromegalic who at birth was as large as a 1-year-old child and whose wife had three enormous babies, the middle one being the only survivor and weighing 17 lb. (7.7 kg.). This giant was in addition enormously fat for the first few years of life; this raises the question of hyperinsulinism resulting from the growth hormone, the question of fatness and growth in relation to the relative effectiveness of the catabolic action of growth hormone on fat and the contrasting anabolic action of the excessive insulin it has produced by stimulation of islet cells. There may, however, be a more prolonged association of adiposity with skeletal growth, since it has been found that a high percentage of fat children and adolescents are taller than their contemporaries.

The fact that the chemists found it very difficult initially to separate the pituitary growth hormone from the adrenocorticotrophic hormone is not without clinical significance. Cushing

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drew attention to the large size of the adrenal cortex, often nodular, in gigantism and acromegaly, but it is questionable whether pure growth hormone stimulates the adrenal cortex. Moon, Simpson, Li, and Evans (1950) found that long-continued injections of pure growth hormone in rats led to marked hyperplasia and neoplastic formation of the adrenal medulla, neoplastic nodules breaking through the cortex, but no evidence of stimulation of the adrenal cortex, although the surface was reported as nodular in 6 out of 15. Long-term experiments with A.C.T.H. should prove of interest. Incidentally, those authors noted other neoplastic stimulation by growth hormone—for example, lymphosarcomatous transformation in areas of peribronchial lymphoid hyperplasia (6 out of 15 rats), with invasion of bronchi, lung, and vascular channels, granulosa-cell tumours, and luteomas of the ovary.

Influence of Androgens on Skeletal Growth

Clinically, male acromegals are hirsute, and hirsutism is a not infrequent complication of acromegaly in females. In one such patient under my care, a female acromegalic of 60 in whom the illness started at 30 and the hirsutism at 45, the urinary 17-ketosteroids were only 5 mg. and 3.4 mg. in two 24-hour specimens, but the adrenals at necropsy were twice the normal size and weight. In one mild acromegalic under my care, an adrenal adenoma, or adenocarcinoma, was removed at the age of 20, the symptoms being amenorrhoea and generalized hirsutism, and the 17-ketosteroids being very high—130 mg. in 24 hours. This was 12 years ago; menstruation has been regular but hirsutism persists, and the 17-ketosteroids remain at about 65 mg. Recent laparotomy showed no neoplasm. Is a pituitary androgenic stimulus to the adrenals responsible for hyperplasia of the left adrenal and neoplasm of the right? Lynch (1950) described a tall boy of 6 with pseudo-sexual precocity from the age of 3 who grew even more rapidly after the removal of an adrenal tumour than before. At 6 years he was 9 in. (22.8 cm.) above the average, and at 9, 13 in. (33 cm.) above the average. Mild androgenic symptoms also persisted. Was a pituitary stimulus responsible for the neoplasm and was that stimulus growth hormone alone or together with adrenotropic hormone? These cases of adrenal sexual precocity also bring us to the question of how far androgens influence skeletal growth.

In contrast to the as yet inexplicable failure of growth hormone used therapeutically, testosterone or methyl testosterone is a powerful stimulus to skeletal growth in man, although its action may not be directly somatotrophic. It is effective in deficient growth associated with hypogonadism and in children in whom normal sexual maturity has not yet been reached. Its action is associated with nitrogen retention, increased appetite, and increased muscular development and strength. Its action on skeletal growth is certainly different in mechanism from that of pituitary growth hormone. Thus Albright (1947) found a raised serum phosphorus in active acromegaly; and this decreased with suppression of pituitary activity by radiation, surgery, or large doses of oestrogens or androgens. Kinsell, Michaels, Li, and Larsen (1948), of the California Medical School, have correlated these findings with the level of growth hormone in the patient's plasma and have divided physiological growth in man into two phases: (1) childhood pituitary type with high plasma phosphorus, and (2) adolescent steroid type, with normal plasma phosphorus and dependent upon adrenal and gonadal androgens, to which might be added progesterone, which is experimentally effective. Androgens and oestrogens also accelerate bone age and epiphyseal union in heavy dosage, but I have not found this an obstacle to androgen therapy for retarded growth.

Adiposity

Last year a distinguished visitor from the U.S.A. crystallized his support for the gluttony theory of adiposity in the telling phrase: "Fat comes from food—where the hell else could it come from?" As a fundamental qualification of this I would cite the clinical history of an infant of 6 months

who suddenly develops a voracious insatiable appetite and monstrous obesity, and at the age of 12 months dies from heart failure, a large adrenal cortex adenocarcinoma being found.

The whole of the aetiology of the adiposity battle has been fought along quantitative mathematical lines, but more recently qualitative considerations have been prominent. Kendall's paper on the subject appeared as long ago as 1945, but it has been much neglected. He studied the action of various adrenal steroids implanted in mice, observed for some six weeks. Compound A (11-dehydrocorticosterone) produced an increase in weight compared with the control mice, and compound B (corticosterone) produced a decrease in weight, but in both animals analysis of the carcass showed a great increase in the percentage of fat and a decrease in the percentage of protein. Compound E (cortisone) showed less significant changes. Thus an exogenous adrenal hormone, which might well be endogenously secreted in certain conditions, could exchange much of the protein of the body for fat with or without an increase in weight. Kendall (1945) suggests that the glucose derived from protein breakdown is converted into fat in the presence of these adrenal compounds, but is oxidized in their absence. It is of interest that degenerative lesions, sometimes complete necrosis, were found in the muscles. Hog's adrenals were examined for compound A, but were found to contain large quantities of compound F (17-hydroxycorticosterone). These results might have been anticipated in some degree by the earlier experiments on adrenalectomy in rats which showed a relative loss of fat compared with control paired-fed normal rats (Simpson, Dennison, and Korenchevsky, 1934).

The fact that body weight can be increased without an increase in diet by the action of hormones has also been demonstrated recently by Young (1951). Thus dogs receiving growth hormone alone, or together with insulin, increased their weight on a diet which was primarily only sufficient for them to maintain it. This apparent contradiction of the laws of energy was explained by the fact that protein was deposited and fat burnt, and the combustion of fat gives much more energy than that of protein. Under other circumstances, and with increased food intake, both fat and protein were deposited. The increased appetite following administration of growth hormone or testosterone usually results in an increased proportion of body protein rather than fat, and this contrasts with the action of A.C.T.H. or of adrenal compound A.

The part played by endogenous insulin in adiposity may be reflected in the fact that an islet-cell carcinoma is probably the only carcinoma (apart from some adrenal cortex tumours) in which the presence of metastases is manifested by increased weight and fat. It is a challenging qualification of hormone theories that hypothalamic lesion adiposity occurs even after hypophysectomy. It will be of interest to see if it can also be induced after bilateral adrenalectomy. Can the hypothalamus influence the metabolism and deposition of fat apart from inducing polyphagia?

It is often argued that these endocrine adiposities have no relationship to the main problem of idiopathic adiposity, but this argument becomes rather tenuous when the widespread incidence of endocrine stigmata is recognized, and from the fact that endocrinopathies may have very long life histories. I was recently asked to see a patient of Mr. Leslie Williams at St. Mary's Hospital, a woman of 35, who weighed 112 lb. (50.8 kg.) before her first pregnancy, 224 lb. (101.6 kg.) after it, and returned to her normal 112 lb. (50.8 kg.) within a year. In the second pregnancy her weight increased from 117 to 238 lb. (53 to 108 kg.) and then again became normal, and in the third pregnancy from 133 to 228 lb. (60.3 to 103.4 kg.) followed by a return to near normal. Surely this is the effect of pregnancy pituitary-adrenal hyperfunction and subsequent involution, an involution which is far less complete in many women. In one such persistent adipose case the glycogen steroids six months after pregnancy were some three times the normal (Simpson and Bornstein, 1951, unpublished observations).

The pituitary adrenal hyperfunction syndrome of adipose gynism that I have recently described (Simpson, 1951a) probably has its counterpart in adult life, as, for example, manifested by the fat mother of such a patient with plethora, mild facial hirsutism, hypertension, and wide areas of reddish cyanotic discoloration on the upper arms, thighs, and inner knees. It is relevant to my thesis of the endocrine origin of adiposity that Robinson and Norton (1951), in a series of cases, found "undoubtedly high excretions" of corticosteroids only in Cushing's syndrome and in those cases "in which there was very marked obesity not necessarily associated with pituitary dysfunction."

Diabetes Mellitus

The classical experiments of Mering and Minkowski (1890) and the discovery of insulin by Banting, Best, and Macleod (1922) appeared to leave the pancreatic islet deficiency origin of ordinary diabetes mellitus in no doubt. However, for many years it has been recognized that acromegaly and Cushing's syndrome may be associated with diabetes mellitus and that the severity of the diabetes waxed and waned with that of the primary endocrinopathy. Young (1941) showed that pituitary extracts could produce permanent diabetes by secondary destruction of the islets of Langerhans. Wilder (1950) quite recently maintained the unitary conception of diabetes mellitus as a deficiency disease of the islets of Langerhans. Two questions arise from these considerations. Could diabetes mellitus exist without an islet-cell lesion, and is pituitary and (or) adrenal hyperfunction a cause of diabetes mellitus in the absence of a major endocrine disorder—the diabetogenic action of pituitary (Young, 1941) and adrenal (Ingle, 1944; Ingle, Sheppard, Evans, and Kuizenga, 1945) hormones having been demonstrated experimentally? Against this background was the clinical differentiation of diabetes into young thin and middle-aged fat types (Falta, 1936) and their rough correspondence into insulin-sensitive and relatively insulin-insensitive (Himsworth, 1936, 1949).

The first blow for the adrenal glands was struck by Sprague, Priestley, and Dockerty (1943). A woman of 49, diabetic for three years, having received as much as 145 units of insulin daily but then 30 to 68 units, with blood sugar 252 mg., no ketone bodies, never hypoglycaemia, and no endocrine stigmata, was found to have a mass in the right upper abdomen. An adenocarcinoma of the right adrenal gland was removed and the diabetes completely disappeared, without relapse during the eight years' subsequent observation. Balfour and Sprague (1949) described another case, that of a boy of 15 who first presented with diabetes and soon developed Cushing's syndrome, in whom large quantities of compound F were found in the urine; necropsy, at death after adrenalectomy, showed enormous hypertrophy of both adrenals. The characteristics of these adrenal diabetics are, as in rats, relative insensitivity to insulin, rapid response to fasting even without insulin, and negative nitrogen balance. In 1948 I described adrenal diabetes in a man of 48 who was very hairy and strong from the age of 9, and developed diabetes at the age of 46. Lister, Nash, and Ledingham (1951) described adipose diabetes with features of Cushing's syndrome in many patients in an ordinary diabetic clinic.

But the deciding division has been made by Bornstein and Lawrence (1951) in their brilliant experimental paper, "Two Types of Diabetes Mellitus, With and Without Available Plasma Insulin." They used alloxan-diabetic hypophysectomized and adrenalectomized rats and measured the blood sugar one hour after the injection of 1 ml. of plasma from their patients. The method was sensitive to 1/2,000 of a unit of insulin or less. They do not as yet conclude that the patients with normal insulin content of the blood must have hyperactive pituitary or adrenal glands, although such seems probable, if not certain; nor have they as yet followed up this type of case to show that at a later phase the insulin disappears from the plasma if and when the islets become destroyed by a persistent hyperglycaemia. I am quite certain that in a large proportion of middle-aged fat diabetics the diabetes is of pituitary-adrenal origin, as in the case of a

woman I saw who was very fat at 14 and again at 43, who developed diabetes at 52, and who died at 60 with a basophil-chromophobe adenoma of the pituitary, hyperplastic adrenals, some pancreatic islets hypertrophied, and others hyalinized.

The secretion of an excess of adrenal corticosteroids in diabetic acidosis was first ascribed to a pituitary-adrenal response to shock or infection, precipitating the diabetic coma and the secretion of corticosteroids, but it also occurs if incipient coma is produced by withdrawal of insulin in young diabetics, and its significance is not clear (McArthur, Sprague, and Mason, 1950).

Houssay (1951) recently reported in London that the incidence of diabetes induced by partial pancreatectomy is greater in male rats than female rats, and that ovarian hormones have a protective action. This is not obviously applicable to man, but it is unexpected and interesting.

Cortisone and A.C.T.H.

It is interesting to reflect that cortisone (compound E) or 11-dehydro-17-hydroxycorticosterone was isolated and correctly formularized more than a decade ago, but its dramatic therapeutic application is of only three years' standing. It has since been hailed as the "miracle drug," although a cold douche has been thrown on this conception by Professor Russell Cecil (1951), of Cornell University, who referred to it as "a glorified aspirin" and, bracketing it with A.C.T.H., said, "Hench and Kendall have only given us two more drugs to fumble with." The truth is somewhere between these two views. The term "glorified aspirin" is more apposite than its user envisaged, since salicylates (as some other drugs—for example, morphine, nicotine, colchicum, histamine, and adrenaline) can produce secretion of cortisone from the adrenals, via the release of pituitary A.C.T.H. In animals, salicylates produce a fall in the content of adrenal ascorbic acid and cholesterol and in blood eosinophils (Van Cauwenberge, 1951); but salicylates, in contrast with cortisone, lessen the glycosuria of partially depancreatized rats and increase clotting-time. Apart from this, salicylates, while effective in rheumatic fever, are ineffective in rheumatoid arthritis or, at least, never approach the dramatic relief of cortisone.

A.C.T.H. is a pituitary hormone which stimulates the adrenals to secrete cortisone and also adrenal androgens. To some extent androgens counteract cortisone—for example, in producing nitrogen retention as opposed to nitrogen loss. This is a theoretical advantage in some circumstances. A.C.T.H. is more likely to produce acne and hirsutism for the same reason, but these effects also occur with cortisone, which in large doses appears to be partly converted to an androgenic substance. Cortisone produces atrophy of the adrenals and a temporary lack of response of the adrenals to A.C.T.H. It also produces atrophy of the gonads, which is less easy to understand. A.C.T.H. produces hyperplasia of the adrenals. In clinical therapeutics, the actions of A.C.T.H. and cortisone are similar, but some differences have emerged, not always with a rational explanation.

Long-term Results

I cannot attempt to review the wide and important field of work already achieved with cortisone and A.C.T.H., but will try to touch on certain aspects. Although Boland (1951) has reported satisfactory long-term results with mild or moderate cases of rheumatoid arthritis, I do not believe that you can completely suppress the disturbing manifestations of the more severe types of rheumatoid arthritis over a long period without employing doses of cortisone which will, in time, produce the not unexpected adverse hormone effects of cortisone. Nor do I believe that this dilemma is solved by the alternate use of A.C.T.H. On my visit to the U.S.A. last year I formed the impression that this problem was troubling workers in this field, and they certainly were experimenting with all kinds of interrupted and alternating courses and gradations of dosage downwards

and upwards, but the problem may be intrinsically insoluble. If cortisone is used with the sole object of completely suppressing symptoms regardless of dosage, one is apt to produce a tendency towards Cushing's syndrome, and I have seen such an induced case, including osteoporosis and spontaneous compression fracture of the spine. Nevertheless, in our present state of knowledge, I agree with the view that cortisone is an invaluable therapeutic agent in rheumatoid arthritis.

The fact that cortisone minimizes the distressing reactions of the body to disease without abolishing the disease itself is not necessarily an objection to its use, and it may be very welcome in this direction. Surely one important principle of conservative therapeutics, in the absence of more specific therapy, is to tide the patient over an illness, to make him comfortable, conserve his strength, and let Nature help him where and when she can. In some conditions, however, cortisone may be hindering Nature, and perforation of corneal ulcer and of gastro-duodenal ulcer, the spread and hiding of peritonitis, and the extension of localized tuberculosis are possible and actual complications of cortisone therapy, caused by its inhibition of the local reaction of the tissues to disease processes. Of this we must be aware. Nevertheless the study of the pioneer work of Selye, of Montreal, on the alarm and adaptation syndrome, and clinical indications, show that the body does react to infection, shock, and sensitization by pituitary-adrenal hyperfunction, and the release of A.C.T.H. and cortisone. In some circumstances the adrenals (or the pituitary) may become exhausted (Selye, 1946) and need to be supplemented. We must study these problems very carefully and try to form clinical and laboratory criteria for sound judgment. The subject is difficult, and sometimes results are almost irrational because of incomplete knowledge.

Adams, Berglund, Balkin, and Chisholm (1951) reported dramatic results in three children with severe general burns. For example, a girl of 7 remained febrile for four weeks, was irritable, and refused to take food. She received numerous transfusions and saline; then A.C.T.H. was given in 20-mg. doses daily, but divided up. After two days her temperature dropped, she gladly took food, and rapidly got well. A boy of 4, very ill, disorientated, and restless, responded in the same way. Contrary to expectations, there was no interference with normal healing or with skin grafts; others even claim benefit in these directions. Sevvitt, of Birmingham (1951), found that in the majority of fatal cases of burns the patients die with eosinopenia and histologically active adrenal glands. The symptoms of a disease may appear worse than the disease process, and Reeder and Mackey (1950) have reported rapid subjective improvement and drop in temperature following cortisone in pneumococcal pneumonia, although animal experiments indicate the danger of bacteraemia resulting. Suzman and Rudolph (1951) reported a life-saving effect of cortisone in very acute dermatomyositis, although the response is not always of this beneficial character.

Effects on Allergic States

I am particularly intrigued about the effects of cortisone and A.C.T.H. on allergic response, and I believe that in this field will be found their greatest usefulness, not only therapeutically but in bringing into prominence again older theories on the allergic symptomatology of many disease processes, whatever might be the initiating morbid process. Long and Favour (1950) have shown that cortisone diminishes periarteritis and endocarditis that have been produced by injections of horse serum, and that cortisone diminishes tuberculin-sensitive reactions in man. It has been observed (A. R. Rich, quoted by Howard *et al.*, 1950) that anatomic lesions in drug hypersensitivity and horse-serum-induced periarteritis bear a close resemblance to those of rheumatic fever. Cortisone and A.C.T.H. may produce dramatic benefit in skin hypersensitivity due to drugs, giant urticaria, angioneurotic oedema, and exfoliative dermatitis and bullous erythema—for example, following penicillin or atropine.

These effects on allergic states are obtained even when anti-histamine drugs are ineffective and cortisone does not affect the reaction to injected histamine or acute anaphylaxis, which is prevented by antihistamine drugs. Cortisone does not usually affect antibodies, but large doses over a long period cause a diminution of new formation of antibodies.

Howard, Harvey, Carey, and Winkenwerder (1950) found A.C.T.H. very valuable in chronic, severe, intractable asthma, and complete remission often followed for some weeks or months after injections ceased; and A.C.T.H. proved superior to cortisone. Natrass and Latner (1951) found A.C.T.H. very beneficial in 13 cases of status asthmaticus. Cortisone, as drops or injected subconjunctivally in very small doses, is proving of great value in a number of eye conditions, including ophthalmic hypersensitivity reactions. The results in periarteritis nodosa and acute disseminated lupus erythematosus are good but variable, and relapses occur. In children, I have seen very good results from A.C.T.H. and cortisone in intractable oedema of lipid nephrosis, but results are not constant, and spontaneous remissions are met with in this condition. A.C.T.H. appeared to be superior to cortisone.

The experimental work of Long, Miles, and Perry (1951) on the effect of A.C.T.H. or cortisone in decreasing local sensitivity to tuberculin injections seems fundamental. Cortisone (or A.C.T.H.) appears to act not directly on this sensitivity reaction but by inhibiting the action of glutathione, or similar -SH substance, in cabbage, which itself prevents the oxidation of ascorbic acid. Ascorbic acid can then be oxidized into dehydroascorbic acid, which is the desensitizing agent. Dehydroascorbic acid is chemically related to alloxan, and both are diabetogenic.

It seems to me that, apart from endocrine disease, A.C.T.H. and cortisone will have their assured application in selected acute conditions or acute phases of more chronic disease, and more especially in allergy and locally in ophthalmic disease, but that their long-continued use in full dosage will often lead to endocrine pathology and psychopathic states.

Methyl Androstenediol

Perhaps one of the most potentially useful therapeutic substances recently available is methyl androstenediol, in 10-mg. tablets, although it was synthesized by Ruzicka as long ago as 1935. It is a steroid structurally related to methyl testosterone but only mildly androgenic by mouth. Its chief action is protein anabolic, and it is being explored with favourable results in a wide field formerly covered by methyl testosterone, including osteoporosis, reversal of negative nitrogen balance, mastitis, menopause, dysmenorrhoea, metrorrhagia, and some neoplasms. It is without the disturbing androgenic effects of testosterone or methyl testosterone—for example, acne, hirsutism, and deepening of the voice (Hall, 1951).

Primary and Secondary Adrenal Insufficiency

Cortisone by mouth can be used with advantage as supplementary therapy in both Addison's disease and Simmonds's disease; A.C.T.H. is theoretically preferable in the latter but of little or no use in the former, as the diseased adrenal cannot respond. Although deoxycortone therapy is theoretically incomplete treatment for Addison's disease, a large proportion of patients do well enough with it. Others may fail to gain weight and strength even with methyl testosterone added, and may also tend to have hypoglycaemic phases. These patients will benefit from the addition of cortisone, 12.5 to 25 mg. by mouth daily, and some may become fat. Since larger doses of cortisone in non-endocrine diseases are known to cause a dissemination of a localized tuberculous process, even when the latter has not been clinically evident, it might be thought dangerous to give cortisone to a patient known, or believed, to have tuberculous adrenals, with or without other obvious tuberculous lesions, and it would seem advisable to limit the dose to the minimum necessary for adequate well-being. However, Thorne *et al.* (1951)

advise that, in crises, 50 to 100 mg. of cortisone should be injected six-hourly, apart from other measures, and no harm has resulted from such short intensive therapy. It is also relevant that adrenalectomized animals and Addisonian patients, both lacking endogenous cortisone, are more liable to intercurrent infection than normal controls.

In Simmonds's disease, methyl testosterone has in my experience proved an invaluable treatment, supplemented by the cautious addition of thyroid; and a small proportion of patients also require deoxycortone. Nevertheless additional cortisone by mouth is often necessary to achieve optimum vigour, libido, and mental well-being. Quite small doses—for example, 12 mg. daily—may prove effective. However, Summers and Sheehan (1951) found depression, moodiness, and obstinacy after initial elation, and Robertson and Kirkpatrick (1951) found cortisone alone of doubtful value in one case although A.C.T.H. was of considerable value. Thorn *et al.* (1951) injected 10 mg. of A.C.T.H. every 12 hours and maintained patients in excellent condition, but in two of Summers and Sheehan's cases migraine and hemiparesis developed. In practice, the addition of cortisone by mouth to the usual regimen, where necessary, seems the best procedure, particularly when the tendency to hypoglycaemia is troublesome. Cortisone by itself is incomplete replacement therapy.

Endocrine Hyperfunction

I would like to draw attention to the problem of endocrine hyperfunction and the limitations of therapy in the absence of a causative neoplasm. It is one of the greatest problems in endocrinology, especially in relation to pituitary-adrenal hyperplasia.

Thyroid hyperplasia was overcome by surgery, made safer by preoperative methyl thiouracil, or by methyl thiouracil itself in some cases, and more recently by radioactive iodine, which I believe, from my American experience, will prove to be the best treatment. It leaves untouched the problem of exophthalmos, which can be produced experimentally by pituitary thyrotrophic hormone in the presence or absence of the thyroid gland. Pituitary-gonadal sexual precocity is very difficult to influence, and subtotal resection of hyperplastic ovaries can be repeated several times, with early regeneration following. Subtotal pancreatectomy for hypoglycaemia may be followed by relapse even when repeated, although we cannot assume with certainty a pituitary-pancreatotropic stimulus.

Unilateral adrenalectomy for the adrenogenital syndrome or for Cushing's syndrome is rarely of appreciable permanent value, and can be compared with hemithyroidectomy. Pituitary irradiation in Cushing's syndrome is very inconstant in its effects, and adrenal irradiation has not proved promising. Radon seeds in the pituitary gland itself may sometimes prove superior to pituitary irradiation. Surgical hypophysectomy in the absence of neoplasm has not been given a trial, and it may be that it should be tried in spite of its radical major character. We badly need radio-isotopes that would be selectively taken up by the pituitary or the adrenals, as is radio-iodine by the thyroid; and further metabolic research in this field is required, although it may prove fruitless. Attempts to inhibit the pituitary by androgens or oestrogens or cortisone or thyroxine are faced with the difficulty of the noxious unwanted systemic effects of large doses of the hormones necessary. Some French workers have recently synthesized a substance whose oestrogenic potency is weak compared with its pituitary-inhibiting capacity, and this is in the right direction. We know that androgens and glucocorticoids can inhibit the secretion of A.C.T.H. and have a reciprocal effect, so that androgens can inhibit the secretion of adrenal glucocorticoids, and vice versa. This is very important, and its therapeutic implications have not yet been fully explored. Initial observations have not indicated radical therapeutic achievements, but much is yet to be done.

Recently, at the Mayo Clinic, I saw examples of good results from bilateral subtotal adrenalectomy in Cushing's syndrome. A paper by Priestley, Sprague, Walters, and

Salassa (1951) has been published and Waltman Walters gave the Moynihan Lecture on this subject at Leeds last year. Of 29 patients, six died before use of cortisone in the pre- and post-operative phases and none have died since. Of the 23 surviving patients, 3 have adrenal insufficiency, 19 have good clinical results, and 3 are still being observed. However, no one will doubt the major character of this procedure surgically or physiologically, and no one would wish to accept this as more than an interim answer to the problem.

The problem of hirsutism is one of especial difficulty and one which causes great distress. Normal or low 17-ketosteroids do not indicate an absence of excessive androgenic stimulus, nor even do adrenals of normal size and weight. Yet some cases in women must be ascribed to a genetic distribution and strength of hair follicles. In others the only detectable abnormality is a limited adrenal androgenic excessive stimulus. This is not necessarily due to an excessive pituitary A.C.T.H. stimulus of androgenic character, since a study of pseudo-hermaphrodites with adrenal hyperplasia shows that the adrenal androgenic cells are genetically in excess to the extent of filling the adrenal glands and causing adrenal glucocorticoid and metabolic insufficiency, and, further, they may replace the germinal tissue in the gonads. It is therefore of considerable interest and potential therapeutic application that Baker and Whitaker (1948) have shown that the local application of cortisone to the skin of the rat causes thinning of the epidermis and failure of the hair follicles to develop; and Baker, Ingle, Li, and Evans (1948) obtained similar results with injections of A.C.T.H. I hope to report on clinical trials in selected cases at a later date, but the difficulty of long-continued therapy with potent hormones is not negligible.

Summary

Experimental and biochemical research in endocrinology has thrown much light on clinical problems, but the clinician must not be overawed or fail to contribute his potentially invaluable observations and judgment. Work with pure growth hormone has shown its influence in wide clinical fields—namely, augmented weight, adiposity, diabetes mellitus, and lactation. The value, dangers, and limitations of cortisone and A.C.T.H. in endocrine and non-endocrine disease are being clarified by experience. The problem of endocrine hyperfunction remains a serious challenge to endocrine therapeutics.

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DARAPRIM IN TREATMENT OF MALARIA

A STUDY OF ITS EFFECTS IN FALCIPARUM AND QUARTAN INFECTIONS IN WEST AFRICA

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During 1949–50 a large series of substituted 2 : 4-diaminopyrimidines was synthesized by Falco *et al.* (1951) and tested against laboratory infections of *Plasmodium gallinaceum* in chicks, of *P. berghei* in mice, and, in certain cases, of *P. cynomolgi* in monkeys. The most powerful schizonticide of the series proved to be 2 : 4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine (compound number 50–63), now known as “daraprim.” Clinical trials in cases of quiescent human malaria were conducted in Lagos by Archibald (1951) on children aged 5 to 10 years; promising results were obtained and no toxic effects were observed. A supply of daraprim having been made available in August, 1951, a clinical trial on subjects having overt attacks of malaria was undertaken at the Medical Research Council's Field Research Station, Fajara, Gambia, between August and November, 1951.

Subjects and Methods

Subjects were selected who showed high levels of parasitaemia and fever and other manifestations of clinical malaria. They were divided into four trial groups consisting of 18

infants (group I), 7 older children (group II), and 4 adults (group III) infected with *P. falciparum*, and 3 small children (group IV) infected with *P. malariae*. Unlike the children investigated by Archibald (1951), these subjects showed considerable variation in the degree of acquired malarial immunity which they possessed. The infants in group I had little or none; the adults in group III all exhibited substantial immunity; the resistance of the children in groups II and IV varied between these two extremes. The characteristics of the groups are summarized in Table I.

TABLE I.—Details of the Four Groups of Subjects Treated with Daraprim and of Their Parasitaemia and Pyrexia

	Group I	Group II	Group III	Group IV
No. { Male	9	5	3	1
Female	9	2	1	2
Total	18	7	4	3
Age { Mean	14 months	3.75 years	36 years	3.25 years
Range	4–24 ..	2.5–5 ..	29–45 ..	1.5–4.5 ..
Weight { Mean	8.0 kg.	13.1 kg.	55 kg.	10 kg.
Range	5–12 ..	11–15 ..	45–60 ..	5–13 ..
Infecting parasite ..	<i>P. falcip.</i>	<i>P. falcip.</i>	<i>P. falcip.</i>	<i>P. malariae</i>
Mean parasite density before treatment:				
Proportion of red cells infected	4.7%*			
Parasites per field of thick film		49	13	1
Pyrexia before treatment (Temperature (°F.):)				
Mean	102.3	103.1	All reported	100
Range	100–106	101–104.5	fever	Irregular
No. in whom spleen was:				
Not palpable	6	2	4	0
Just palpable	4	2	0	0
Palpable up to 3.5 cm. below costal margin ..	7	2	0	1
Palpable 5 cm. or more below costal margin ..	1	1	0	2
No. in whom liver edge was:				
Not palpable	5	3	4	0
Palpable up to 3.5 cm. below costal margin ..	7	3	0	2
Palpable more than 3.5 cm. below costal margin ..	6	1	0	1

* 5 cases in this group had peripheral schizogony.

together with their average levels of parasitaemia and pyrexia before treatment. Among the children a number had other diseases which almost certainly contributed to their fever, so that changes in temperature cannot be wholly attributed to malaria (cf. notes to Table II). Thus five had enteritis, four had pulmonary infections, and one each had trypanosomiasis, exfoliative dermatitis, septic gingivitis, cancrum oris, and whooping-cough. The presence of these complications makes the results of daraprim treatment the more striking.

Parasitaemia was investigated by the use of both thick and thin films. Thick films were prepared by the standard method of Field (1948) and stained by Field's rapid method. Thin films were stained with Giemsa. In estimating density of infection two methods were used. In very heavily infected subjects thin films were examined and the percentage of parasitized red cells was ascertained by counting at least 1,000 cells. In less severe infections the average number of parasites per field of thick film was counted, using an oil-immersion 1/12 objective and ×8 eye-pieces in a binocular microscope. Two hundred fields of thick film were always examined. Blood films were taken at least six-hourly for the first two days after treatment and thereafter twice daily.

The drug was administered by mouth, under strict supervision by one of us, in a single dose calculated in relation to body weight. In the early cases 10-mg. tablets of daraprim were ground up with pulv. tragacanth. in a measured volume of glycerin and water to make a uniform suspension, and a volume proportional to the calculated dose was given; later 5% lactic acid was substituted for water, as the drug is said to form a stable solution in weak acids; eventually a syrup prepared by Messrs. Burroughs, Wellcome and Co. containing 5 mg. of daraprim per ml. was used exclusively.