

CORTICOTROPHIC HORMONE IN THE TREATMENT OF INVOLUTIONAL MELANCHOLIA WITH HYPO- PITUITARISM AND PITUITARY CACHEXIA.

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DURING the past three years some clinical applications of corticotrophic hormone have been studied, and in this paper is described a form of involutional melancholia in which hypopituitarism and secondary hypoadrenalism are factors. Nine such cases were treated with corticotrophic hormone; in addition two cases of pituitary cachexia in young women were similarly treated.

There is as yet no complete agreement as to what justifies a definite diagnosis of hypopituitarism in adults in the absence of a demonstrable destructive process of the pituitary; reasons for this diagnosis in our cases are given later and supported by the therapeutic results.

Various physical and endocrine changes are not infrequently seen after the menopause, and in later life in both sexes; in mental patients they may be associated with depressive illnesses. An attempt has been made to separate types according to prominent endocrine disturbances (Hemphill and Reiss, 1940). The group of cases we have treated and describe here are characterized by the combination of certain melancholic symptoms with hypopituitarism and secondary hypoadrenalism. We have distinguished tentatively the following group:

INVOLUTIONAL MELANCHOLIA WITH HYPOPITUITARISM.

The history, onset and important mental and physical features common to this group were as follows:

History and onset.—There was no evidence of previous mental illness before the menopause. In one male there had been an earlier mental attack of unspecified nature. Two females were married; of the remaining four, one was childless and two had had miscarriages as well as a normal confinement. The menopause in all had been sudden and free from hot flushes and the usual associated symptoms. Most patients were reported to have aged unduly and lost much of their former mental alertness thereafter.

A psychological factor such as a bereavement, marital infidelity or war stress was ascertained in nearly every case.

Physical state.—The physical picture included a sallow complexion, appearance of age beyond the years, asthenia present but not extreme, usually some loss of weight, hair brittle and lacking lustre, scanty or lost in axilla and on pubis, reduction or loss of sweating and change in the condition of the skin, which was the most constant and striking single characteristic. The skin was thin, with loss of subcutaneous fat, dry, rather smooth and non-scaly—what may best be described as the "desiccated" skin. The systolic pressure was rather low in most cases, but above 170—110 mm. Hg. in E. M. B—. In two cases, K. S— and W. B— (male), there was some appreciable arterial degeneration; in the remainder the principal systems were normal. There was no evidence of pituitary tumour and no neurological abnormalities.

Endocrines.—The thyroid was impalpable or very small. The breasts and external genitalia were shrunken and atrophic; loss of sexual desire was present in the males. Urinary excretion of the 17-ketosteroids estimated in three females

Name.	Sex.	State.	Age.	Meno- pause.	Previous attack.	Preg- nancies.	Mis- carriages.	Psychic factor.	17-Ketosteroids excretion mgm. in 24 hours.		Ant. pit. hormones.	Diagnosis.	Result.
									Before.	During.			
A. S. M—	F.	S.	55	48	Nil	Nil	Nil	Yes	—	—	—	Inv. mel.	Rec.
E. M. L—	F.	M.	51	43	44	4	2	"	—	—	—	"	"
C. L. H—	F.	M.	42	42	Nil	Nil	Nil	"	>3	10'0; 8'3	Gon. t. Thy. t. } <i>nil</i> (Cort. t.)	"	Phys. and ment. imp.
E. M. B—	F.	M.	51	50	"	2	1	?	—	—	Ditto	"	Ditto
B. D—	F.	S.	55	54	54	Nil	Nil	Yes	2'9	3'5; 4'7	—	"	"
K. S—	F.	M.	57	52	Nil	6	"	Nil	2'3	6'3	—	Inv. mel. with card. vasc.	Phys. impr.
W. C. F—	M.	M.	50	—	"	—	—	Yes	—	—	—	Inv. mel.	Rec. (relapse)
A. G. I—	M.	M.	60	—	"	—	—	"	—	—	—	"	Phys. and ment. imp.
W. B—	M.	S.	59	—	743	—	—	?	—	—	—	Inv. mel. with card. vasc.	Slight impr.
A. M—	F.	S.	22	—	Nil	—	—	?	4'2	6'7 8'8	Gon. t. Cort. t. } <i>nil</i>	Inv. mel. with card. vasc. Pit. cach.	Rec.
M. G—	F.	S.	28	—	"	—	—	Yes	2'6	10'9 4'6 5'9 10'7	Cort. t. <i>nil</i>	"	Impr.

Abbreviations used in table : Gon.t. = gonadotrophic ; Cort. t. = corticotrophic ; Thy. t. = thyrotrophic ; Inv. mel. = involuntional melancholia ; Pit. cach. = pituitary cachexia ; Rec. = recovered ; Ment. imp. = Implies loss of visceral delusions as well as some general mental change.

was subnormal, a customary finding in hypoadrenalism and hypopituitarism, and in two females there was no biologically assayable excretion of gonadotrophic, thyrotrophic (Heyl and Laqueur, 1935), corticotrophic (Reiss, 1936) hormones in total urine passed in 24 hours. Insulin and sugar tolerance tests and estimations of basal metabolic rate were not employed; their accuracy apart from utility could not be relied upon in unco-operative subjects.

Mental state.—The mental picture was that of a well-marked melancholic depression with loss of interest and impoverished ideation. Especially prominent were delusions of visceral derangements; the patients complained of being "unable to eat," of "the bowels stopped up," that "nothing passes through," etc. Associated ideas of guilt and self-denunciation were common, refusal of food a constant symptom. A tendency to spontaneous remission was seen in two cases only: B. D—improved slightly but relapsed in a few months; E. M. L—had been treated for a depressive illness just after the menopause.

Details of the individual cases and the results of treatment are summarized in the accompanying table.

Corticotrophic hormone.—Six female and three male patients were treated with a purified extract of corticotrophic hormone free from growth, gonadotrophic and thyrotrophic fractions administered intramuscularly in standardized sudanophobic units (Reiss, 1936). As yet so little is known of its action or requirements in the human that dosage was empirical, and as only limited quantities were available for this work the doses we employed were necessarily rather low. We have used 15 to 20 units daily over a period of months, 50 units daily for one week, and up to 50 units daily for several weeks. Although effects were observed even with the smallest doses, it is our impression that in some patients a much more concentrated and heavier course of treatment might be indicated. Treatment should be given for at least a month in most melancholics.

Effects of treatment.

Physical changes.—In all patients there was some improvement in general appearance accompanied by an increased sense of wellbeing. The sallow complexion disappeared, asthenia lessened, and the tone of muscles improved. A constant effect was alteration in the "desiccated" skin. In every case the skin soon began to look and feel to the touch more supple and thicker; later there was a deposition of subcutaneous fat, and this, coupled with other changes, prompted some relatives to remark that patients looked very much younger. The hair of the head regained lustre, losing some of the dry brittle quality. We have not noticed any tendency for axillary or pubic hair to grow, nor a return of sweating. There was at first little change in weight, though most patients gained later, to some extent, in proportion to the pre-existing loss. Excretion of 17-ketosteroids was increased with treatment.

Mental changes.—The first effect observed was a return of the desire for food, so that most patients, spontaneously, took an adequate diet by the end of a week. As the appetite improved and with it the general physical condition, visceral delusions disappeared completely in seven cases and were noticeably lessened in the remaining two (K. S— and W. B—). Some patients argued, "I always feel so hungry, there cannot be anything the matter with my bowels." There was an increase in bodily activity; it was possible to get patients to occupy themselves, and the majority showed a desire to help in ward work or sewing in marked contrast to their previous state. Two females, A. S. M— and E. M. L—, made quick recoveries with no other form of specific treatment. One male, W. C. F—, apparently recovered, but relapsed later when outside hospital and no longer receiving treatment.

PITUITARY CACHEXIA.

In many cases diagnosed as anorexia nervosa, the physical picture resembles that of Simmond's disease, and it seems unreasonable to rule out hypopituitarism in the former on the grounds only that there is no suggestion of pituitary necrosis, and that a serious psychological disturbance has been disclosed. Cases have been cited (Davis, 1939; Doane *et al.*, 1940; Megendantz and Proger, 1940) to support the opinion that either a functional suppression of pituitary activity, perhaps as

the result of psychic stress in constitutionally susceptible individuals, can occur, or that pituitary hyosecretion may follow prolonged inanition provoked by some abnormal psychological situation. Hypopituitarism has been reported where there has been a severe and prolonged loss of weight (Kerpolla, 1939).

Two cases of pituitary cachexia have been examined and treated by one of us (M. R.) and will be briefly described. There was a significant psychogenic element in one, but in both definite endocrine disturbances were noted and objective results obtained with corticotrophic hormone therapy and an adequate diet, without special psychotherapy.

A. M—, aged 22, university student, unmarried. She was stated to have had a normal childhood and adolescence with no significant illnesses until 19, when she began to lose weight. At this time she was working hard for examinations. Menses commenced at 16, were regular, accompanied by pain, lasting seven days. At 19 there was amenorrhoea for six months and further subsequent amenorrhoea after one period. She was a nervous, introspective girl, 5 ft. 6 in. high, weight 6 st. 7 lb. She complained that she had lost 2 st. in two years, that she was quite eager to eat, but had no real appetite and was frequently sick after meals. She preferred sweet things and sugar and had an abnormal craving for salt. She would pour salt on her food so as to make it practically uneatable for anybody else. There was a general loss of flesh, most noticeable around the hips; muscle tone was poor. The complexion was pale, the skin smooth, thin and dry; the hair was brittle; there was none on the axilla and little on the pubis. The heart sounds soft and short, blood pressure 92/65 mm. Hg. The thyroid was impalpable and the breasts underdeveloped; there was no excretion of gonadotrophic or corticotrophic hormones in 6,000 c.c. urine, 17-ketosteroids, 4.2 mgm. per 24 hours.

6. xii. 41: Corticotrophic hormone, 20 units daily, continuously.

6. ii. 42: Much improved, eating well, no vomiting, skin normal, breasts a little fuller; weight 6 st. 10 lb.

2. iii. 42: 17-ketosteroids 6.7 mgm. in 24 hours.

22. iv. 42: Fat deposited round hips and breasts, appetite normal, feels "bright and energetic."

5. v. 42: Weight 7 st. 10 lb. Menses for three days, pubic hair growing; 17-ketosteroids 8.8 mgm. in 24 hours.

5. vi. 42: Weight 8 st. Normal menses for seven days; 17-ketosteroids 10.9 mgm.

7. viii. 42: Appears quite well, eats and works normally; weight maintained at 8 st.; normal menses.

In this case corticotrophic hormone appears to have been responsible for restoration of the general condition, normal appetite, skin, deposition of fat, and the return of normal menses. Excretion of 17-ketosteroids increased from 4.2 mgm. daily to 10.9 mgm. in six months. There was no special psychotherapy; a full diet was insisted on from the first.

M. G—, aged 28, a nun. Her history was incomplete, but she was stated to have had normal mental and physical health until 23, with an average weight of 8 st. Since then she had lost energy and appetite, and had developed strange preferences in the matter of food; she had lost 4 st. On examination she complained of having no appetite and of being unable to eat any fats, including butter and fatty meat. She enjoyed all sorts of sweet things, and seemed unable to relish her meals unless large quantities of salt were added. She was reserved and uncommunicative. A difficult psychological situation was suspected, but could not be proved. She was much emaciated, maximum loss of flesh round hips and thighs, breasts were wasted; there was no axillary or pubic hair, the skin was very dry; menses were irregular and scanty, thyroid impalpable. Heart and main systems normal; no abnormality in central nervous system or sella; blood pressure 95/70 mm. Hg. Height 5 ft. 5 in., weight 4 st. 4 lb.; 17-ketosteroids 2.6 mgm. per 24 hours; no assayable corticotrophic hormone in 48 hours' urine.

11. xi. 41: Corticotrophic hormone, 30 units daily, continuously.

28. xi. 41: 17-ketosteroids 4.6 mgm. per 24 hours.

26. i. 42: 17-ketosteroids 6.9 mgm. per 24 hours.

6. ii. 42: 17-ketosteroids 10.7 mgm. per 24 hours.

In this patient there was an early improvement in the condition of the skin, the appetite seemed more normal but the aversion from fats and addiction for salt and sugar persisted. There was an improvement in the sense of wellbeing and in general muscle tone. Obvious difficulties in treating this patient existed; it was suspected that instructions were not fully carried out, nor diet adequately supervised. The total gain of weight was 10 lb.

DISCUSSION.

Therapy with corticotrophic hormone was employed on the assumption that some of the symptoms in our cases were due to adrenal insufficiency, perhaps secondary to hypopituitarism and lack of corticotrophic fraction.

The effects may be considered as (a) direct, namely, improvement in appetite, nutrition, tone and strength of muscles, condition of skin and hair and deposition of fat, (b) associated, such as sense of wellbeing with brighter outlook, increased activity and loss of delusions of alimentary malfunction, (c) increased urinary excretion of 17-ketosteroids. In all cases irrespective of age or type of illness, appetite, complexion, skin and strength showed improvement and in the majority of melancholics specific delusions disappeared.

The physiological function of corticotrophic hormone is to promote growth and activity of the adrenal cortex which atrophies after hypophysectomy. Hyperadrenalism does not result, in our experiences, from administration of, at least, moderate doses in healthy animals or normal humans. Its action has been investigated chiefly in experimental animals. Asthenia, loss of fat and certain disturbances of carbohydrate metabolism follow hypophysectomy in rats. The first has been relieved by adrenal cortical extracts of pituitary containing corticotrophic hormone (Atwell, 1932; Evans, 1932), the others by injected corticotrophic hormone (Reiss *et al.*, 1937 and 1938). Probably the improvement in strength and metabolism in our cases was achieved in a similar way, and better nutrition and fat storage would account for changes in the desiccated appearance of the skin. The intra- and extra-cellular water balance is known to be upset in hypo-adrenalism (Kepler and Willson, 1941). Evidence pointing to the possibility that this balance may be restored by corticotrophic hormone has already been advanced (Hemphill, 1942).

The production of 17-ketosteroids in females is probably related to adrenal cortical activity, and we believe that a very low output suggests hypoadrenalism. It has been claimed that it is reduced in inanition and myxoedema (Fraser and Smith, 1941), but we are not aware that correction of these conditions has been followed by a corresponding rise. The adrenal cortex is susceptible to exhaustion, chronic infection and prolonged bodily disturbances and suppression of its activity may thus have been indirectly responsible for the reduced production of 17-ketosteroids.

The beneficial psychiatric effect may be attributed to the recovery from physical results of hypoadrenalism. Involutional melancholia presents a complex picture with psychic and somatic elements. It may be that after the menopause functional activity of the anterior pituitary is in some cases subnormal, causing a degree of adrenal and thyroid atrophy through lack of an adequate output of corticotrophic and thyrotrophic hormones. The resulting weakness and physical defects coupled perhaps with psychogenic factors may act on a susceptible mental constitution to produce the melancholic reaction. The already existing bodily symptoms might be interpreted in the psychosis as secondary delusions of visceral malfunction and incurable illness. Failure to take adequate nourishment would accentuate the physical condition and a vicious circle would result. The alternative hypothesis that the hypopituitarism and hypoadrenalism are secondary to inanition seems unlikely, for in the melancholic cases refusal of food is usually the result of delusions and in the early stages loss of weight is not severe.

All the females except one were unmarried, nulliparous or had had miscarriages, the menopause was abrupt and there was no history of previous mental illness. These facts together may point to some degree of depression or abnormality of anterior pituitary activity even before the menopause, becoming more pronounced when ovarian and menstrual functions had ceased. Such a condition might pass unnoticed until the mental illness to which it contributed set in. Cardiovascular changes may occasionally be responsible for pituitary hypofunction in later life, and this may account for the rather poor results in K. S— and W. B—. Simmond's disease in old age had already been described (Laub, 1940). Whatever the precise origin, a severe hypopituitarism existed in the two cases who failed to excrete any assayable corticotrophic, thyrotrophic or gonadotrophic hormone in 48 hours urine.

Although the above applies chiefly to females, we have encountered much the same mental and physical picture in males. Three have been treated, of which

one recovered but relapsed later when away from hospital; appetite, skin, general condition and specific delusions were benefited in the others. Two females recovered quickly with corticotrophic hormone therapy alone. This can be attributed to restoration of normal adrenal function, with return of appetite, sense of wellbeing, and ability to be active, which gave scope for institutional treatment and general psychotherapy. In the others, visceral delusions gradually disappeared as the desire for food returned. A reduction in blood pressure was noticed in one case, E. B—, who had been turned down for shock therapy on account of an unexplained post-menopausal hypertension. After treatment with corticotrophic hormone there was some improvement and the blood pressure remained at 130/80. She recovered with subsequent shock treatment and has remained well for more than 18 months.

Prior to the introduction of convulsive therapy, chronic melancholia and the depressions of later life were among the most intractable mental illnesses. Shock treatment has completely altered the prognosis, so that a high percentage of recovery is now regularly anticipated. A dramatic improvement may be seen during the first week of treatment. The explanation of this satisfactory state of affairs may be that shock therapy improves pituitary function. It has already been shown (Hemphill *et al.*, 1942) that electrical convulsion treatment frequently causes a substantial increase in the output of 17-ketosteroids, which is probably affected by liberation of corticotrophic hormone from the anterior pituitary. Increases followed treatment with injected corticotrophic hormone in some of the cases described here. It seems possible that part of the therapeutic effect of shock therapy may be attributed to increased anterior pituitary activity with the production of more corticotrophic (and probably other anterior pituitary) hormones, as evidenced by the altered output of 17-ketosteroids. The endogenous hormone produced in this way may be much more active than the doses we employ, for the greatest increases followed shock therapy.

Improvement has already been described in two cases of pituitary cachexia; one recovering completely. Although it may be objected that these are cases of anorexia nervosa, the bodily picture was that of hypopituitarism and hormone analyses corresponded. The strange preference for salt appears to be a valuable symptom in the diagnosis of hypoadrenalism. It is often seen in dogs and other animals after epinephrectomy and has been reported with a destructive neoplasm of the adrenals (Wilkins *et al.*, 1940). It disappeared during the treatment of case A. M—.

Fraser and Smith (1941) have differentiated between anorexia nervosa and hypopituitarism on the basis of 17-ketosteroids assay and insulin tolerance test. We cannot agree that hypopituitarism in so-called anorexia nervosa is necessarily excluded, provided there is some output of 17-ketosteroids.

It has still to be shown that hypopituitarism secondary to inanition is not a later development in severe anorexia nervosa. It is our opinion that, whatever may be the primary cause, a degree of hypoadrenalism is indicated in anorexia nervosa if the 17-ketosteroids output is low and the task of psychotherapy and diet can be greatly assisted by simultaneous use of corticotrophic hormone. The progressive improvement in 17-ketosteroids output in our two cases supports this contention.

We think that injected corticotrophic hormones stimulates a subnormal or exhausted adrenal cortex. Later when the general condition and nutrition have improved, spontaneous adrenal cortical activity becomes adequate and treatment can be discontinued. In severe functional or organic hypopituitarism continued administration might be necessary.

Corticotrophic hormone is not here proposed as a cure for involuntional melancholia in general—shock therapy is at present the elected method. However, where it is contraindicated, treatment with corticotrophic and other anterior pituitary hormones may be a useful alternative. Our experience suggests that corticotrophic hormone has a definite value, especially in psychiatry, in treating exhaustion, anorexia and prolonged refusal of food.

SUMMARY.

(1) A special type of involuntional melancholia with hypopituitarism has been described.

- (2) Treatment with corticotrophic hormone produced improvement in appetite, nutrition, condition of skin and hair and loss of delusions of alimentary malfunction.
- (3) Two cases of pituitary cachexia have been recorded, and effects of treatment noted.
- (4) The output of 17-ketosteroids showed a progressive increase with administration of corticotrophic hormone.
- (5) The origin of the disorders and the action of corticotrophic hormone have been discussed.
- (6) It has been suggested that the therapeutic effects of shock treatment in involutional melancholia may be due to an increase in anterior pituitary activity.

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