THE HORMONE TREATMENT OF ACROMEGALY.

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THE demonstration by Zondek (1936), subsequently confirmed by Cramer and Horning (1936), Gardner (1937), Collip (1936), Noble (1938), Deanesley (1938, 1939), Pybus and Miller (1938), that large doses of oestrone will impair and partly suppress the functions of the pituitary anterior lobe, especially the gonadotrophic and the growth hormone production and will produce partial degeneration of the acidophil cells, led Kirklin and Wilder (1936) to adopt this method of treatment for patients suffering from acromegaly. Their series consisted of eight patients, four men and four women, and their results may be briefly summarized as follows: There was a general improvement in three patients; headache which was originally present in six cases disappeared in four, but returned in one case, though this may have been due to a discontinuance of treatment; in three patients there was a decrease in size, in one a smaller hat was required and her dental plate became loose, in one the hands became smaller, and in one shoes became looser; the visual fields were originally altered only in three of the eight patients, and in one of these the fields returned to normal, in one there was no change, and in the third a progressive hemianopia accompanied by erosion of the sella turcica developed during treatment; hyperidrosis and intolerance of heat, originally present in two, disappeared in both; finally there was loss of libido in three cases.

Schrire and Sharpey-Schafer (1938) thought that a more objective method of assessing the results would be preferable. Schrire and Zwarenstein (1933, 1934) have shown that, in animals, pituitary activity may be judged by the quantities of creatine and creatinine in the urine, and can be altered by injections of testicular and ovarian extracts. Schrire found that creatine and creatinine excretion was abnormally increased in acromegaly; it was decided to treat cases suffering from acromegaly with oestrin and testosterone, and to assess its effect by estimating the urinary creatine and creatinine output (a special creatine-free diet being used). In four patients so treated it was found that large daily doses of oestradiol benzoate reduced the output of creatinine in the urine to normal levels; during the period of injection the creatinine excretion ceased to fluctuate, and was constant as in the normal; large doses of testosterone in one case produced similar results.

Stephens (1939) also published the report of one case of acromegaly, in which, during oestrogenic therapy, there was suppression of abnormal lactation associated with striking subjective clinical improvement, lowering of an elevated blood pressure, and slight increase in glucose tolerance, but with no change in the general clinical appearance, or in the B.M.R.

Varying dosages have been used. Kirklin and Wilder and Stephens gave relatively small doses, usually 1,000 I.U. daily, or every other day. Schrire and Sharpey-Schafer used very large doses, 100,000 I.U. of oestrogen or 100 mgm. testosterone daily.

In the present series of four cases, one man and three women, the dosage has been 10,000 to 50,000 I.U. oestrogen. Clinical changes have been carefully observed, and excretion of gonadotrophic hormone and ketosteroids have been investigated. Investigation of ketosteroid excretion was carried out after Callow's method.

Case Histories.

(1) M. G—, female, aged 37. Had only menstruated for one day at the age of 15, and mammary glands were completely undeveloped. About 1940 began to notice an alteration in size; her ring had to be enlarged, and size of shoes increased from four to six, the shape of her face altered, and her features became coarser. No headaches, and the ocular symptoms not entirely typical of acromegaly. In August, 1941, the left eye became misty, and in September the visual fields showed a small scotoma to temporal side of fixation spot; discs normal in colour; right field full. In January, 1942, visual activity of the left eye was reduced to perception of hand-movements only; the visual field was contracted, especially the temporal side, and disc slightly red. An X-ray of the skull at this time showed considerable deepening of the pituitary fossa and much erosion of the clinoid processes. On admission to the Institute, 17.ii.42, typical appearance of acromegaly, coarse features, prognathism, hands showed considerable thickening of the phalangeal joints, broad toes, with large bunion on left foot. Breasts were entirely undeveloped, pubic hair very scanty. Could not count fingers with the left eye; both fundi appeared normal; there was considerable restriction of the temporal half of right field. Treatment was begun on 23.ii.42, with 50,000 units of oestrone daily. By 7.iii.42 patient began to report subjective improvement in the vision of the left eye on the temporal side, and slight enlargement of the breasts. 1.iv.42: She could move her ring more easily. 5.iv.42: Menstrual bleeding for a few hours. 9.iv.42: Again menstrual bleeding for a few hours. 13.iv.42: Began menstruating again, and continued until 16.v.42; no dysmenorrhoea. 17.iv.42: Visual activity of left eye improving; could count fingers at 3 ft.; right visual field normal, left visual field restriction. Could move her ring quite easily, bunion no longer troublesome, and was able to wear shoes which she had been unable to wear for past two years because they had become too small for her. 6.vi.42: Continued subjective improvement. At present no subjective symptoms. Fields of vision completely normal. Breasts are now normal size.

17-Ketosteroid, 24 hours' excretion:

19.ii.42	2·1 mgm.
11.iii.42	2·2 ,,
8.vi.42	3·5 ,,

(2) M. C—, female, aged 58. Complained of increasing insomnia for six years. Excessive thirst and polyuria (2 quarts daily), and sudden outbreaks of sweating, lasting a few minutes only, for past five years. Sweating has been less frequent during past year. Four years ago noticed swelling below eyes, and complained of general weakness. Diagnosis of acromegaly was made at this time. During past 2½ years had had brief attacks of severe supra-orbital pain, brought on by coughing or laughing, and associated with profuse tears. Noises in ears for 18 months, loss of appetite for 6 months and general bodily weakness. Enlargement of hands and feet during past two years. Had to change her shoes from size 5 or 5½ to size 7; past two years required much larger hats; her ring had to be enlarged once, and was again becoming tight.

Eighteen years ago received radium treatment for menorrhagia, and subsequent amenorrhoea was induced.

29.iv.42: On admission, acromegalic appearance of the face, hands and feet. X-ray shows enlargement of sella turcica. Optical discs normal, visual fields normal.

11.v.42: Injections of 15,000 units oestrone daily.

16.vi.42: Menformone 15,000 units daily by mouth; injections omitted.

14.vii.42: General improvement. Rings loose; can now wear No. 6 shoes instead of 7. No longer suffers from attacks of supra-orbital pain.

17-Ketosteroid 24 hours' excretion:

5.v.42	8·6 mgm.
21.v.42	8·7 ,,

(3) M. L—, aged 31, serving soldier, admitted 4.xi.40.

Complained of diplopia. On September 30, on waking, found difficulty in opening his eyes; had to push them open; felt heavy and noticed that he had diplopia on rising. Felt giddy and vomited once after breakfast. Felt as if drunk; staggered and saw double. Reported sick and put to bed. Diplopia persisted.

On admission: Coarse features, marked prognathism, broad nose, thick lips and overhanging brows. Occipital protuberance much increased in size. Hands very large with broad fingers, not clubbed. Remembers that he used to wear ring on ring finger; two years ago had to have ring enlarged, now wears it on little finger. Feet broad, spatular toes.

On examination: Eye movements apparently well performed, but diplopia referable to superior oblique. Vision $\frac{6}{6}$. Bilateral cutting-off of upper nasal and temporal quadrants. Fundus oculi in normal limits. Sense of smell bilaterally normal. Thyroid easily palpable, slightly increased in size. Gonads and all sexual characteristics well developed; chest, arms and legs well covered with hair. X-ray examination of the skull shows a considerably enlarged and

deepened sella turcica. Mandible enlarged; hands show typical tufting of distal phalanges. Examination of photographs shows development of heavy brows and prognathism during past two or three years. Zondek-Aschheim reaction positive. Urine: No glycosuria, no polyuria. Excretion of prolan increased. 17-Ketosteroid excretion remarkably increased (28·4 mgm. in 24 hours).

From 9.xi.40 patient received injections of 50,000 I.U. Dimenformon twice daily.

24.xi.40: For a week had ceased to notice diplopia; said that vision was "clearer;" no headaches, felt perfectly well. Injections continued, but dose diminished to once daily 50,000 I.U. Dimenformon.

5.xii.40: General sense of well-being; no trace of diplopia, no headaches. Visual fields show no apparent change. Treatment continued with 10,000 I.U. Dimenformon daily.

17.xii.40: Complains spontaneously of complete loss of libido and of mammary enlargement. Face undoubtedly undergoing feminising change; skin tighter, slimming of facial contours.

1.i.41: During the last weeks the hair of chest and extremities started to fall out. Chest was now completely hairless. Breasts remarkably increased in size. Patient noticed that his ring was much looser, and on one occasion it actually fell off. Occipital protuberance was been found to be much smaller. The face showed perceptible feminine change, and the injections of Dimenformon were suspended and 10,000 I.U. Dimenformon given daily by mouth.

8.i.41: Patient did not feel well. For last three or four days fatigue and sleepiness.

14.i.41: Had a transient attack of diplopia. Dimenformone increased to 50,000 I.U. daily.

20.i.41: Has no further diplopia, no complaints. Testicles very soft, hair on body disappeared, pubic and axillary hair diminished, hair on head much softer than before. Growth of beard diminished. Patient continued to assert that he was absolutely sexually frigid and had no erections. This condition did not cause him any anxiety. The ring, worn on his little finger, falls off now with shaking and can be slipped to second joint of third finger—formerly could only admit tip of third finger. Urine: Prolan excretion not increased. 17-Ketosteroid 24 hours' excretion, 26·2 mgm.

During the following 15 months the patient was seen every four weeks. Discontinuation of treatment was tried several times, but a few days afterwards the patient complained regularly of drowsiness, headaches and sometimes of diplopia, so that treatment with high doses had to be started always over again. At present the patient is being treated with 10,000 I.U. Dimenformon weekly, and feels continuously well. The 17-ketosteroid 24 hours' excretion was investigated several times and in spite of treatment varied between 23 mgm. and 26 mgm.

5.v.42: Patient was again examined, and, in consequence of the softness of the testicles and the state of degeneration of the genital system, it was decided to supplement his treatment with gonadotrophic hormone. In addition to the oestrone 400 I.U pregnant mare serum gonadotrophic hormone (Gestyl) were injected daily.

8.vi.42: Patient feels very well. Consistency of testicles improved, pubic hair increased, hair on chest started to grow again; patient has noted improved libido. Had three times intercourse during the last months. 17-Ketosteroid 24 hours' excretion remarkably decreased—13·4 mgm.

22.vi.42: Patient feels very well. Further growth of hair can be observed. 17-Ketosteroid 24 hours' excretion, 12·4 mgm.

(4) Mrs. I. M—, aged 36. For several years she had been very sleepy and drowsy, suffered rom hot flushes and sudden outbreak of sweating. She complains further of a queer, painful sensation above the malar bone. Has had two nervous breakdowns previously; cannot make any decisions and is unable to do any work. Two children, aged 5 and 2 years respectively. During both pregnancies she put on much weight. During the second pregnancy she and her husband noticed her hands and feet growing larger. She had to wear larger stockings and shoes half a size larger. Periods irregular, sometimes 4 to 8 days, and other times only 1 to 2 days late.

On admission, 23.vii.40: Rather coarse features, particularly the soft tissue above the malar bone, while the lips showed characteristic acromegalic enlargement. Breasts very large. Thyroids soft and increased in size. Fingers of both hands showed the typical acromegalic deformation. Palpable increase of cartilage on point of lower jaw. X-ray examination showed moderate enlargement of sella turcica. Visual fields were normal. Hair falling out. Prolan excretion increased, positive Zondek-Aschheim reaction. 17-Ketosteroid excretion increased (see below).

Clinical diagnosis: General hyperfunction of the pituitary anterior lobe; especially increased production of growth hormone, the acromegalic syndrome being the prevalent one.

3.ix.40: Treatment was started with 20,000 I.U. Dimenformon injected daily.

11.xi.40: All subjective symptoms have disappeared, no drowsiness, no sweating; patient able to go for long walks without getting quickly tired as before. Menstrual period lasted for ten days. Hair stopped falling out. Features now almost completely normal. One month ago the ring the patient wore on her right hand had to be made smaller as it slipped off her finger. The increased growth of cartilage which could be felt before under her chin had disappeared. Treatment continued. Prolan excretion no longer increased.

6.iii.41: Excessive prolongation of periods was stopped by pregnyl injections of 200 I.U. given for six days. Subjective symptoms considerably improved; patient was now leading normal life, all acromegalic features completely gone. Treatment continued with five injections

10,000 I.U. Dimenformon weekly. The periods were at first rather irregular, but were regularized by pregnyl and were now absolutely normal.

17-Ketosteroid 24 hours' excretion :

1.xii.41	17·2 mgm.
9.iv.42	16·4 mgm.

Discussion.

Four cases are described, three showing well-developed acromegaly and the fourth case an incipient acromegalic syndrome. All four were treated by oestrogens with improvement of the clinical condition.

The following changes were noted :

(1) The decrease in size of the thickened phalangeal joints.

(2) An extremely rapid improvement of the subjective symptoms, headaches, giddiness, amblyopia, etc.

(3) Visual improvement, the extent of which is, of course, entirely dependent on the degree of optic atrophy present before commencement of treatment.

The main drawback of this treatment is the high oestrogen dosage necessary particularly as such large amounts of oestrogen profoundly influence the function of the gonads.

In the case of M. L—, several attempts were made to decrease the dose, or to discontinue treatment, but within a very short period the subjective symptoms always returned. The effect of gonadotrophic hormone administration in the case of M. L— indicates that some of the difficulties may be overcome by using this hormone in addition to oestrogen. The rapid improvement following administration of oestrogen suggests that the hormone in addition to influencing the pituitary hyperplasia exerts a direct influence on some of the concomitant symptoms, possibly by improving the cerebral circulation impaired by the enlargement of the gland (Reiss and Golla, 1940).

The ketosteroid excretion was increased in two of the cases, M. L— and I. M—, within normal limits in one case, and much decreased in the fourth. The seat of production of ketosteroids is probably the adrenal cortex, which, in turn, is regulated by the corticotrophic hormone of the anterior pituitary lobe. It is a well-known fact that, if overproduction of growth hormone is occurring in the pituitary anterior lobe, the production of the other hormones may be either increased or decreased ; e.g., in the case of M. G— the production of gonadotrophic hormone was markedly decreased, while in that of M. L— it was somewhat increased. A similar explanation may be involved to explain the effect of the disturbance of the ketosteroid excretion of these patients. It is noteworthy that oestrogen treatment was not successful in reducing the ketosteroid excretion in the case of M. L—, whereas gestyl decreased it by 50 per cent. No explanation of this fact can yet be offered.

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