DISAPPEARANCE OF DIABETES DURING ESTROGEN THERAPY IN ACROMEGALY

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THE development of diabetes in acromegaly is a rather common occurrence. Coggeshall and Root,[1] in reviewing 153 cases of acromegaly, including the 100 formerly reported by Davidoff and Cushing,[2] found glycosuria present in 36 per cent and diabetes in 17 per cent.

Barnes et al,[3] Nelson and Overholser,[4] and more recently Rodriguez,[5] have reported the favorable effect of estrogen administration in experimental pancreatic diabetes in dogs, monkeys, and rats as well as in animals made diabetic

Table 1

ACROMEGALY

Date	Therapy	Hand Volumes	
		R.	L.
8- 6-48	Ethinyl estradiol 1 mg./day for 13 weeks	485 cc.	450 cc.
8-26-48	No therapy for 20 days	500 cc.	485 cc.
9-30-48	No therapy for 53 days	550 cc.	515 cc.
7-28-50	Ethinyl estradiol 1 mg./day 2 mg./day for 52 weeks	525 cc.	438 cc.
11- 9-50	No therapy for 10 weeks	545 cc.	520 cc.

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by crude anterior pituitary extracts. They postulated an estrogen suppression of the pituitary activity concerned with carbohydrate metabolism.

There is some evidence to suggest that estrogens are capable of inhibiting pituitary growth hormone. Thus Zondek,[6] in 1936, produced inhibition of sexual development and dwarfism in the rat and chick by means of estrogenic hormone administration, inhibition which was overcome after administration of Evans' growth hormone. Beneficial clinical results have been reported after the use of estrogens in the treatment of acromegalic patients, by Kirklin and Wilder,[7] Schrire and Sharpey-Schafer,[8] Goldberg and Lisser,[9] Stephens,[10] Reifenstein et al[11] and Kinsell et al.[12] The doses used varied from 1,000 I. U. (as theelin) to 10 mg. per day (estradiol benzoate) parenterally, or up to 5.0 mg. (natural conjugated estrogens) orally. Beneficial results were judged by amelioration in the clinical condition[7-12] as well as a drop in the serum phosphorus and growth hormone levels.[12] These results were variously interpreted as due to inhibition of pituitary growth hormone activity[7,9-12] or to suppression of an abnormality of metabolism associated with the gonadotropic hormones of the overactive pituitary gland.[8]

The observations of Young[13,14] on the production of diabetes in the dog, cat, and ferret by means of a relatively pure growth hormone preparation, suggest that in the acromegalic, diabetes is due to an excess production of this principle. However, since the absolute purity of these preparations is uncertain, other pituitary principles may be involved.

The reversal of diabetes by treatment with large doses of estrogen in one case of acromegaly constitutes the subject of the present report. Other observations on a larger group of patients similarly treated will be reported later.

Methods

Glucose tolerance tests were done using a 100 Gm. single oral dose of dextrose. With this technic the upper limits of normal blood glucose, in our experience, are considered to be as follows: fasting 110 mg., ½ hour 170, 1 hour 170, 2 hours 130 and 4 hours 110 mg. Hand volumes were measured roughly by water displacement, a technic which, though not accurate enough, clearly demonstrated the trends in hand size.

Case Report

A 45 year old woman was referred to the Clinic because of acromegaly, prolapse of the uterus, and an accompanying arterial hypertension. Coarsening of the facial features, enlargement of the hands and feet (figs. 1a and b), and moderate hair growth on the arms and legs had been progressing for at least 8 years. Amenorrhea had occurred abruptly 6 years previously. There were severe headaches daily and 3 weeks prior to her examination she had first been advised of the presence of hypertension. Family and personal histories were noncontributory.

Physical examination revealed the features associated with severe acromegaly, including dorsal kyphosis which prevented the patient from lying flat. There was moderate hirsutism and acne over the face and chin. The thyroid was slightly enlarged

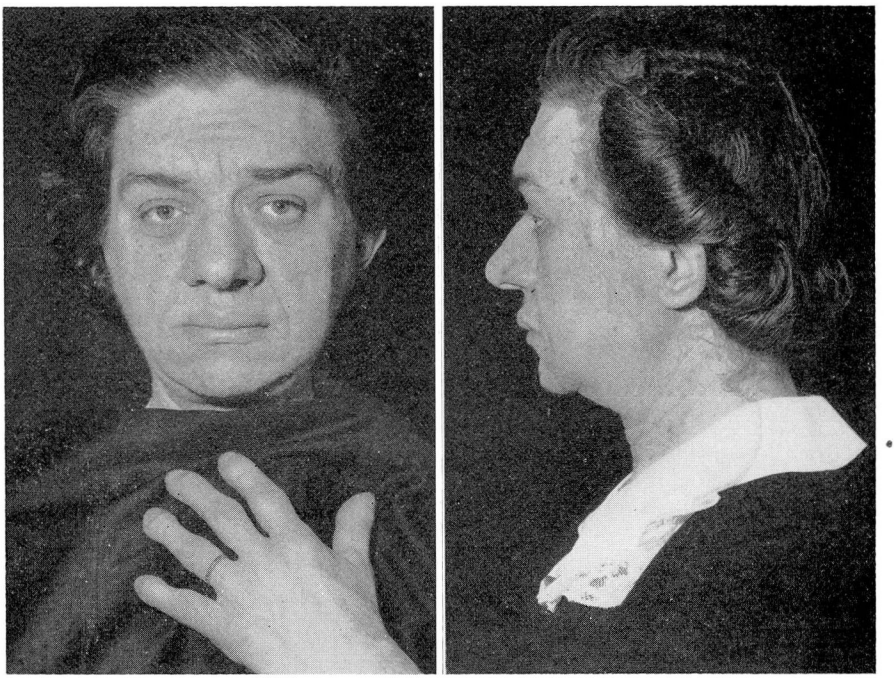


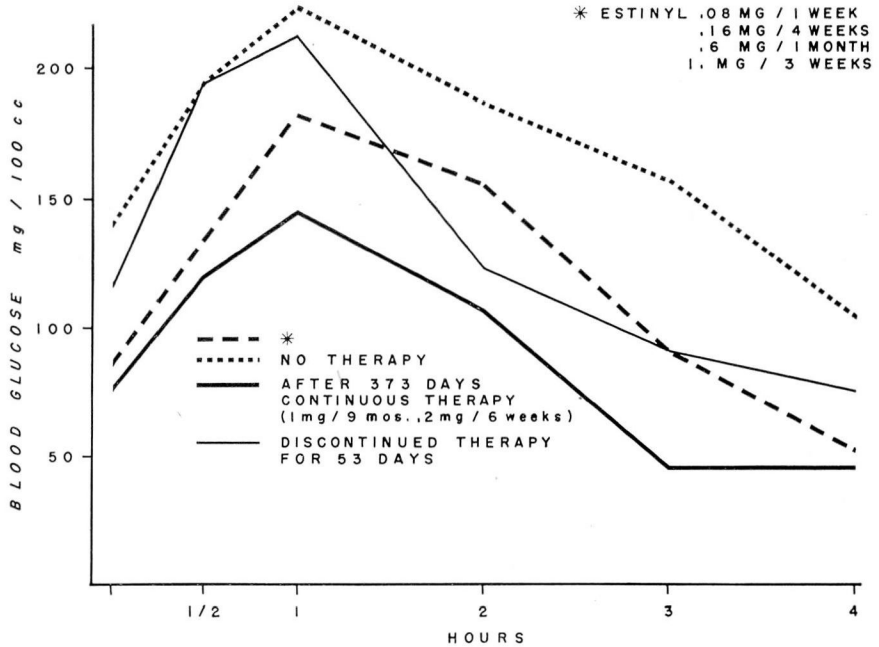
FIG. 1

and nodular. The heart was enlarged to the left. Blood pressure was 194/130. There was a severe uterine prolapse.

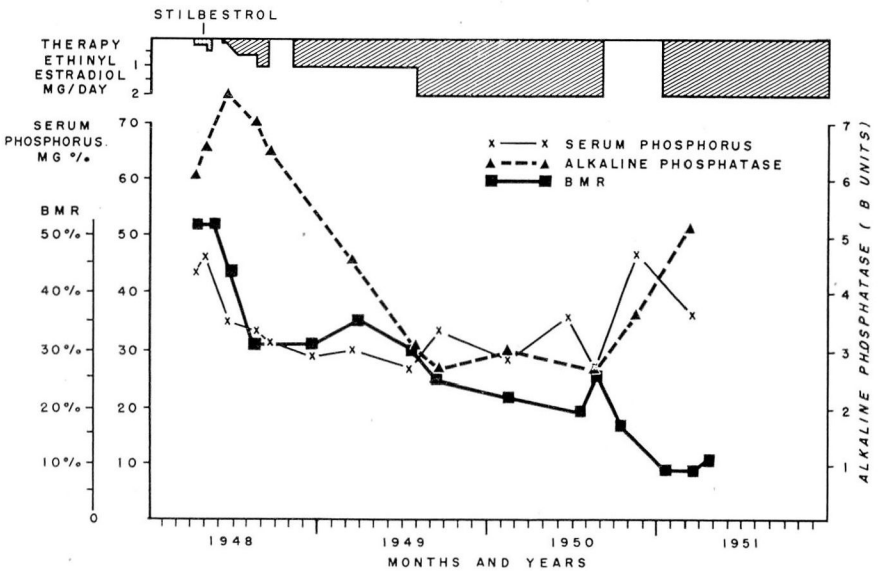
Laboratory examinations were as follows: the urine showed a specific gravity varying from 1.012 to 1.020, with a trace of albumin on several examinations. Hemoglobin, white blood count, blood sugar and blood urea were normal. Wassermann and Kahn reactions were negative. The serum phosphorus was 4.3 mg. per hundred cc., serum calcium 11.5 mg. and the alkaline phosphatase 6.1 Bodansky units. Basal metabolic rate was plus 51 per cent and serum cholesterol 187 mg. per hundred cc. Radioactive iodine uptake was 8 per cent at the end of 2 hours. The glucose tolerance curve was definitely abnormal. Urinary gonadotrophins were less than 13 m.u. and less than 6.6 m.u. per 24 hours, on consecutive examinations. X-ray of the sella turcica showed great enlargement with depression of the floor, and thinning of the dorsum sellae and posterior clinoid processes. There were abnormally prominent frontal sinuses, hyperaeration of other sinuses, and prognathism. X-ray examination of the hands showed tufting of the terminal phalanges. Visual fields for form and color were not diagnostic.

Stilbestrol therapy, 1 mg. daily increasing to 2 mg. daily, was begun but was discontinued after one month because of severe nausea. Ethinyl estradiol* was begun in 0.04 mg. doses per day, increasing gradually to 1 mg. per day, which was continued for 3 months with disappearance of the severe headache and backache, decrease in the coarseness of the features and a diminution in the size of the nose, hands and feet.

Estinyl was supplied through the courtesy of Dr. Edward Henderson and the Schering Corporation.



Graph 1



Graph 2. A decimal point should be inserted in the figures for serum phosphorus on the left hand scale.

Hand volumes after treatment were: left 450 cc., right 485 cc. Therapy was discontinued for 2 months during which time the hand volume increased to: left 515 cc., right 550 cc., along with a return of occipital headache, backache, increase in the size of the nose, lips and tongue.

One milligram of ethinyl estradiol daily was resumed again for a 9 month period after which the dosage was increased to 2 mg. daily for the next year, when treatment was again discontinued. During this period there was complete subsidence of all symptoms and a noticeable increase in strength; her rings became loose, thimbles fit her fingers for the first time since the onset of her illness, and fine movements again became possible. Excessive perspiration ceased. No alteration in blood pressure occurred. Changes in hand volume are shown in table 1.

During the succeeding 4 months the patient was re-examined. Symptoms returned as on the previous cessation of estrogen administration.

Alterations which occurred in the glucose tolerance, serum phosphorus, alkaline phosphatase levels and basal metabolic rate are demonstrated in graphs 1 and 2.

Shortly after the cessation of estrogenic therapy the patient developed a mild cerebrovascular accident from which she gradually recovered. It was at this time that she first noticed blurring of vision, especially laterally, and visual field examinations done repeatedly showed a progressive development of a bitemporal hemianopsia. Because of this finding and the return of active acromegaly ethinyl estradiol, 2 mg. daily was begun again. However, since no immediate improvement in visual fields occurred, the patient received a course of x-ray therapy directed at the pituitary, calculated to deliver approximately 2,000 roentgen units to the gland. This produced no additional effect. There has subsequently been a slow progressive improvement on continued estrogenic therapy and, when last seen after 11 months of continuous treatment, she felt greatly improved, more so than for many years in her own estimation. Arterial hypertension, however, had not diminished. Average blood pressure was 210/120 mm. Hg.

Discussion

We feel that the reversal of the abnormal glucose tolerance test in acromegaly during estrogen administration is further evidence of a potent hormonal inhibition to the pituitary. This is a clinical demonstration of what has been shown previously in experimental animals.[3,6] Whether this improvement in carbohydrate metabolism is due to an inhibition of growth hormone or some other pituitary factor is still a matter of conjecture. To our knowledge this is the first reported instance of complete reversal of diabetes caused by estrogen in the human. Whether or not the pituitary growth hormone or other pituitary factors have a bearing on the etiology of the average case of clinical diabetes remains for future studies to demonstrate.

Summary

A case of acromegaly accompanied by diabetes and arterial hypertension in a 45 year old woman has been presented.

Administration of estrogen was followed by a shift in the glucose tolerance curve from diabetic type to complete normality.

There was also a fall in elevated inorganic serum phosphorus levels to

normal, and considerable clinical improvement including reduction in size of the nose, hands and feet. No effect on the elevated blood pressure was seen.

Discontinuance of estrogen therapy resulted in reappearance of the diabetic type of glucose tolerance.

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