17-KETOGENIC STEROID EXCRETION IN OBESE CHILDREN BEFORE AND AFTER WEIGHT REDUCTION

BY

HAROLD COHEN, M.B., M.R.C.P.

Senior Registrar, Sheffield Royal Hospital

Obesity must be due to overeating, although it may result indirectly from other abnormalities. Simpson (1951) described a type of obesity in children as a minor endocrine disorder, and named the syndrome "adipose gynandrium" in boys and "adipose gynism" in girls. On the other hand, Wilkins (1957) states that endocrine abnormality is rarely encountered in obese children; and Newburgh (1942), in a review of the subject, found no evidence that obesity in children was directly due to endocrine imbalance.

The case histories recorded in this paper are of four patients, children and adolescents, who were very fat, and who, when first investigated, had a daily excretion of 17-ketogenic steroids in excess of the normal for their age. This finding led to a suspicion that the condition was due to endocrine imbalance, although in each case the clinical diagnosis was that of simple obesity. However, with dietary restriction alone the 17-ketogenic steroid excretion fell to normal.

Methods

The 17-ketosteroid and 17-ketogenic steroid excretion were determined by the method of Norymberski, Stubbs, and West (1953) with the modification of Gibson and Norymberski (1954). The 17-ketosteroids are the products of testicular and adrenal cortical hormones excreted as 17-ketones. The 17-ketogenic steroids are steroids in which the side chain on C17 is oxidized to a ketone group by the method of Norymberski *et al.* (1953). The 17-ketogenic steroid assay therefore involves, of necessity, estimation of the 17-ketosteroids. Levell *et al.* (1957) estimated the normal range using this method and discussed the clinical value of the 17-ketosteroid and 17-ketogenic steroid assays. They considered that the 17-ketogenic steroid excretion probably gave a measure of the adrenal function concerned with the production of hydrocortisone and that it was the assay of choice in following changes in adrenal function, as, for example, in observing the response to corticotrophin.

Case 1

A boy aged 14 attended the out-patient clinic at the Sheffield Royal Hospital in June, 1956. He had no symptoms, but was extremely obese. His weight was 12 st. 12 lb. (81.6 kg.). His mother stated that he had always been big for his age, but had started to become fat after he had a tonsillectomy at the age of 7. He had always been a big eater, particularly of bread. He did not play much with his contemporaries, partly because he found it difficult to run about and partly because of the derision that he had to contend with. He preferred adult company. He attended a secondary modern school and had no difficulty with the work.

Apart from tonsillectomy and an operation for a deviated septum at the age of 7 there was no previous illness of note. He was an only child. Both parents were small and thin. The father died of heart disease in 1947.

Physical examination showed an obese boy with kyphosis. Red striae were seen over his thighs and buttocks. There was no axillary hair, but pubic hair was present. His testes were descended and his genital development was normal. He had a thyroglossal cyst, but there was no other abnormality.

The blood pressure was 120/80. His height was 66 in. (167.5 cm.), and span 68½ in. (174 cm.).

Investigations.—Urine, blood count, E.S.R., and chest and skull x-ray films were normal. B.M.R. approximately +5%. Bone age between 13 and 15 years. Excretion urogram, no abnormality. 17-Ketosteroid excretion, 17-ketogenic steroid excretion, weight reduction, and progress are recorded in the Table.

Case 2

A girl aged 6 was admitted to Nottingham City Hospital in April, 1956, for the investigation of obesity. She had begun to gain weight excessively at the age of 3½. Her appetite was said to be normal, although she was fond of starchy food. Apart from the obesity she was quite well and did well at school. Her history revealed nothing relevant. Her mother weighed 16 st. (101.6 kg.) at 16 years. Both maternal grandparents were large. Two maternal uncles were over 6 ft. (183 cm.) and weighed 18 st. (114.3 kg.). Her father and two sisters were of normal size. There was no family history of diabetes.

Physical examination showed obesity, particularly of the chest and abdomen. Her weight was 7 st. 2 lb. (45.4 kg.); height, 46½ in. (118 cm.); girth at umbilicus level, 37 in. (94 cm.); at nipple line, 36½ in. (92.7 cm.). Her skin was delicate and soft. There were no striae, no axillary or pubic hair, and no other abnormal physical signs.

Investigations.—Blood count, glucose tolerance test, and x-ray examination of skull and wrist were all normal. Other results are shown in the Table.

She was discharged from hospital in June, 1956, having lost 20 lb. (9.1 kg.) in weight. She was readmitted in June, 1957, having gained 48½ lb. (22 kg.). Since her previous admission she had been quite well and lively, and had been doing well at school.

Physical examination showed little change from the previous examination except that there were red striae on the outer aspects of her hips. Her weight was 9 st. 2½ lb. (58.3 kg.); height 49 in. (124.5 cm.); girth at chest, nipple line, 37½ in. (95.3 cm.); waist, 33½ in. (85 cm.); hips, 39½ in. (100 cm.); abdomen, 38½ in. (97.8 cm.).

Her blood pressure was 120/70, blood count normal; no glycosuria.

Case 3

A girl aged 14 attended the out-patient clinic at the Sheffield Royal Hospital in May, 1957. She had been overweight since the age of 3, but had become increasingly obese in the past two years, having gained 70 lb. (31.7 kg.) in that period. Her appetite was very good and she had never been on a reducing diet. Menstruation, which was scanty and irregular, had started at the age of 13½. She had had tonsillectomy at 8 years, but no illness of note. Her mother, father, and two sisters were all overweight: mother 16 st. (101.6 kg.), father 15½ st. (98.4 kg.), sister aged 21, 13 st. (82.5 kg.).

She was an obese girl with dark hair on her upper lip and pubic and axillary hair. Red striae were present on her abdomen, but none on her thighs. Blood pressure was 130/80; weight, 18 st. 8 lb. (118 kg.); height 66½ in. (168.6 cm.); girth at nipple line, 43½ in. (110 cm.); waist, 41 in. (104 cm.); hips, 50 in. (127 cm.).

X-ray examination of the chest and skull showed no abnormality. There was no glycosuria. Results of other investigations are shown in the Table.

Case 4

A boy aged 10 attended the out-patient clinic at Staincliffe General Hospital in May, 1957. He had no symptoms other than pain due to flat-feet. He had always been overweight. His birth weight was 8 lb. 6 oz. (3.8 kg.). At the age of 4 years he weighed 56 lb. (25.4 kg.). His history revealed nothing relevant. He had no brothers or sisters. His parents were plump but not grossly obese.

Date	Weight		17-Ketosteroid Excretion (mg./ 24 Hrs.)	17-Ketogenic Steroid Excretion (mg./ 24 Hrs.)	Notes
	lb.	kg.			
Case 1					
22/6/56	180	81.6			Advised to diet. Admitted to hospital; 1,000-calorie diet started
23/8/56					
26/8/56	174	78.9	23.7	32.1	Discharged. Diet continued as O.P.
28/8/56			20.8	25.2	
30/8/56					Admitted; 800-calorie diet started
21/9/56	176	79.8			
6/1/57					Discharged
10/1/57			10.4	17.7	
13/1/57	175	79.4			Admitted; 1,000-calorie diet started
14/2/57					
28/2/57	174	78.9			Discharged
26/3/57					
31/3/57	178	80.7			Admitted
7/4/57	173	78.4			
14/4/57	170	77.1			Discharged
19/4/57			10.6	8.5	
20/4/57					Admitted
6/5/57	171	77.6			
28/5/57	164	74.4			Discharged
29/5/57			9.9	9.2	
31/5/57					
Case 2					
16/4/56	100	45.4	2.4	11.8	Admitted to hospital; reducing diet started
23/4/56	94	42.6			
30/4/56	92	41.7			Normal diet started
8/5/56	90	40.8	1.6	3.7	
12/5/56	88	39.9			Discharged
19/5/56	87	39.5			
25/5/56	86	39			Second admission; reducing diet started
7/6/56	82	37.2			
16/6/56	80	36.3			Discharged
19/6/56					
16/7/56	88	39.9			Discharged
13/8/56	90	40.8			
14/6/57	128	58.3			Discharged
18/6/57	122½	55.6	4.3	9.1	
25/6/57	121	54.8			Discharged
9/7/57	118	53.5			
19/7/57	114½	51.9	1.5	3.5	Discharged
24/7/57	114	51.7			
Case 3					
13/5/57	260	118			Admitted to hospital; 1,000-calorie diet started
19/6/57			7.3	18.4	
20/6/57	258	117			Discharged. Continued on diet
23/6/57	255	115.7			
28/6/57					Discharged
19/7/57	239	108.4			
8/8/57	228½	103.6	5.8	11.0	
Case 4					
15/5/57	130	59			Started on reducing diet
18/5/57			5.6	16.4	
7/7/57	121½	55.1			
20/7/57			4.1	9.7	
21/7/57			3.6	8.7	

Physical examination showed no signs of precocious puberty. Striae were present on the hips and flanks. Blood pressure 110/70. No other abnormal physical signs. His weight was 9 st. 4 lb. (59 kg.); height, 59 in. (150 cm.); span, 57 in. (145 cm.).

Investigations.—No abnormality was found on x-ray examination of the skull and abdomen. His bone age was 11 to 12 years. Serum chemistry: sodium, 156 mEq/l.; potassium, 4.2 mEq/l.; chlorides, 112 mEq/l. Urine showed no abnormality. Other results are shown in the Table.

Results

The details of weight reduction, dietary restriction, and 17-ketosteroid and 17-ketogenic steroid excretion are set out in the Table. The weights are recorded to the nearest half-pound. In Cases 1 and 3 some weighings were made in the out-patient department and some in the ward, and an allowance of 2½ lb. (1.2 kg.) was made for the difference in clothing.

It is apparent that in every case the 17-ketogenic steroid excretion was considerably in excess of the normal for the

age before the patient began to reduce weight by dieting. With the exception of Case 1 the 17-ketosteroid excretion was only slightly raised or at the upper limit of normal. Weight reduction due to dietary restriction was always associated with a fall in both 17-ketosteroid and 17-ketogenic steroid excretion.

The first patient (Case 1), although on a reducing diet, apparently gained a little weight initially, yet there was a fall in his 17-ketosteroid and ketogenic steroid excretion. This suggests that the calorie intake rather than the weight loss may be the determining factor in producing the fall in 17-ketogenic steroid excretion.

Discussion

17-Ketogenic Steroid Excretion.—The upper limit of normal 17-ketogenic steroid excretion in boys aged 11 and 14 is 9 and 12 mg. a day, and in girls aged 7 and 14 is 5 and 11 mg. a day respectively (Levell *et al.*, 1957). In the above cases the values recorded before dieting started were all well above normal. If the patients were compared with normals of their own weight rather than age, then with one exception (Case 1) the 17-ketogenic steroid excretion would be within normal limits. Norval and King (1950) found the urinary excretion of corticosteroids (expressed as milligrams of 11-dehydrocorticosterone) in normal children to be closely related to their weight. In the above cases the raised 17-ketogenic steroid excretion may be due, therefore, merely to increased weight, but this is unlikely, as a small loss of weight produced such a marked fall in 17-ketogenic steroid excretion. Gray *et al.* (1956) have shown that in children with adipose gynism and adipose gynaecism (see above) the urinary excretion of hydrocortisone was significantly increased above that of normal children, although there was no significant difference between adipose and normal children in the excretion of 17-ketosteroids. They compared the groups of children by age and did not take weight into account.

Overnutrition in Childhood.—Wolff (1955) studied obesity in childhood. In a careful investigation he found that obese children were taller than normal children (normality being based on measurements of children from all social classes), but the height of obese children was not significantly above that of children of the professional class. He suggested that this provided evidence that the obese child's height was not outside the normal range and was merely the result of very adequate or more than adequate feeding. During a period of rapid weight reduction obese children gained height at less than the expected rate. He also showed that in obese children the onset of puberty occurred approximately one year in advance of the time of its onset in normal children.

Endocrine Changes in Malnutrition.—Landau *et al.* (1948) studied the effect of starvation on 17-ketosteroid excretion. Three normal men and one obese woman were starved for four days, being given water or water plus salt supplements only. In every case there was a decrease in 17-ketosteroid excretion by at least 50%. In an investigation on convicts, Hamilton and Hamilton (1948) found that the ketosteroid excretion of these men was slightly lower than normal. They observed that most of the prisoners disliked their diet and had lost weight during imprisonment.

Undernutrition produces no change in steroid excretion in Cushing's disease. A woman aged 24 who had Cushing's disease weighed 21 st. (133 kg.) when first seen. On a reducing diet her weight fell by 3 st. (19 kg.), but her 17-ketosteroid and 17-ketogenic steroid excretion remained consistently raised.

Extreme inanition in a Japanese prisoner-of-war camp produced, in American prisoners, loss of libido and loss of hair, changes similar to those seen in a castrated male, suggesting a decrease in the production of sex hormones (Jacobs, 1948).

Perloff *et al.* (1954) investigated gonadal, thyroid, and adrenocortical function in five patients, four of whom were

undernourished owing to anorexia, and one of whom had sprue. They found a decrease in all glandular activity, and concluded that the functional activity of the pituitary gland may be greatly impaired by starvation. This functional hypopituitarism was reversed in one case by refeeding.

In children the results of underfeeding afford a direct contrast to the changes noted in obese children. Undernourished children are small and thin, and skeletal and sexual maturation may be retarded. Signs of decreased pituitary activity can result, in children, from malnutrition, the intensity of the signs being roughly proportional to the degree of undernutrition (Talbot *et al.*, 1952).

Speculation

There is abundant evidence that undernutrition produces hypopituitarism. The converse, that overnutrition produces hyperpituitarism, would explain the observations made on obese children. Increased growth, earlier puberty, and increased adrenocortical activity could be explained on the basis of this hypothesis. The change in 17-ketogenic steroid excretion described in this paper might be due to an alteration in pituitary activity resulting from the change from overnutrition to undernutrition.

This hypothesis might reconcile the views of those who consider obesity in childhood to be entirely nutritional in origin and those who consider the condition to be an endocrine disorder.

Summary

The case histories are recorded of four patients—children and adolescents—who suffered from obesity. Each patient initially had a raised urinary excretion of 17-ketogenic steroid, which became normal after weight reduction due to dietary restriction. In one patient this phenomenon was observed on two occasions. Obesity in childhood is briefly discussed, and it is suggested that overnutrition may produce functional hyperpituitarism.

I am grateful to Dr. Arthur Jordan, director, department of biochemistry, United Sheffield Hospitals, for his assistance and advice. I thank Dr. A. P. M. Page, Dr. M. W. Arthurton, and Professor G. M. Wilson for permitting me to borrow case records and allowing me to publish them. I am grateful to my chief, Dr. T. E. Gumpert, for allowing me to publish details of cases I have seen on his wards, and for his useful criticism; and I thank Dr. D. V. Hubble for his advice.

REFERENCES

- Gibson, G., and Norymberski, J. K. (1954). *Ann. rheum. Dis.*, 13, 59.
 Gray, C. H., Lunn, J. B., Popd, M. H., and Simpson, S. L. (1956). *J. clin. Endocr.*, 16, 473.
 Hamilton, H. B., and Hamilton, J. B. (1948). *Ibid.*, 8, 433.
 Jacobs, E. C. (1948). *Ibid.*, 8, 227.
 Landau, R. L., Knowlton, K., Anderson, D., Brandt, M. B., and Kenyon, A. T. (1948). *Ibid.*, 8, 133.
 Levell, M. J., Mitchell, F. L., Paine, C. G., and Jordan, A. (1957). *J. clin. Path.*, 10, 72.
 Newburgh, L. H. (1942). *Arch. intern. Med.*, 70, 1033.
 Norval, M. A., and King, N. (1950). *Biometrics*, 6, 395.
 Norymberski, J. K., Stubbs, R. D., and West, H. F. (1953). *Lancet*, 1, 1276.
 Perloff, W. H., Lasché, E. M., Nodine, J. H., Schneeberg, N. G., and Vicillard, C. B. (1954). *J. Amer. med. Ass.*, 155, 1307.
 Simpson, S. L. (1951). *Proc. roy. Soc. Med.*, 44, 453.
 Talbot, N. B., Sobel, E. H., McArthur, J. W., and Crawford, J. D. (1952). *Functional Endocrinology*, p. 473. Harvard Univ. Press, Cambridge, Mass.
 Wilkins, L. (1957). *The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence*, p. 473. Oxford.
 Wolff, O. H. (1955). *Quart. J. Med.*, 24, 109.

A recent publication from the Ministry of Fuel and Power summarizes pneumoconiosis statistics obtained from the Ministry of Pensions and National Insurance and the National Coal Board. It is *Digest of Pneumoconiosis Statistics, 1956* (H.M.S.O., 3s.). The introduction summarizes the legislation relating to pneumoconiosis, describes the administrative procedures, and gives explanatory comments on them and on the tables. The statistics cover Scotland as well as England and Wales.

GUSTATORY SWEATING AND PILOMOTION

BY

ANDREW HERXHEIMER, M.B.

Lecturer in Therapeutics, St. Thomas's Hospital Medical School, London

It has been known for some years that pathological gustatory sweating may follow cervical sympathectomy, but the phenomenon has not been satisfactorily explained. In the case reported here, accidental operative damage to the sympathetic was followed by gustatory sweating and gustatory pilomotion, a condition not hitherto recorded. An explanation of these symptoms is put forward.

Case Report

A woman developed pulmonary tuberculosis in 1946 at the age of 21. In 1947 she had a three-stage thoracoplasty on the left side, in which the upper eight ribs were removed. The presence of many adhesions made the operation difficult. The disease has now been inactive for several years.

She first noticed gustatory sweating in 1948. Since then it has gradually increased in intensity. Sweating begins at once when she eats chocolate, certain sweets, fruit cake, Swiss roll, pickles, or cheese. It is confined to the left side, and is so profuse on the neck and shoulder that she often has to wipe the skin. She also has goose-skin in the same areas; this is accompanied by a tingling sensation.

When seen in 1956, she appeared healthy, though thin. An incomplete Horner's syndrome was present on the left side, with the left pupil smaller than the right. In the fasting state, sweating was detected by Wada's (1950) method on the left side of the face and neck, but not on the right. This sweating was much less than that evoked by the foods mentioned.

Indirect heating by immersion of the legs in warm water caused her to sweat considerably on the normal side, but very little on the left side of the face and neck and the left shoulder and arm. Finger and hand plethysmography showed that the vessels of the right hand constricted sharply in response to nervous stimuli, such as a sudden noise; on the left side no constriction occurred.

The taste of chocolate induced sweating and pilomotion within half a minute. Sweating could be detected by Wada's (1950) method on the whole of the left arm, except on the palm, but was much less intense than on the left side of the neck and shoulder. Goose-skin was observed as far down as the middle of the forearm. Proximally, on the neck and shoulder, it appeared in an almost continuous sheet; distally it was patchy and less intense. Occlusion of the arterial supply to the arm by a pneumatic cuff prevented neither sweating nor the development of goose-skin below the cuff in response to the taste of chocolate. Pressure on the carotid sinus did not cause pilomotion or an increase in sweating.

Discussion

The absence of thermal sweating on the left side of the face and neck and the left arm shows that the sweat glands in these areas have lost their normal innervation. That the gustatory sweating and pilomotion is not due to a substance reaching the skin by the blood stream is shown by the fact that arterial occlusion did not prevent sweating or pilomotion, and this suggests that a nervous mechanism is responsible. Haxton's (1948) observation that gustatory sweating can be temporarily abolished by procaine infiltration of the region of the cervico-thoracic ganglion points in the same direction.

The simplest explanation of this patient's symptoms appears to be that suggested by Murray and Thompson