THE TREATMENT OF ADIPOSE GYNANDRISM*

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The object of this paper is to report my experience of adipose gynandrism over the past 15 years, during which I have treated more than 30 patients. It is submitted simply as a clinical memorandum in the hope that others will be encouraged to test the efficacy of the treatment described.

CLINICAL FEATURES

Adipose gynandrism is defined by S. Leonard Simpson[1] as '. . . a syndrome commencing in childhood and characterized by adiposity, delayed development of the penis and testicles, a gynaecoid pelvis and feminine physical and behaviour characteristics'. He chose the word gynaecoid to indicate a mixture of female and male characteristics.

These boys appear rather feminine in build because of the gynaecomastia, and because of a broad pelvis with excessive deposits of fat on the hips and buttocks. They tend to be broader across the hips than the shoulders. They may have knock-knees and the waddling gait of a fat female. The penis and testes may be quite minute. Often the penis is buried in excessive suprapubic fat, further accentuating its smallness.

Boys with adipose gynandrism tend to look like the popular conception of Frohlich's syndrome (adipose genital dystrophy) and they are frequently sent up with this label by practitioners. Frohlich's syndrome is also characterized by adiposity and genital underdevelopment, but whereas adipose gynandrism is a benign condition not associated with any space-occupying lesion, Frohlich's syndrome is usually due to encroachment upon the pituitary-hypothalamic system by a cyst or tumour, e.g. a craniopharyngioma. Neighbourhood signs eventually develop in addition to the endocrine manifestations. It is an excessively rare condition, quite unlikely to be encountered in the ordinary course of general practice, whereas adipose gynandrism is quite common.

What brings these patients to the doctor? Sometimes it is the *obesity* which causes the parents to bring the boy to the doctor. More often it is the marked *smallness of the penis and testicles* which has given rise to anxiety. This is especially likely to occur when there is a younger brother in the family whose genital development far exceeds that of the elder. Under these circumstances the parents may notice the defect at as early an age as 8 years. At the age of about 10 or 11 the boy is likely to notice it himself, especially if he has a younger brother or if he is at boarding school. He may be teased about it quite mercilessly by his schoolmates, and it then often becomes an important psychological problem. The difference between him and other boys is accentuated by his obesity, gynaecomastia, etc. He becomes self-conscious and will not go bathing, although such boys are usually good swimmers and have a predilection for the sport. The boy's withdrawal from bathing is therefore the more striking and worrying to the parents. He makes excuses not to continue taking part in any game involving undressing in the presence of others, and the gulf between him and his friends may widen. The parents notice he has become shy, introspective, irritable and unable to concentrate on his work. It may only be after questioning the boy repeatedly about the reason for his change in behaviour that his parents elicit the truth. This psychological trauma by no means occurs in all cases. Some boys are quite happy and normally self-assured, but the great stress which may sometimes be caused by this condition is often not fully appreciated.

What happens to the untreated patients? They do eventually attain puberty, but usually at the late age of 15 - 17 years. They become capable of having children, but many of the stigmata of their disability remain. Thus they usually retain much of the ungainly configuration of their childhood, including the gynaecomastia, the abdominal roll of fat, and the fat hips and buttocks. The pelvis remains gynaecoid. They shave infrequently. The penis and testes are small. One or more offspring may have the stigmata of adipose gynandrism.

TREATMENT

1. *Weight Reduction*

The boys are put on to a low-carbohydrate, low-fat, low-salt regime, with fluid restricted to two pints a day. I do not hesitate to use dextro-amphetamine sulphate to help control the appetite and sustain morale. The usual dose given is 5 mg. on waking, 7½ mg. ¾-hour before lunch, and 5 mg. at 5 p.m. In contrast to adults, it rarely interferes with sleep in youngsters of this age group. If it does, the afternoon tablet is given earlier. In the past two or three years, a 'dexedrine' or 'drinamyl' 'spansule' given on waking has been preferred. These have the advantage that they need be given only once a day, but they are more expensive. Alternative preparations such as diethylpropion ('tenuate'), phenmatrazine ('preludin'), etc., may be used. The boys, on the whole, cooperate remarkably well, better indeed than do most adults. Loss of 20 - 30 lb. in a few months is quite commonly achieved. It is not

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unusual for the boys to remonstrate with their mothers when food which deviates from the written instructions is given. Their strict adherence to instructions is probably a measure of their great anxiety to look more normal.

Habituation to dextro-amphetamine sulphate has never occurred in any of these cases. In fact in 15 years I have not encountered addiction in several hundred adults treated for obesity with dextro-amphetamine sulphate. The few cases of addiction to this drug which I have encountered in the course of practice have been in persons who took it originally for depression and similar conditions. It would seem that where it is used to induce an unpleasant effect such as anorexia, it does not cause habituation, whereas when used to produce a pleasant effect, such as elevation of the mood, the danger of habituation arises.

The possibility had to be considered that weight reduction alone might improve the endocrine state and lead to the improved gonadal development, but observation made it quite clear that this did not happen.

2. *Gonadotropic Hormone Injections*

The product used in all cases has been 'pregnyl' (Organon Laboratories). This is a preparation of chorionic gonadotropin obtained from the urine of pregnant women. The dose is 500 units by intramuscular injection into the buttock 3 times a week for 24 injections. The course of injections thus lasts 8 weeks. As might be expected with treatment directed at inducing growth in organs, there is a lag between administering the injections and obtaining results. The patient is therefore re-assessed 3 or 4 months after the end of the course of injections.

If the improvement is adequate no further hormonal treatment is given. The pregnyl seems to act as a trigger mechanism inducing puberty, and thereafter the development usually proceeds very satisfactorily. If only slight benefit is seen, a second course of gonadotropic hormone is given. In the uncommon cases, where no improvement is obtained after 2 courses, it is assumed that the trouble is not a pituitary deficiency but a primary testicular failure, and substitution therapy with testosterone is instituted.

Results of Treatment

The results of weight reduction plus gonadotropic hormone injections are usually very satisfactory. The regions where weight is lost usually include the hips, breasts and buttocks, and so the boys become less effeminate-looking. This is reinforced by the effects of the gonadotropic hormone on the gonads and secondary sexual characteristics.

The increase in *size of the penis* is the most striking and consistent effect of the hormone injections. The improvement continues sometimes for years after the injections and many of the patients when seen in their twenties have a penis well above average size. *The testes* usually enlarge to some extent, but do not as a rule attain average normal size. *Pubic hair* usually appears quite abundantly following the injections, but the upper border tends to remain horizontal for a few years at least. Seen several years later, however, it has in most cases extended towards the umbilicus in the normal masculine manner. Facial hair growth is encouraged. There appears to be very little effect on axillary hair growth in the months immediately following the injections.

The *gynaecomastia* becomes less gross owing to weight loss, but improvement is never more than partial, and the hormone has no beneficial influence. Testosterone injections likewise do not help the gynaecomastia and operative treatment is required if the patient is sufficiently distressed by its presence. Similarly, the decrease in *pelvic girdle fat* as part of the general loss of weight improves the appearance of the hips, but the gynaecoid shape of the pelvis persists, preventing a completely satisfactory result.

In many cases there is a marked spurt in *height* during the months following injections, as is common during normal puberty.

Muscle-building exercises are of value in assisting the development of a masculine appearance.

Undesirable side-effects. These are very few. Occasionally a parent is a little concerned that the degree of penile development is greater than thought desirable. In only one case did the parents report that the son had begun to take an unhealthy interest in little girls. The injections were well tolerated and not painful. In only two cases did the patient complain of not feeling well during the course of injections, and in one of these 1,000 units of hormone were being administered instead of the usual 500 units per injection.

SAMPLE CASE HISTORIES

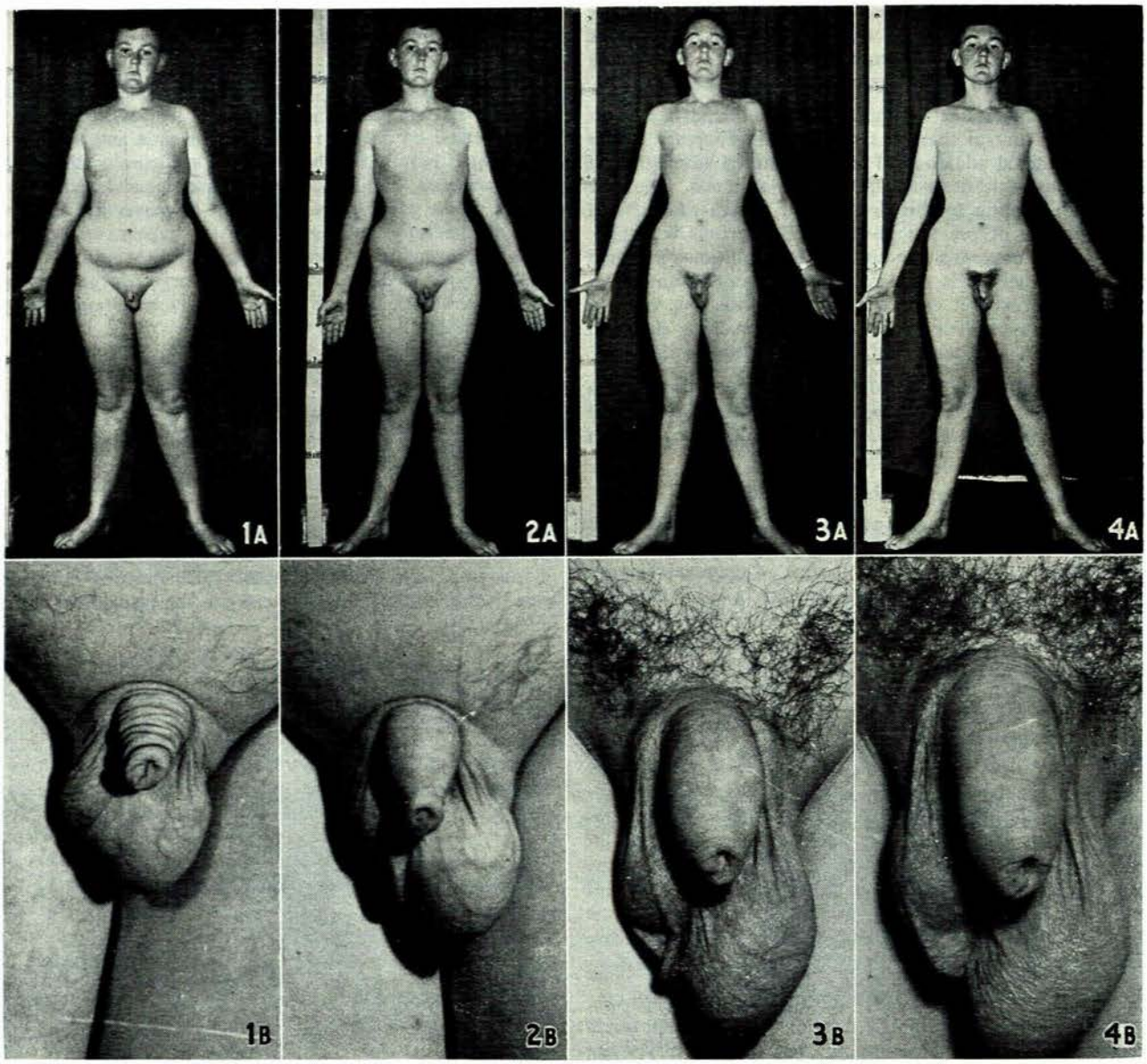
The following two subjects have been selected as examples of the response to treatment, because they are of special interest in that they are brothers with a 3-year age difference who started treatment at exactly the same time. The two were so similar in all respects that it was reasonable to assume that the younger brother would have followed the same course as the older brother if left alone. His improvement within a few months of treatment is therefore reasonably related to the treatment given.

Case 1. W.D., born 5 October 1939

Photographs taken on 15 January 1955 at the age of 15 years 3 months (Figs. 1A and 1B) show a typical picture of adipose gynandrism, viz. obesity, hypogonadism, gynaecomastia, knock-knees, and broad pelvis with deposition of fat around the pelvic girdle. X-ray of the pelvic inlet showed it to be gynaecoid in type. The penis and testes were extremely small (compare with size of thumbs in picture). The left testicle was in the scrotal sac. The right testis was usually retracted into the inguinal canal, and could be brought down into the scrotum with difficulty. A large left varicocele and lesser right varicocele were present. He had never ejaculated. His voice was unbroken. He had very scanty pubic hairs. (These appeared following a few testosterone injections he had received previously from a doctor.) No facial or axillary hairs were present. Height 5 foot 7 inches, weight 183½ lb.

A weight-reducing regime, as described above, was instituted. Gonadotropic hormone was withheld to see whether weight reduction alone would induce any gonadal development. Figs. 2A and 2B, 29 March 1955, show his appearance after 2½ months of weight reduction. Weight 140 lb., i.e. a loss of 43½ lb. There is considerable improvement in appearance owing to the loss of weight, but no gonadal improvement or further development of pubic hair.

On 1 May 1955 it became clear that no improvement was occurring with regard to the sexual characteristics on weight reduction alone, and treatment with gonadotropic hormone (pregnyl) was commenced, 500 units being given 3 times a week for 8 weeks.



Figs. 1 - 4. Showing progress of elder brother, W. D., aged 15 years 3 months at the beginning of treatment. Fig. 1*A* and *B*: Appearance before institution of treatment. Fig. 2*A* and *B*: After 2½ months of weight reduction without hormone therapy. Note improvement in general appearance from weight loss, but lack of gonadal improvement. Fig. 3*A* and *B*: 4½ months after completion of first course of gonadotropic hormone injections. Note gonadal improvement. Fig. 4*A* and *B*: 8½ months after completion of first course of injections. Note striking change in general appearance and marked gonadal improvement. (Figs. 1B, 2B, 3B and 4B are all to the same scale.)

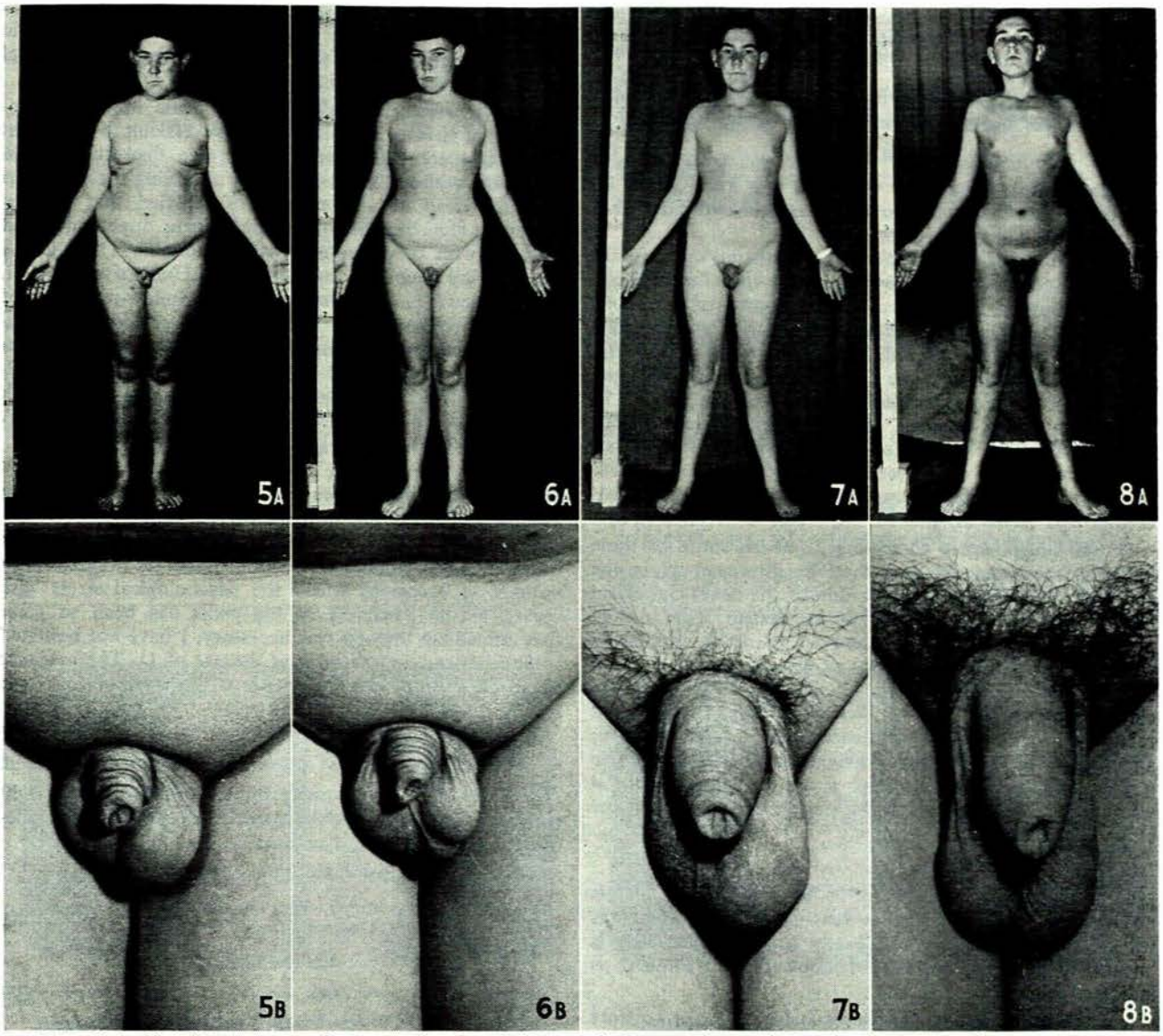
10 July 1955. At the conclusion of an 8-week course of injections he was seen again. There was a striking difference in his appearance. He had lost his babyish look and had a most confident and aggressive bearing. The gonads had increased in size very definitely, and the pubic hairs were increasing. The right testis had come down permanently into the scrotum. He had ejaculated semen on two occasions. His voice had broken.

September and October 1955. A second course of 18 injections of pregnyl was given extending over 6 weeks.

On 19 November 1955 he was seen again 4½ months after the first course of gonadotropic hormone had been completed. Figs. 3A and 3B show the same features that were seen in July. He had developed further growth of pubic hair.

On 27 March 1956 he was photographed again (Figs. 4A and 4B). The striking improvement 9 months after the conclusion of the first course of injections can be seen by comparing these pictures with Figs. 1A and 1B. It is highly unlikely that a change of this magnitude could have occurred spontaneously in this period. He had grown 3 inches in height, now being 5 foot 10 inches, and his weight was 146 lb. Note that in spite of the general improvement in appearance the pelvis is still gynaecoid, considerable gynaecomastia remains, and the upper border of the pubic hairs is horizontal.

December 1956. Height 6 foot 1 inch, weight 150 lb. Thus, in spite of having grown 6 inches he was still 33½ lb. below his weight when first seen.



Figs. 5-8. Showing progress of younger brother, I. D., aged 12 years 2 months at the beginning of treatment. Fig. 1*A* and *B*: Appearance before institution of treatment. Fig. 2*A* and *B*: After 2½ months of weight reduction without hormone therapy. Note improvement in general appearance from weight loss, but lack of gonadal improvement. Fig. 3*A* and *B*: 4½ months after completion of first course of gonadotropic hormone injections. Note gonadal improvement. Fig. 4*A* and *B*: 8½ months after completion of first course of injections. Note striking change in general appearance and marked gonadal improvement. (Figs. 5B, 6B, 7B and 8B are all to the same scale.)

Case 2. I. D. (Brother of W. D.), born 18 November 1942

In January 1955 he was 12 years 2 months old. The story runs *pari passu* with that of his brother.

15 January 1955. Figs. 5A and 5B show the typical appearances of adipose gynandrism as described above. Height 5 foot ½ an inch, weight 149½ lb. Like his elder brother he had a left varicocele. He too was initially put on a weight-reducing regime without any gonadotropic hormone therapy.

29 March 1955. Figs. 6A and 6B. Weight 117 lb., i.e. a loss of 32½ lb. in 2½ months. As with his elder brother there was considerable improvement in appearance owing to weight loss, but no gonadal improvement or development of pubic hair.

On 1 May 1955 it was clear that weight reduction alone was producing no improvement of his hypogonadism, and treatment with gonadotropic hormone was commenced, 500 units being given 3 times a week for 8 weeks.

On 10 July 1955 he was seen again at the end of this course of injections, and the same improvements as described above with regard to his brother were noted.

September and October 1955. A second course of 18 injections of pregnyl, extending over 6 weeks, was given.

19 November 1955. He was seen again 4½ months after the first course of gonadotropic hormone had been completed. Figs. 7A and 7B demonstrate the improvement.

27 March 1956. Height 5 foot 4½ inches, weight 120 lb. Although he had grown 4½ inches, he weighed 29½ lb. less than when seen originally. Figs. 8A and 8B show the marked improvement 9 months after the conclusion of the first course of injections. It is highly unlikely that such an improvement

could have occurred spontaneously, especially since his elder brother with the same condition went on to the age of 15 without any improvement until he received hormonal treatment.

Note: The skin sexing of both boys was done in October 1956 and showed the features of chromosomal males.

DISCUSSION

The satisfactory results of treatment are exemplified by the two cases described above. Puberty is induced within a few months in most patients.

Observation of more than 30 patients in the past 15 years has convinced me beyond doubt that the development of puberty so soon after the course of injections is beyond coincidence. The case histories of the two brothers selected for detailed description are of special interest in this connection. They presented on the same day. Since the older brother had reached the age of 15 without attaining puberty, it seemed probable that the younger aged 12 would follow a similar course if not treated. Moreover, improvement occurred in both before the first course of injections was completed and proceeded *pari passu* in spite of the 3-year difference in age.

It was suggested at a meeting at which some of these patients were demonstrated, that the improvement in the sexual characteristics might be due to the beneficial effect of the weight loss on the endocrine system. This sort of phenomenon is sometimes observed in obese women in whom menstrual irregularities and infertility may improve considerably after weight reduction. It was therefore decided to note what results could be obtained by weight reduction alone. This produced some improvement in appearance, especially where weight was lost on the pelvic girdle and the chest (see Figs. 1 and 2, 5 and 6) but it was clear that it did not produce any improvement in the sexual characteristics.

Is Treatment Worth While?

Common practice seems to be to offer these patients no treatment. The patient is reassured that the gonads will ultimately develop adequately and that the boy is 'meant to be fat'. In my opinion active treatment is indicated because:

(*a*) *Relief of present disabilities is frequently a pressing need.* The condition is often a source of great unhappiness and anxiety because of the obesity, the gynaecomastia and the minute gonads. To prolong the psychological stress for several years is unjustifiable.

(*b*) *Improved end result occurs.* While immediate improvement is invariable, it is of course difficult to prove that these boys are still better in later life than they would have been without treatment. After observing these patients over a period of 15 years I am satisfied that without treatment they remain more feminine in appearance and manner, with considerably smaller genitalia. This view is also held by Svend G. Johnsen of the University Hospital, Copenhagen.[2] In 1957 he reported a follow-up study of 'fat feminine boys' who had not been treated. He found that a considerable number displayed hypogonadism in adult life, and some had severe genital underdevelopment. He concluded that 'this risk has proved to be of such magnitude that the disease should be treated if possible'.

At what Age should Treatment Commence?

Dietary control of the obesity can be started at 8 or 9 years of age which, with rare exceptions, is the earliest age these patients are brought for consultation.

I prefer to delay administration of the gonadotropic hormone until about 13 years of age. However, on a number of occasions where the psychological stress with regard to the smallness of the penis has been so great that immediate therapy was necessary, I have not hesitated to begin hormone treatment at the age of 11. The response has been as satisfactory as when it has been given at the age of 13 or 14.

SUMMARY

1. The condition called adipose gynandrism is described.

2. The results of treatment by a combination of weight reduction, gonadotropic hormone injections and muscle-building exercises are described.

3. Justification for instituting treatment is discussed.

I wish to thank Mr. B. Todt of the Photographic Unit of the Groote Schuur Hospital, Cape Town, for producing the photographs.

REFERENCES

1. Simpson, S. L. (1948): *Major Endocrine Disorders.* London: Oxford Medical Publishers.
2. Johnsen, S. G. (1957): Acta endocr. (Kbh.), suppl. **31**, 191.