After a single intramuscular injection of 4 or 5 ml., serum-iron levels attained a variable peak in one or two days and returned to about normal after six or seven days in both anæmic patients and healthy people.

There was no evidence of increased urinary excretion of iron after injection of the preparation.

The injected iron disappears from the serum more slowly than does saccharated iron oxide.

In spite of serum-iron levels as high as 13·8 mg. per 100 ml. no toxic reactions were observed after intramuscular injections.

38 out of 40 cases of iron-deficiency anæmia responded adequately to intramuscular treatment with the iron preparation. It was found that 43 mg. of iron intramuscularly would raise the Hb level by 1%, and the period taken to achieve the maximum rise in Hb was 4–9 weeks.

A difference in Hb response was observed between the present preparation and saccharated iron oxide.

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THE ACTION OF CHORIONIC GONADOTROPHIN IN THE OBESE

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IN most cases of obesity the distribution of excess fat somewhat resembles that obtaining in Fröhlich's syndrome. It therefore seemed worth while to experiment with the anterior-pituitary-like chorionic gonadotrophin derived from human pregnancy urine * which has long been advocated for the treatment of Fröhlich's syndrome.

Method and Results

Daily injections of a small dose—125 I.U.—were preferred to a wider spacing of larger doses. The results observed were not enhanced by increasing the daily dose.

Simple Obesity

When obese patients were allowed to continue their usual feeding-habits, gonadotrophin distinctly decreased in ten days the measurements round the hips and the waist without a significant loss of weight. The patients invariably noticed a partial loss of appetite, and particularly that the sudden compulsive hunger, from which many suffered even a few hours after a substantial meal, had completely disappeared.

The change in measurements was interpreted as a dispersal of fat away from the more favoured sites, and it was thought that fat "in transit" might be more readily available for metabolic purposes than fat in "fixed deposit," in which case it should be possible to keep such patients on 500 calories a day without their feeling weak or hungry.

Gonadotrophin was given three or four days without dietary restriction; then the patients were restricted to two meals a day, each consisting of 100 g. of lean meat, a normal helping of leafy vegetables, an unsweetened rusk, and an apple or the equivalent in fruit, with salt and fluids ad lib. The average daily loss of weight was 250–600 g., without any inconvenience being caused, even to patients doing a hard day's work. In well over 500 cases, treated during the past twenty years, this effect was regularly observed in all types of obesity, in both sexes, at all ages, including women who had had both ovaries removed.

After about forty days of this treatment and a loss of 20–30 lb. a normal appetite returned in spite of continued injections, evidently owing to the well-known "immunity" which the body develops to gonadotrophin. This lasted for about six weeks, after which another course could, if required, be given with the same effectiveness as the first. In extreme cases a third and even a fourth course could be given in this manner. In cases in which only a slight reduction was required the same feeling of inadequacy of the diet arose abruptly as soon as the visibly superfluous fat was removed. Similarly, patients who stopped the injections but continued the diet found that they could manage this for about three days, during which time they continued to lose weight, but that they then suddenly felt weak and hungry and were forced to increase their diet and ceased to lose weight. Three days after the last injection patients were allowed to resume an unrestricted diet and only held to weigh themselves regularly and to compensate a gain after an excessive meal by skipping the next one. About 70% of the patients had no difficulty whatever in maintaining the weight reached, provided neither pregnancy nor the menopause intervened, in which case another course could be given.

When patients were given quantitatively and qualitatively exactly the same food every day, the weight would occasionally remain stationary for three or four days and then suddenly drop to the usual average. During such phases there was either more thirst or less urinary output, or both.

Though signs of protein or vitamin deficiencies were never observed, some patients occasionally complained of the typical symptoms of hypoglycæmia. A teaspoonful of sugar controlled these at once and did not, when taken in these circumstances, interfere with the loss of weight.

The treatment did not deplete the cutaneous or other essential fat, the face retaining its freshness and turgor throughout.

When, unknown to the patient, physiological saline solution was substituted for the gonadotrophin, the regular loss continued for about three days, after which the patients complained of feeling weak or dizzy, became irresistibly hungry, lost no further weight, and either ate secretly or declared themselves unable to continue the treatment. As soon as treatment with gonadotrophin was resumed, they again felt fit and perfectly satisfied with their 500 calories.

Diabetes

When overweight diabetics were reduced in this way they did not develop acetonæmia, and in mild cases with blood-sugar levels ranging up to 200 mg. per 100 ml., the blood-sugar level remained normal after the treatment so long as the weight was not regained. When, as occasionally happened, some weight was later regained, with a concomitant rise in the blood-sugar level, a second course

* 'Antuitrin S' (Parke Davis) and 'A.P.L.' (Ayerst Laboratories Inc.) were used.

had the same effect as the first. At least twenty injections were necessary to produce this effect. Apart from the fact that it is almost impossible to keep a diabetic on 500 calories a day for several weeks, a more gradual reduction with diet only did not have this effect on the blood-sugar level. Gonadotrophin alone given in any dose to underweight diabetics had no effect whatsoever on the blood-sugar level.

Gout

Analogous conditions obtained in gout. After a gonadotrophin diet treatment the blood-uric acid level was much reduced or even normal, and though most patients experienced an acute attack during the treatment they remained well after the treatment, regardless of what they ate so long as they did not regain weight.

Blood-cholesterol

An abnormally high blood-cholesterol level behaved in the same way, with the further interesting feature that during treatment the free cholesterol increased while the esterified fraction decreased until values otherwise only seen in pregnancy were sometimes reached.

Effect on Gonads

Apart from its action on abnormal fat, which appeared to be independent of the gonads, treatment stimulated the generative system. There was a great increase in libido in its broadest sense, and the frequency with which pregnancy took place during or soon after treatment was such, even in women who had hitherto considered themselves sterile, that it became an ethical obligation to warn women of childbearing age about this before treatment was started. Oligomenorrhœa and hyperœstrogenic dysmenorrhœa were promptly relieved. Fluor albus simplex usually ceased within ten days. An abnormal loss of head hair stopped. Brittle finger-nails became normal. Professional singers noticed an improvement in the quality of their voices.

The characteristic "pituitary" headaches and the lethargy of the obese were relieved within a week. As in pregnancy, arthritic and vaguer "rheumatic" pains disappeared to a great extent, long before the loss of weight could furnish a mechanical explanation of the phenomenon.

Peptic Ulcers

It was repeatedly observed that, though peptic ulcers did not necessarily heal, symptoms therefrom were completely relieved.

Skin Disease

During treatment a large variety of dermatoses cleared up in a matter of days, particularly those of allergic origin; even psoriasis showed an unmistakable, though temporary, improvement. Again the analogy to pregnancy was striking.

Conclusion

These results seem to suggest that chorionic gonadotrophin plays a rather more important rôle in the body's endocrine regulations than has hitherto been assumed; that there are vitally important reasons for its overproduction in pregnancy; and that it is in some way specifically concerned with the control of obesity in both sexes and at all ages. Although gonadotrophin alone does not reduce weight, it does make a very drastic caloric curtailment possible, and is then therapeutically active in comparatively small doses in all those clinical conditions which are known to improve during pregnancy.

Summary

The results of administering small daily doses of chorionic gonadotrophin from pregnancy urine, combined with a severely restricted diet, to obese patients are reported.

In such patients gonadotrophin appears to render abnormal fat deposits readily available, enabling the obese to live comfortably on 500 calories a day for several weeks.

Other conditions often associated with obesity rapidly improved.

It is suggested that chorionic gonadotrophin is specifically concerned with the control of obesity.

DETERIORATION OF ADRENALINE SOLUTIONS

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SOLUTIONS of adrenaline are frequently used at operations, in order to produce vasoconstriction, to prolong the action of local anæsthetic agents, or, occasionally, to stimulate contraction of the heart in cases of cardiac arrest. The *British Pharmacopœia* dose for adrenaline is 0·1–0·5 mg. (= 0·1–0·5 ml. of a 1 in 1000 solution), and in several reported cases overdosage has resulted in death (Killpack 1952).

We have recently seen several cases where the response to the drug was much less than would be expected with potent solutions. Two cases, not from the same hospital, are of particular interest in that the lack of effect probably saved the patients' lives.

Case 1.—A 7-week-old baby was operated on for congenital heart-disease. During the operation the heart stopped and 10 ml. of 1 in 1000 adrenaline solution was injected into the left ventricle. The heart re-started at the prick of the needle and the child made an uneventful recovery.

Case 2.—A 35-year-old woman was about to undergo exploration of the hip. A 1 in 200,000 adrenaline solution was to be infiltrated, to reduce bleeding at operation. A reply to the anæsthetist's request for a final check as to the nature of the solution was not given until the surgeon had already injected 10 ml. It was then stated to be 1 in 1000 adrenaline. After some delay an attempt was made to lay open the infiltrated area, but as this was very deep the efficacy of this measure seems doubtful. The patient showed no effect from this injection, and she made an uneventful recovery after the operation, which was completed without further incident.

The factors affecting the deterioration of adrenaline solution are well known (Somers and West 1944, West 1945, Bacq 1949). Adrenaline in solution is an extremely unstable compound which is susceptible to light, heat, air, and variations in pH.

Methods

We have investigated stock solutions of adrenaline and have found, as suspected, that some were pharmacologically inactive. In addition we have subjected fresh solutions of adrenaline to the conditions prevailing in their clinical use and have shown that deterioration can take place in these conditions. The same types of syringes, gallipots, and containers were used in these experiments as in clinical work, and these instruments were sterilised in the same sterilisers under identical techniques.

Standard pharmacological tests were used; the effect on the blood-pressure of a cat under chloralose anæsthesia, or the vasoconstrictor effect produced in the perfused hind-limb of a rat.

Results

Samples of 1 in 1000 adrenaline solution were taken at random from the theatre stock cupboard and tested