EDITORIALS

TESTOSTERONE TREATMENT OF HEMOCHROMATOSIS

In recent years there have been reports[1] suggesting that in patients with hemochromatosis the use of testosterone may be of benefit, at least symptomatically, with apparent improvement in strength and sense of well-being. Such beneficial results have been thought to be related to the gonadal hypoplasia commonly seen in hemochromatosis and to the anabolic effect of testosterone on protein metabolism. Consequently, the paper of Pirart and Franken[2] of the Brugmann Hospital in Brussels is of interest.

They studied 9 patients with proven hemochromatosis of whom 7 were men aged 44 to 70 years and 2 were women aged 56 and 59 years, respectively. The iron content of the serum of the 9 patients averaged 225 gamma per cent (range = 40 to 360 gamma per cent) whereas that of 10 normal subjects averaged 84 gamma per cent. The oral administration of 176 mg. of bivalent iron as ferrous gluconate did not cause any elevation of serum iron during the 4 hours following ingestion. However, when 20 mg. of iron in the form of an organic compound only slightly ionizable, were given intravenously and the iron content of the serum determined at 5 and 120 minutes following injection, a characteristic curve was obtained in both normal subjects and in patients with hemochromatosis.

Patients were then treated by injection of testosterone propionate in dosage of 50 mg. twice weekly for 3 weeks. No effect was seen clinically. At the end of the treatment period, iron was again injected intravenously in order to obtain tolerance curves to compare with those secured prior to testosterone treatment. A moderate though definite average lowering of the curves was obtained suggesting that, if anything, iron found its way more readily into the tissues following a course of testosterone treatment.

As the result of these studies, the authors conclude that the giving of testosterone has no specific benefit in hemochromatosis and that it may even act deleteriously by favoring the transfer of iron from the blood into the tissues. However, since in the oral tolerance test, no change in serum iron was obtained and since there is no evidence that testosterone favors the absorption of iron from the intestinal tract, there would appear to be no basis for fearing aggravation of hemochromatosis by testosterone unless iron is being administered parenterally. The real value, if any, of testosterone in the treatment of hemochromatosis awaits further study.

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REFERENCES

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TRYPSIN TREATMENT OF SUPERFICIAL GANGRENOUS LESIONS

The vulnerability of the lower extremities of older diabetics, on account of the tendency of the skin and subcutaneous tissues to become necrotic following local injury or infection, represents one of the major problems relating to diabetes today. When there is no serious impairment of the circulation and when the lesion is not extensive, conservative measures may lead to separation of the necrotic tissue and subsequent healing. However, even with thorough control of the diabetes with diet and insulin and the effective use of antibiotics to combat infection, a prolonged period of hospitalization may be necessary. Every physician or surgeon responsible for

the care of diabetic patients with lesions of the feet will welcome any form of treatment which may improve results or shorten the prolonged period of disability.

Surgical debridement has been disappointing unless the lesion is such as to permit total excision and immediate split-thickness graft and this is the rare type of lesion. Chemical or enzymatic dissolution of the necrotic tissue has likewise given unsatisfactory results up to this time. Encouraging results following the use of trypsin are reported by Pote elsewhere in this issue. My limited experience with this agent has been less impressive. The true value of this method will be indicated by the role it plays in the management of these lesions in well-organized diabetes clinics in the years ahead.

Until the efficacy of this or any unproven method of local therapy is definitely established, great care must be exercised by all concerned lest injudicious or unnecessarily prolonged trial of enzymatic treatment may lead to unnecessary expense to the patient, delay in the institution of radical treatment when indicated and even to unnecessary loss of limb or life.

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INSULIN-ZINC SUSPENSIONS

Insulin-zinc suspensions may soon complicate the depot-insulin situation still further. Eighteen years after the development of the first depot preparation, just as clinicians began to feel secure in the possession of an array of different insulins which fit the needs of practically all diabetics under all conditions, new preparations now enter the scene. If they had been discovered twenty years ago, it seems doubtful that any of the protein depot insulins would have emerged at all.

In 1935 D. A. Scott and A. M. Fisher, working in Dr. Best's section of the Connaught Laboratories, showed that the addition of a relatively large amount of zinc (0.01 per cent) to solutions of insulin caused a great prolongation of the action of insulin when injected subcutaneously in rabbits[1].

About two years ago Hallas-Møller and his colleagues at the Novo Terapeutisk Laboratories in Copenhagen, reported the precipitation of insulin in simple combination with zinc in the form of amorphous ("semi-lente") and crystalline ("ultra-lente") suspensions[2]. The amount of zinc required for precipitation in insoluble form is in the range of 0.5 to 2 mg. per 1000 units. Amorphous precipitation then occurs at *p*H 4.5 to 8 and crystals form at *p*H 5 to 6. Suspensions of the amorphous material show time-action only slightly more prolonged than that of insulin in solution, but suspensions of the crystalline preparation act in a true depot-insulin manner, with timing similar to that of protamine zinc insulin. Mixtures of the two types of material in proportions of about 30 per cent amorphous and 70 per cent crystalline material give a suspension, called "insulin lente" by the Novo Laboratories, which has an intermediate type of action similar to that shown by NPH, globin and protamine insulin mixtures in common use.

Clinical confirmation of the timing features of these three new preparations was quick to appear[3]. It was claimed that some patients with severe diabetes showed better control, chiefly with the "lente" or intermediate form. Local allergic reactions were said to be less common than with insoluble protamine modifications. Experimentation with various extemporaneous mixtures of the amorphous and crystalline forms to suit individual diets and patients has begun, chiefly in Great Britain. Clinical trials in the United States are now under way. The report to appear in a coming issue of DIABETES by Peck et al summarizes current data and adds significant new evidence on timing[4].

A judicial appraisal of the potential practical benefits of these new preparations must await further clinical trials. It seems clear at the present time, however, that any required timing can be produced with only the aid of zinc and control of the *p*H, and that the protein-precipitated insulins could be replaced with such suspensions, if this were desired. It remains to be determined whether predictability of action can be improved or consistency of response enhanced.

Several words of caution should be expressed to those clinicians who may use these new preparations in comparison with standard insulins. The addition of regular insulin to any of them may yield surprising results. They are suspended in an acetate buffer; this permits the insulin-zinc crystals to remain constant in size and form. Alterations in zinc content may change them and therefore the rate at which they go into solution or release their insulin after injection. Acid solutions of ordinary insulin added to insulin-zinc suspensions may alter the zinc content of the crystals, and therefore their physical form and rate of action. In other words, if the Novo preparations (or any similar products) are used they must not be altered much in *p*H nor mixed with phosphate buffer, or their time-action will be changed radically. Finally, if the views of this commentator are fairly representative of those of clinicians in the American Diabetes Association, the insulin manufacturers are begged to be cautious, in their zeal to be