The Influence of Diet upon Insulin Dosage in Diabetes Mellitus

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The average daily insulin secretion of the pancreas of a normal person has not been established. From experiments in animals and deductions based upon their body weight, the insulin need of pancreatectomized humans has been theoretically estimated to be about 200 units.[1] In contrast, as a result of total pancreatectomies in nondiabetic human subjects the insulin need was found to be usually not more than 40 to 50 units daily. Indeed these patients are rather sensitive to insulin.[2-4] In a diabetic the requirement for exogenous insulin is variable, ranging from none to 30, 60, or in unusual cases 100 or more units daily. Attempts have been made to classify diabetics according to the amount of insulin required to control the disease, but so many extraneous factors must be considered that classification on this basis is unsatisfactory.

The importance of a carefully measured diet in diabetes is generally accepted, but it is not always appreciated by the patients and even by some physicians, because of the lifesaving, life-prolonging action and easy administration of insulin. The experience of older physicians, who treated diabetics for years before the discovery of insulin, is probably the best evidence for the importance of dietetic control in diabetic therapy. The present data are offered to emphasize this principle.

In recent years patients have come to the clinic with histories of taking many units of insulin for control. Yet after a short period in the hospital much smaller dosages proved adequate. For this reason we studied the case histories and hospital course of 100 consecutive diabetic patients, who reported that prior to admission they took 80 or more units of insulin daily for periods of weeks to months. Patients admitted for treatment of diabetic acidosis and coma and pregnant diabetic women temporarily requiring large doses were excluded. The underlying cause for this relatively high insulin requirement was established and the cases were accordingly divided into three major groups. An analysis of the 100 patients as to age, sex, onset and duration of diabetes is presented in table 1.

In group I (thirty-six patients) were included all cases with a recognized cause for such a high dose. Insulin resistance, requiring several hundred units daily, occurred in nine patients. The possible etiology and the management of this condition have been reviewed by many others.[5-11] Twelve patients had an infection or gangrene as explanation of the unusual insulin requirement. The hospital course of these patients depended on the course of their infection and insulin decreased only when this came under control. In fourteen patients the dose during controlled hospital conditions remained the same. It was felt that this was due to the nature and severity of their disease. Hemochromatosis, lymphoma or a hidden infection may at times be revealed by the necessity for an increase of the insulin dose. Hyperthyroidism was the cause in the last patient of group I and the insulin dose was lowered when the primary condition was controlled. Hypersecretion of other antagonistic hormones, treatment with cortisone, or liver disease may at times be causes for high insulin doses, although we did not have patients in these categories.

The largest group (group II—forty-five patients) while in the hospital under controlled conditions and

TABLE 1

Diabetic patients taking 80 units or more of insulin daily

Age group	Duration of diabetes (in years)	Group I (resistance, infection, etc.)	Group II (excess of food)	Group III (not hospitalized)
Juvenile diabetics*	up to 5 years	3	5	2
	5-15	2	4	2
	above 15	6	4	1
Nonjuvenile diabetics Age 15-40	up to 5 years	2	4	2
	5-15	1	10	1
	above 15	0	2	0
Nonjuvenile diabetics Age above 40	up to 5 years	2	1	1
	5-15	9	9	6
	above 15	11	6	4
Total	Men	16	25	10
	Women	20	20	9
		36	45	19

*Juvenile diabetic: by definition,[12] every person with onset of diabetes before age fifteen, irrespective of present age.

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diet developed low blood sugars and hypoglycemic reactions and the insulin dose required drastic reduction. In these patients no obvious reason for the large dose could be found except excess food intake. An increase in insulin had been substituted for a controlled diet. They were eating a more or less free diet and tried to "cover" the glycosuria by additional insulin. At other times they were in insulin reaction and were forced to overeat to cover the excess of insulin they had taken earlier in the day. They lived in a vicious cycle and increased the insulin dose for the excess food and the food for the excess insulin. On admission these patients were taking an average of 99 units of insulin daily, with range from 80 to 160 units. After a few days' hospitalization they were discharged on an adequate diabetic diet, according to standard rules[12] and an average insulin dose of 56 units (range from 6 to 100). In other words, 43 per cent of the insulin they had been taking was not necessary, if they followed the prescribed diet. When subsequently followed up some of these patients had increased their food intake again and were forced to increase their insulin.

Some physicians argue that there can be no harm in taking enough insulin to cover a free diet. It is true that, unlike the oral hypoglycemic agents, insulin can cover practically any amount of food, if given in large enough doses. But excess of food leads to overweight and obesity, bad companions to diabetes. Actually twenty-nine patients out of the forty-five in this group were found to be up to 90 lb. (41 kg.) above their estimated optimal weight. Others probably believe that by taking "plenty" of insulin they would not need to bother about their diet and could also avoid the complications of the disease. Unfortunately this is not so. At least fifteen out of the forty-five patients had diabetic retinopathy and five had clinical evidence of diabetic nephropathy (Kimmelstiel-Wilson disease).

Aside from the possibility of weight gain and the liability to insulin reactions, with their added dangers,[13,14] there are also other disadvantages to excessive dosage, viz.: the cost of needless insulin; the need for special syringes for doses over 80 units; discomfort from the large volume of fluid injected; varying absorption. Furthermore lipodystrophies may be favored. Insulin resistance with its problems in management, including the high mortality (41 per cent reported[11]) may be encouraged by these needlessly high doses.[15] Another consideration is that many of these cases might respond to treatment with the sulfonylureas and they are not considered only because of this factitiously high dose. Actually a few were controlled by tolbutamide when placed under controlled conditions and a restricted diet.

The analysis of the patients in table 1 shows a fairly good distribution in all groups and no preponderance of any particular type. They included patients of the obese-elderly, insulin-insensitive type as well as of the juvenile, insulin-sensitive type, all with one common factor—excess food intake.

The patients in group III (nineteen cases) were seen as outpatients. In most of these the large dose was obviously due to excess food (at least eleven patients). They were given a diabetic diet and advised to decrease their insulin dosage gradually.

The dose of "80 units and above" in this study was taken arbitrarily; similar results would be obtained by selection of a lower level. Eighty units was found more frequently than other doses, because it is easy for such patients to take a "syringeful" of insulin in the morning, hoping to forget for the rest of the day that they have diabetes!

SUMMARY

An evaluation of the causes of high insulin dosage in a group of 100 diabetic patients, who came to the Joslin Clinic taking 80 units or more of insulin daily, showed that excessive food intake was the most frequent. The possible disadvantages and dangers of this type of diabetes control are discussed.

SUMMARIO IN INTERLINGUA

Le Influentia Del Dieta Super Le Dosage De Insulina In Diabete Mellite

Un evalutation del causas de alte dosages de insulina requirite per un gruppo de 100 patientes diabetic visitante le Clinica Joslin—illes prendeva 80 unitates de insulina o plus per die—monstrava que excessos in le ingestion de alimentos esseva le plus frequente. Le possibile disavantages e periculos de iste typo de controlo de diabete es discutite.

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Trans-Acids as Essential Fatty Acid Antagonists

The possibility of finding competitive inhibitors to the essential fatty acids (EFA) has occurred to many workers interested in fat metabolism. Thus, such inhibitors might be used to prevent certain types of rapid or abnormal growth as in tumors (I. Smedley-MacLean and L. C. A. Nunn, *Biochem. J. 35*:983, 1941), or might be formed during hydrogenation of vegetable oils to the detriment of the users of these products (H. M. Sinclair, *Lancet* 270:381, 1956). However, the search for this type of inhibition has not been rewarding. No enzyme in which the essential fatty acids have been shown to play a definite role has been obtained from animal sources; attempts to produce inhibition in the usual test animals are complicated by their relatively large stores of essential fatty acids and their ability to alter or destroy the postulated inhibitors.

The logical compounds for trial as inhibitors would be those fatty acids possessing multiple double bond systems as do the essential fatty acids, but not in the 1:4 cis configuration. Such acids would be those containing conjugated double bonds or double bonds in the 1:4 trans arrangement. R. T. Holman (*Proc. Soc. Exp. Biol. & Med. 76*:100, 1951) and Homan and S. I. Greenberg (*Arch. Biochem. Biophys. 49*:49, 1954), reported that the supplementation of a fat-free diet with conjugated "linoleic" acid resulted in lower weight gains and greater deficiency symptoms in rats than in control animals without any supplementation. D. Melnick and H. J. Deuel, Jr. (*J. Am. Oil Chem. Soc. 31*:63, 1954; *Nutrition Reviews 13*:53, 1955), on the other hand, reported that although some of the trans positional isomers of oleic acid could not replace biotin for *L. arabinosus* and showed some toxicity, they were not inhibitors of oleic acid activity. Similarly these authors found no evidence for EFA inhibition for rats from hydrogenated oils.

Recently, Holman and E. Aaes-Jorgensen (*Proc. Soc. Exp. Biol. & Med. 93*:175, 1956) tested the effect of trans isomers of linoleic acid upon the development of EFA deficiency in rats. Male rats which had been on a fat-free diet containing 1 per cent each of cholesterol and hydrogenated coconut oil to accelerate the onset of deficiency symptoms were, after three months, divided into nine groups receiving the following supplements: ethyl elaidate, ethyl linoleaidate (with or without linseed oil), methyl cis, trans linoleate (with or without linseed oil), methyl linolenate, ethyl linoleate, linseed oil or no supplements. After three weeks of the supplements (0.1 gm. per day), the rats were killed and the severity of the deficiency state, if any, was assessed by examination for skin symptoms, weight gain, carcass fatty acids, condition of spermatogenic tissue and deposition of dietary trans acids. Since each group contained only two rats, differences had to be very marked to be significant. The lowest weight gains were recorded with the cis, trans linoleate and the linolelaidate supplements although the other trans acid, ethyl elaidate, produced a weight increase somewhat greater than that for the fat-free diet. Linseed oil counteracted the effect of the trans dienes and gave weight gains similar to those for the other supplements.

It is difficult to say, on the basis of these experiments, whether the trans acids indeed acted as competitive inhibitors of EFA action. That trans monoenoic esters from hydrogenation of triolein do not, was recently confirmed by R. B. Alfin-Slater et al. (*Ibid. 95*:521, 1957) in very similar experiments. However, it was not to be expected that the trans monoenoic acids would act in this manner, and the cis, trans and trans, trans dienoic esters apparently acted as inhibitors in that they increased the requirement of EFA and aggravated the deficiency symptoms resulting from a fat-deficient diet.

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