Clinical Impact of Insulin

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A number of serious problems have emerged with the long-term use and diverse actions of insulin. If some of the following statements appear to deprecate the value of insulin, they are made only in the spirit of Dr. William Bean's definition of criticism: "an open and honest look at the world and at ourselves must be desired actively and courted assiduously—The ordering of facts, the discovery of relations, and the synthesis into new and luminous comprehensions constitute the true goal of that disciplined intellectual force which is science."[1]

LONGER SURVIVAL

In fatal cases, the average duration of life after onset of diabetes, according to the most reliable data of Joslin, is 18.2 years in the present decade, in contrast to 4.9 years in the period from 1897 to 1914.[2] Concomitant advances in other areas, notably fluid and electrolyte balance, nutrition, surgical technics, anesthesia, better understanding of physiologic and biochemical factors underlying the diabetic pregnant female and her fetus, as well as the introduction of a variety of broad spectrum antibiotics and antibacterial agents have helped prolong the life of diabetic patients. It is insulin, however, which has been the open sesame to the door of long survival of diabetic patients and has thus allowed the physician to employ these other effective therapeutic agents. Many studies are available concerning statistics on longevity of patients with diabetes and the factors involved in determining these statistics.

A particularly significant study of correlated clinical and autopsy material of 2,529 cases of diabetes mellitus is that of Bell[3] who has presented data for three periods: Period I, extending from 1911-1930; Period II, covering the years 1931-1945; and Period III, encompassing the years 1946-1957 (figure 1). In Period I, few of the patients had adequate insulin treatment. Those persons dying in Period II had the benefit of insulin but not of antibiotics. In Period III, both insulin and antibiotics were available.

FIGURE 1

An impressive but less striking improvement is noted in those diabetics having an onset of diabetes between the ages of forty and sixty years. As would be expected, the figures do not reveal a significant extension of the lives of patients whose diabetes began after the age of sixty.

With longer survival, increasing social and economic problems have arisen, and the physician as well as the community must of necessity become involved in considerations of education, and the insurability of the diabetic patient whose life expectancy has increased. The problem of marriage amongst diabetics has now become increasingly important, and with it the need for increasing knowledge concerning the genetics of diabetes, since with the advent of insulin we have interfered with natural selection and have increased the reservoir of potential or prediabetics quite considerably.

HYPOGLYCEMIC REACTIONS

Insulin therapy produced in its wake a number of clinical problems previously unknown to the medical profession. Chief among these was the need for an understanding and rational management of life-threatening hypoglycemic reactions. It soon became apparent that the more rapid the blood glucose fall, the more pronounced become those features which are essentially the typical warning symptoms of acute hypoglycemia.

Presented at the Symposium on Insulin and Its Metabolism sponsored by The Clinical Society of the New York Diabetes Association, Inc., on Dec. 1, 1961.

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The diabetic patient, the physician and, we hope, even the policeman have now become acutely aware of this insulin-induced reaction. A stage, however, frequently develops in which classical symptoms do not manifest themselves. Cerebral manifestations predominate, particularly when hypoglycemia develops slowly and insiduously. This has become an urgent and serious problem with the introduction of the long-acting and newer intermediate-acting insulins. The changes are subtle and frequently not readily apparent, either to the patient or to the physician. Changes in personality, work performance, study habits, retrograde amnesia, aphasia, choreiform movements, mental deterioration, psychotic behavior, transient paralyses, epileptiform seizures, narcolepsy and even Parkinsonism may occur. Warning symptoms, which frequently escape recognition, include lassitude, headaches and slowing of speech and thought processes. Reactions frequently occur during sleep and are easily overlooked. These can be elicited only by the most painstaking history and direct observations. Nightmares, crying-out during sleep, unusual sleeping positions and inability to be easily aroused are red-letter signposts. The legal, social and economic implications of these hypoglycemic reactions are overwhelming. It is requisite that the most astute attention be given by all in attendance to the complaints and behavior patterns of insulin-treated diabetic patients. It is inherent in the complete care of such patients that the attending physician must extend his relationship outside the confines of the routine office, hospital or clinic visit. In this sense, the care of the diabetic belongs in the home and his physician must truly be a family doctor.

SPONTANEOUS HYPOGLYCEMIA

Chance observations to the prepared mind (serendipity) have led to fundamental and monumental advances. Dr. Seale Harris, visiting with Drs. Banting and Best in Toronto in 1923, quickly related the hypoglycemic convulsive changes induced in dogs treated with pancreatic extracts to similar symptomatology occurring in some of his patients several hours after a heavy meal. He ascribed these symptoms to spontaneous overproduction of insulin with consequent hypoglycemia, and forthwith presented a paper on hyperinsulinism and dysinsulinism at the 1924 meeting of the American Medical Association.[4] In 1927, the first case of hypoglycemia with recurring attacks of convulsions and coma due to a carcinoma of the islets of Langerhans was reported by Wilder and his associates in the Mayo Clinic.[5] This impact of the discovery and knowledge of physiologic actions of exogenously administered insulin is beautifully exemplified in this direct quotation from Wilder's recent essay *Recollections and Reflections on Education, Diabetes, and other Metabolic Diseases.*[6] "On October 29, 1926, a man was brought to the St. Mary's Hospital in an emergency. He was seen there first by Florence Smith, our dietitian. It seemed to *her* that the patient was in shock from an overdose of insulin and straightaway she sent for me. I was lecturing to diabetic patients in the sunparlor nearby. I, too, thought the man had taken too much insulin and we drew blood without delay. The value of the blood sugar was very low but before this had been reported back, we had given dextrose intravenously and observed rapid restoration of consciousness, a response with which we had now become familiar. We then learned to our surprise that this man had never taken insulin, and that he had had several episodes like the one we had observed."

Dr. Wilder and his colleagues surmised that this patient may have had an insulin-producing lesion, most likely in the pancreas. The patient was subjected to a laparotomy where the first proven carcinoma of the islets of Langerhans with hepatic metastases was found. Extracts of the metastatic lesions, moreover, behaved in an identical fashion to insulin when injected into rabbits. This patient subsequently died, but many patients with benign and entirely curable islet cell adenomas have since been reported.

IATROGENIC BRITTLE DIABETES

As experience with insulin accumulated, it became evident that not all diabetic patients responded in the same manner. The terms "stable" and "labile" diabetes have been employed to denote certain of these differences. Recent studies with insulin antagonists indicate that the same pathogenetic factors may underlie brittle as well as stable diabetes.[7] Most patients with unstable diabetes are from that group whose ability to produce or release endogenous insulin is quite limited. These patients are dependent upon injected insulin. General experience has shown that successful management of the patient with unstable diabetes is usually possible by careful prescription of food (type, amount and distribution) and of insulin (type, dose and time of administration) for each individual patient. Be that as it may, the management of unstable diabetics is frequently an extremely difficult problem with insulin therapy. We have been cautioned in the past against the use of the term "brittle" diabetic, since it has been claimed that it is more frequently the attending physi-

cian who is "brittle" rather than his patient. The most stalwart diabetologist must agree, however, that many of his diabetic patients show wide fluctuations of their blood sugar levels, with wide daily as well as diurnal variations in the extent of glycosuria and ketoacidosis. Approximately 10 per cent of insulin-treated patients fall into this category, but it is likely that there are many more insulin-treated patients, who are not included in this group, who show subtle, but still clinically significant, daily swings between hyperglycemia and hypoglycemia. Credit must be accorded Somogyi, whose investigations over the last twenty-five years indicate that this situation in such labile diabetics, particularly young adults, is a direct consequence of excess insulin activity.[8] The premise, simply stated, is that *hypoglycemia begets hyperglycemia and eventually ketosis.* Physicians who are unaware of this paradox usually attempt to combat patients who present themselves with glycosuria with increasing insulin dosage. The obvious result is an increase in frequency and severity of hypoglycemia, with subsequent fluctuations of the blood sugar in both directions. A vicious cycle develops which ultimately leads to marked increases in insulin dosage. The severity of the diabetes, as judged by insulin need, progressively increases, and an extremely unmanageable and unstable state develops. This is a source of considerable concern for all physicians who attend diabetic patients. It is imperative that a proper comprehension should exist not only of the underlying physiologic and biochemical derangements of diabetes mellitus but also of the consequences of insulin administration, since much of the clinical difficulty just described may be related more to ignorance, haphazard attitudes, and smugness on the part of the physicians who prescribe insulin than to the potent agent itself.

RELATION TO VASCULAR DISEASE

In the last twenty-five years, reports from clinics throughout the world have established beyond question that the single most important factor in the development of vascular disease in diabetes is the duration of the disease. The statistics of White[9] are clearly representative. Five to ten years after the onset of diabetes the incidence of vascular change in juvenile diabetics is low, in sharp contrast to the 50 and 80 per cent incidence of "nephritis" and "retinitis," respectively, after twenty years of diabetes.

Since the introduction of insulin was followed by marked immediate improvement in the metabolic aberration of diabetic patients but with eventual deterioration from widespread vascular disease, it seemed logical that a direct or indirect role of insulin should become implicated in the genesis of vascular disease in diabetes. I am speaking, of course, of the specific lesion of small blood vessels in diabetes. The fact that, among forty-two autopsies on diabetic patients performed at the Mallory Institute of Pathology in the years prior to the introduction of insulin, only one patient was observed to have nodular glomerulosclerosis is cited in partial support of this concept.[10] It is conceivable that the lesions which are found may be due to a reaction of the involved tissues to exogenously administered insulin. This has become a particularly interesting concept in view of the recent recognition that autosensitization may be associated with a variety of diseases. In support of this hypothesis are the following considerations. Extensive deposits of gamma globulin have recently been demonstrated in diabetic nephropathy. Specific fluorescence was produced in Bowman's capsule, in glomerular tufts, in Kimmelstiel-Wilson nodules and in tubules. The gamma globulin could be eluted at *p*H 3.3 from diabetic kidneys as well as from cases suspected of being definitely immunogenic in origin—namely, glomerulonephritis, systemic lupus erythematosis, polyarteritis, and amyloidosis.[11] Whether the presence of gamma globulin represents secondary absorption to damaged tissues or the result of antigen-antibody union remains to be determined. Significant fluorescence in nodular glomerular lesions has recently been observed in diabetic kidneys studied with fluorescein isocyanate.[12] It has also recently been pointed out that a proliferative vascular lesion which is widespread in the tissues of patients with long-term diabetes closely resembles the vascular lesions produced by immunogenic mechanisms.[13] The disturbing feature with this hypothesis is that many diabetics with advanced microangiopathy have never received exogenous insulin. Furthermore, a late review of forty-five cases, examined at autopsy at Massachusetts General Hospital between 1899 and 1919, showed that five patients had nodular Kimmelstiel-Wilson lesions, and sixteen had diffuse glomerulosclerosis.[14] Bell[15] describes an incidence of 12.4 per cent of nodular renal lesions in males, and 19.4 per cent in females, in a study of diabetic patients dying in the pre-insulin era. When diffuse lesions are included, the total incidence is 19.5 and 30 per cent, respectively, for males and females. Additionally, the finding at postmortem of nodular glomerulosclerosis in mild diabetics who have never been treated with insulin occurs more commonly than is formally reported.[16] Aberrations of host responses to endogenous insulin still require consideration.

ALTERED DIETARY CONTROL

Before the introduction of insulin, diet was the only therapeutic measure of regulation of patients with diabetes mellitus. Restriction of carbohydrate intake, almost to the point of starvation, was the rationale of most diabetic diets. In the severe diabetic, the balance between marked glycosuria and starvation could be achieved only by meticulous regulation of caloric and, chiefly, carbohydrate intake. In the early days of insulin therapy, the same attention to dietary measures was given. It soon became apparent that, in general, the diabetic patient's intake need not be much different from the nondiabetic if insulin was administered. The immediate symptoms of polyuria, polydypsia, pruritus, and weight loss could be controlled effectively and, as early as 1927, reports appeared which encouraged an unrestricted food selection, including cakes and candy, to juvenile diabetics.[17] This so-called "free" diet was soon taken up by a number of clinicians both in Europe and in this country. Since the acute symptoms of diabetes were adequately controlled, it was argued that the absence of dietary restrictions produced major psychologic improvement in the handling of the diabetic youngster. Is it possible that these changes in clinical management in the dietary habits are involved in the development of vascular disease in the long-term diabetics? It recently has been demonstrated that hyperlipemia can be induced by increased dietary carbohydrate intake. The significance of this carbohydrate-induced lipemia in the pathogenesis of vascular disease remains to be ascertained.[17b]

The relation of control of diabetes to the development of angiopathy is most difficult to evaluate, since precise definition of good control when applied to diabetes is so controversial. It is also obvious that any practical assessment of the excellence of control of patients for a long period of time can only be based on intermittent observations of the level of blood or urinary glucose. One questions seriously whether such evidence can ever be sufficiently accurate to support some conclusions which have been made. It is true that data exist from many clinics which substantiate, at least, the impression that the incidence of retinopathy and nephropathy is higher with poor levels of control. Nevertheless, a fair percentage of patients with good control, even as defined by the most rigid criteria, exhibit angiopathy, while an equally significant proportion of patients with poor control escape this complication. In a well-studied recent series of 189 patients with diabetes of twenty- to twenty-five years' duration, 24 per cent with good control had moderate, marked or severe retinopathy. Thirty-three per cent, defined as being under poor control throughout their diabetic lifetime, had little or no retinal changes.[18] It has also become increasingly evident that severe clinical as well as histologic evidence of angiopathy may occur in patients with diabetes of such mild character that it escapes clinical recognition. Indeed, in a recent study of renal biopsies, severe renal glomerular and vascular changes were obtained in individuals with prediabetes and early diabetes, while minimal changes occurred in some cases of poorly controlled diabetes of long duration.[19] Such observations have led experienced and concerned students to conclude that retinopathy and nephropathy and perhaps generalized microangiopathy in diabetes may be virtually inescapable and perhaps independent of the disturbed carbohydrate metabolism.

It has been suggested that vascular change is not a complication of diabetes or insulin therapy but rather an independent concomitant of the disease, perhaps genetically determined. Any theory of the cause of these vascular lesions must depend on a clear demonstration of whether or not they are related to the complex metabolic abnormalities induced by insulin deficiency. In this connection, recent isolated case reports as well as systematic studies of the incidence of retinal microaneurysms and nodular glomerulosclerosis in patients with diabetes secondary to known causes are of great significance. Such lesions have now been reported in patients with diabetes secondary to total pancreatectomy, chronic pancreatitis, acromegaly, pheochromocytoma and hemochromatosis.[20] The duration of diabetes ranges from four to ten years. The number of cases is small and the possibility exists that these patients had a co-existing primary genetically determined diabetes. Of importance to the present issue is that most of these patients had never received insulin. Under any circumstances, these data lend support to the concept that microangiopathy may be a true complication of disturbance in carbohydrate metabolism rather than an inevitable expression of the genetic defect, and that insulin might exacerbate metabolic alterations which would bring vascular changes more explicitly to the forefront.

ALTERED METABOLISM OF MUCOPOLYSACCHARIDES AND LIPIDS

It is entirely conceivable that biochemical abnormalities, apart from hyperglycemia, may play a decisive role in the production of vascular disease. Experimentally, it has been demonstrated that insulin affects the metabolism of a variety of substances which have been

suspect in the genesis of vascular disease. Normal rates of metabolism of acid mucopolysaccharides appear to be insulin-dependent. Randerath and Diezel[21] have demonstrated fibrillar, highly polymerized mucopolysaccharides in the muscular arteries of diabetics in greater amounts than in nondiabetics. They postulate that, as a result of insulin deficiency, protein-bound carbohydrates of the blood, including hexoses and hexosamines, accumulate in the intima of the artery and eventually become transformed from slightly to highly polymerized compounds. Our own studies on the serum polysaccharides and glucosamine in diabetics with a variety of complications are of interest in this connection.[22] Increases of serum-bound polysaccharide concentrations are constantly demonstrable in patients with retinopathy and nephropathy. To a lesser extent similar changes are noted before the onset of clinical evidence of microangiopathy.[23] Increased urinary excretion of hexosamine-containing compounds has also been reported in patients with diabetic vascular lesions.[24]

In recent years the role of fat in the development of vascular disease has attracted the efforts and energies of many investigators. It is true, both from our studies[25] as well as from recent investigations by means of gas chromatography,[26] that diabetic patients not in acidosis and free from clinical nephropathy have cholesterol levels quite similar to those of nondiabetic patients. Other lipid fractions, however, appear to be of particular significance. Fasting and postprandial blood ketones and plasma free fatty acids have recently been found to be elevated, despite relatively normal blood glucose concentrations, in stable diabetics without clinical evidence of vascular complications.[27] These alterations may simply reflect abnormal intracellular enzymatic processes in the early stable and controlled diabetic. Substances such as plasma free fatty acids are influenced by a variety of hormonal agents. One may speculate that exogenous insulin, with its abnormal mode of administration and distribution in the body and, therefore, attendant alterations in carbohydrate and lipid metabolism, might accentuate such lipid changes and, over a long period of time, accelerate and potentiate the development of vascular lesions. In partial support of such a concept is the recent experimental observation that in alloxan-diabetic dogs, direct intra-arterial injection of insulin produces a significant increase in the cholesterol and fatty acid content of the vessel wall.[28] This has not been observed in normal animals. In this connection, a study of the small vessels of the kidneys and retinas and other capillaries throughout the body of patients with hyperinsulinism associated with pancreatic adenomas might be informative.

Another aspect of this problem is the possible harmful effect of increased fat in the diabetic diet, particularly since the introduction of insulin. A vast body of evidence incriminates diet, particularly fat, among a variety of other environmental factors in the pathogenesis of vascular disease in the nondiabetic as well as in the diabetic patient. This has recently been stated succinctly by LeCompte: "A formula has been evolved: too much of some kind of lipid in the diet, hence too much in the blood, hence too much in the arterial wall."[29] This would appear to be an oversimplification of the facts. Nevertheless, recent studies with extremely low fat intakes over a period of months have indicated that retinopathy may be partially reversed.[30,31] Striking differences have been noted in the vascular complications of insulin-dependent diabetic Zulu Africans and Natal Indians.[32] It is certainly possible that various genetic, endocrine, metabolic, and other environmental factors may be responsible for this difference. Most impressive, however, is the extremely *low fat intake* of the Zulu African, in contrast to that of the Natal Indian whose diet more closely approximates the American and European intake (figure 2). The daily fat intake of the Japanese male is about 20 to 30 gm., accounting for 10 per cent of the caloric intake. Atherogenesis is markedly decreased in such patients. It would be of interest to know the actual incidence of microangiopathy in long-term insulin-dependent Japanese diabetics who

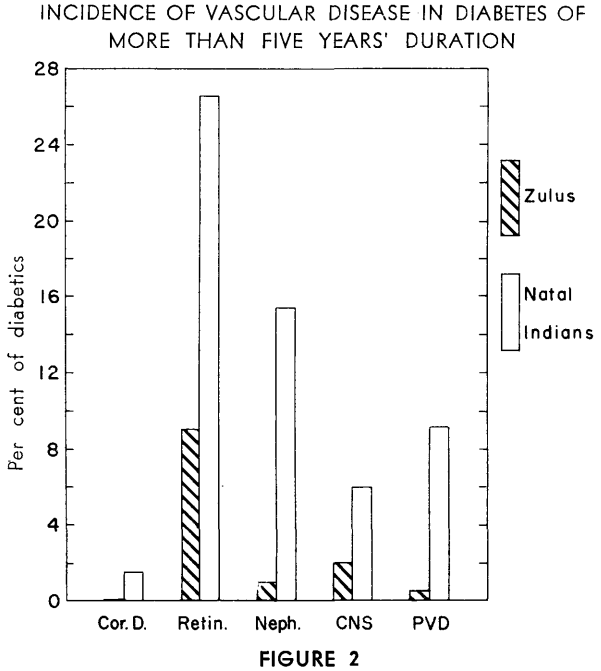

FIGURE 2

have been maintained on this dietary regimen throughout their diabetic lifetime.

One may further speculate that insulin has not only allowed fuller and freer intake of total calories, including fat, but that because of greater palatability much of this fat is of the saturated type supplied by salad oils, spreads, various types of dressings and nicely marbleized steaks. Obviously, attention should be given not only to the quantity of fat but to the type.[33] There is much impetus today, among groups interested in vascular disease, to substitute polyunsaturated fatty acids for the saturated-mono-unsaturated fatty acids in the American diet, since it has been demonstrated that such substitution results in lowered serum cholesterol and serum lipid levels. Certainly, one should consider this seriously in planning the diabetic menu.

ALTERED METABOLISM OF HORMONES

Prolongation of life of necessity is accompanied by recurrent exposure to stress. Stressful situations such as hypoglycemia and/or acidosis occurring during the course of diabetes result in periods of adrenocortical hyperactivity, and perhaps it is these intermittent spikes which may trigger sensitized capillary end-organs.

In an attempt to obtain information about the relationship of the pituitary-adrenal axis and the complications of diabetes we have measured various parameters of adrenal cortical function.[34] These have included measurements of the plasma 17-hydroxycorticosteroids, the urinary excretion of total 17-hydroxycorticosteroids, the total and individual urinary 17-ketosteroids, as well as the production of these substances in response to exogenously administered ACTH in diabetic patients with retinopathy and nephropathy. The results obtained indicate that the total identifiable ketosteroids, that is, the 11-desoxy- plus the 11-oxysteroids excreted by patients with uncomplicated diabetes are essentially normal while in patients with diabetic retinopathy and nephropathy these metabolites vary from relatively normal to low values. In contrast, much smaller quantities of these steroidal metabolites are excreted by nondiabetic patients with renal insufficiency.

The excretion of the urinary 17-hydroxy-corticosteroids by a smaller but similar group of patients was essentially normal. No significant deviations of the plasma 17-hydroxy-corticosteroid from the values obtained in control patients were observed.

The variations produced by the intravenous administration of 40 mg. of ACTH over a six-hour period indicate that the plasma 17-hydroxycorticosteroids, the urinary 17-hydroxycorticosteroids, and the urinary ketosteroids, both total and the two subgroups, namely, the 11-oxy and the 11-desoxy components, rose in a manner quite indistinguishable from that expected in normal control subjects.

It is possible that other adrenal products, presently unknown, secreted in response to recurrent episodes of insulin-induced hypoglycemia, may be involved in the development of diabetic vascular disease, but that these products are not measured by the methods we have employed. Efforts are being continued to obtain more definitive data.

Finally, in discussing the clinical impact of insulin, it is conceivable that insulin, if administered early in the course of the diabetic's lifetime or even in the subclinical or even prediabetic phase, may delay, prevent, or actually inhibit the emergence of the overt diabetic state. Almost all diabetologists have noted improvement in patients whose insular system has been rested by diet, insulin or both. Attention is called to Conn and Fajans'[35] provocative concept of the prediabetic state.

In conclusion, an attempt has been made to appraise certain impacts of the discovery of insulin on the natural history of diabetes. There is continuing need for increasing research into the basic physiologic, biochemical, and clinical changes demonstrable in the diabetic patient since the discovery of insulin. Approximately forty years *before* the discovery of insulin, Claude Bernard stated that "if in the field of diabetes all the pathologic obscurities have not as yet been completely elucidated, it is because the knowledge of normal function is still imperfectly understood."[36] How appropriate this statement still remains!

SUMMARIO IN INTERLINGUA

Le Impacto Clinic de Insulina

Varie problemas clinic ha resultate ab le perdurative uso e le diverse effectos de insulina. Un plus lucide comprension de subtil reactiones hypoglycemic se ha disveloppate—con enorme consequentias ab le punctos de vista legal, social, e economic. Nostre familiaritate con le reactiones hypoglycemic secundari al administration de insulina exogene ha rendite plus facile un delineation de conditiones clinic in que hypoglycemia spontanee es un manifestation presentatori. Le relation inter insulina e instabile diabete de origine iatrogene es discutite. Finalmente, le medios es explorate que permitte incriminar insulina in le disveloppamento de angiopathia diabetic.

ACKNOWLEDGMENT

This study was supported in part by the United States Public Health Grant No. A-3161. The author

wishes to express his gratitude to Drs. Louis Leiter and James Berkman for their suggestions, criticisms, and advice.

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