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PRE-HYPERGLYCEMIC MANIFESTATIONS OF DIABETES MELLITUS

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Typical textbook definitions of Diabetes Mellitus almost invariably include the terms "hyperglycemic" and "glycosuria" and indeed in clinical practice most cases of Diabetes are diagnosed because patients exhibit these manifestations of carbohydrate intolerance. However, in the past fifteen to twenty years a wealth of knowledge about diabetes has accrued, much of which indicates that by equating diabetes with hyperglycemia we are making our definition of this condition much too narrow.

A full discussion of the evolution of our present concept of this disease is beyond the scope of this paper. However, there are several observations made by clinicians through the years which have led the way to expanding this definition. For one thing, it has been known for some time that women who have excessively large babies have a tendency for later showing overt abnormalities of carbohydrate metabolism. Secondly, many clinicians have been struck by the high correlation of obesity and diabetes in those patients who manifest their disease in later life. Thirdly, physicians occasionally found themselves treating more than one member of a family with this condition, or, on inquiring, discovered that their diabetic patients had a diabetic grandparent or a diabetic cousin. The first two observations led some thinkers on this subject to wonder if perhaps there were metabolic abnormalities present long before a person developed overt diabetes; that large babies and obesity were reflections of the metabolic defect which years later resulted in hyperglycemia and glycosuria. The third observations cited above, that is the familial occurrence of diabetes resulted in the supposition that this was a genetically transmitted condition although the exact mode of transmission was for some time not known and indeed is still questioned by several authors. That diabetes is an inherited disease has been amply substantiated in recent years. That is not to say that all patients who exhibit loss of carbohydrate tolerance do so on a genetic basis. It is well known for instance, that patients with Acromegaly, Cushings' Disease, Carcinoma of the pancreas, etc. may manifest an abnormality of carbohydrate metabolism with hyperglycemia and glycosuria, but clearly this is not the same disease as that of the typical diabetic.

Once it was shown that diabetes is an inherited disorder, investigators of this disease re-evaluated the concept that diabetes meant hyperglycemia. They reasoned that diabetes is genetically determined and whatever way this genetic determinant eventually brings about deficient insulin activity, the basic abnormality has been present since conception.

Diabetes, then, begins not with hyperglycemia, but when the ovum is fertilized. This is when genetic potential, later to result in hyperglycemia, is put into motion. Hyperglycemia may start at birth or it may begin at age 75 or anywhere in between; but whether hyperglycemia is present or not, the genetic disturbance still exists.

From this reasoning has evolved the picture of Diabetes mellitus as a life-long condition with several different stages. Overt diabetes with elevated blood sugars and symptomatology is a late stage in this picture. It is preceded by an asymptomatic stage, demonstrable only by blood and urine tests following a glucose load. Indeed, at times, abnormal glucose tolerance may be brought to light only by going a step further and creating a state of metabolic stress by administering steroids to the individual in the hours preceding a glucose tolerance test. This asymptomatic stage may be called "Chemical Diabetes".

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But what about the period prior to this when there is no demonstrable loss of glucose tolerance by even the most sensitive tests at our disposal?

This is the stage which has been commonly called "Pre-diabetes". This Pre-diabetic stage has been receiving increasing attention by investigators in the past few years and will probably continue to do so. And this is the stage to which the balance of my paper is devoted.

The term pre-diabetes strictly speaking means before diabetes and therefore implies that diabetes does not yet exist. But since Diabetes is an inherited disorder, the genetic abnormality has been present since conception and diabetes therefore really exists from that time. It is perhaps preferable to follow Levine's suggestion and call this phase "Diabetic Pre-mellitus", that is diabetes before it becomes "sweet", before hyperglycemia and or glycosuria.

The Pre-mellitic phase of Diabetes may be defined as that period of time from conception to the demonstration of diminished insulin activity by whatever method is considered to be the most sensitive in this respect at the time. Practically speaking it means the interval between conception and the time when hyperglycemia develops in response to a provocative glucose tolerance test. Although the duration of this phase is extremely variable, except for cases that have their onset in childhood, it may be the longest stage of diabetes.

The clinical diagnosis of Diabetes Pre-mellitus can be justified only when we can detect an early abnormality which precedes and is not dependent on insufficient insulin activity. When the parameter measured does depend upon diminished insulin activity even though transient, the situation should be regarded not as diabetes pre-mellitus, but as chemical or subclinical diabetes. I stress this point because there is disagreement in the literature as to the use of the term pre-diabetes. Some authors use it to signify the period which I have defined above as Diabetes Pre-Mellitus while others use it to denote the asymptomatic phase I have called "Chemical Diabetes". As you can see, this leads to no end of confusion and difficulty in ascertaining just what period an author is discussing.

It should now be evident that the concept of diabetes which has evolved in the last decade or two is much broader than that expressed in textbook definitions of this disease. Diabetes must now be thought of as a disease whose basic abnormality is present from before birth, not just when glucose intolerance begins, for this point, the point where insulin activity becomes deficient is probably a fairly late one in the course of the disease. It is this concept that has led to a search for clinical features, chemical and histological indicators of the genetic disturbance preceding hyperglycemia.

I have already mentioned one clinical feature commonly associated with the pre-hyperglycemic phase of diabetes, namely the birth of oversized infants. Priscilla White has pointed out that the birth of an infant weighing more than eight pounds, fourteen ounces predicts the possible future development of maternal carbohydrate intolerance. The frequency of overt diabetes actually parallels the degree of oversize; 90% when the birth weight is thirteen pounds, and virtually all women who have infants in excess of 14 pounds will later show overt diabetes. Likewise there is a higher rate of perinatal mortality of infants born to women who later lose carbohydrate tolerance.

It has been shown that not only do pre-mellitic women often have an abnormal course

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of pregnancy with toxemia, hydramnois, premature delivery, etc. but their histories also reveal an early menarche. Thus women who developed overt diabetes after the age of eighteen years had the earliest published mean menarcheal age.

In spite of these and other associated features, recognizing a pre-mellitic on clinical grounds is as yet extremely difficult, and most authors agree that a diagnosis of diabetes pre-mellitus can be made with certainty only in retrospect, once diabetes has declared itself. However, in order to study possible histological and chemical abnormalities during the pre-mellitic phase of diabetes it is necessary to make a prespective diagnosis so that subjects to be studied may be chosen. Such a prespective diagnosis may be made with a high degree of probability on genetic grounds. As revealed by Steinberg, susceptibility to Diabetes is likely to be associated with a recessive gene. Children of both a Diabetic mother and a diabetic father must, therefore be considered homozygous for the Diabetic gene, that is potential overt Diabetics or Diabetics in the pre-hyperglycemic phase.

I should point out at this juncture that not all authors on the subject are satisfied with the simple Mendelian recessive mode of inheritance. In a recent article, Dr. Nancy Simpson of Toronto, states that the genetic basis for diabetes may be multifactorial and not simply the recessive member of a pair of alleles at a single chromosomal locus.

I think it is fair to say however, that the majority of physicians now feel that diabetic susceptibility is transmitted by an autosomal Mendelian recessive. Certainly, those investigators inquiring into the changes of the pre-hyperglycemic state consider this to be the case. They have chosen for their subjects two types of individuals. First, those who have both a diabetic father and a diabetic mother and secondly, identical twins of diabetics. These two groups are considered to be genetic diabetics in the pre-mellitic phase (providing of course, that they have normal glucose tolerance tests).

It is from studies comparing these subjects with normal controls and with overt diabetics that most of our knowledge of the pre-hyperglycemic changes is derived. The studies thus far reported in the literature are, for the most part, preliminary reports of long term projects in which follow up examinations are to be performed at six month intervals for several years. Also, in most cases, the number of subjects studied to date is still relatively few and results obtained may later not stand up to statistical analysis. With these qualifications in mind, let us now look at what has been shown about the pre-hyperglycemic phase of diabetes.

Carbohydrate metabolism of subjects considered to be in this phase was, by definition, normal when tested by oral standard, oral cortisone, and rapid intravenous glucose tolerance tests.

The serum insulin-like activity (ILA) of these subjects however, was not normal. In one study, the mean value of fasting serum insulin-like activity in thirty controls was 83 microunits per milliliter as compared to 203 u/ml. for the 24 so called pre-diabetics. In another study the mean value for 56 controls was 91 u/ml while 42 persons judged to be in the pre-mellitic phase of diabetes gave a mean of 172 u/ml. In short, the insulin like activity of persons in the pre-mellitic phase was significantly elevated above that of the controls. When compared to 33 untreated, clinically overt diabetics, however, there was no significant difference in the serum (ILA) of these pre-mellitic subjects. In other words, the serum ILA of so-called pre-diabetics is greatly elevated as compared to normal controls but virtually the same as that found in overt untreated Diabetes.

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Since high fasting ILA in these pre-mellitics was not associated with a tendency for hypoglycemia, studies on the state of insulin in the blood were carried out. It has been shown that insulin in blood is found in both the "free" form and as a bound complex, the ratio depending on the metabolic state. In the fasting state, the predominant form circulating in the blood is the inactive complex. A rise in blood glucose results in increase of free insulin and a decrease in the concentration of insulin complexes to the point of near-disappearance.

In five of six persons in the premellitic phase it was found that after an overnight fast, insulin was present primarily as the bound complex, and this form was still predominant with a smaller than normal decrease after the administration of intravenous glucose. Nevertheless, there was a rise in "free" insulin which was within normal limits.

Studies of renal function in pre-mellitic subjects have all yielded normal results. Urinalysis, creatine clearance, protein excretion and kidney size on X-ray were all within normal limits.

Likewise, nerve conduction velocity in the ulnar, median and peroneal nerves of pre-mellitics was found to be normal as were x-rays of the legs, pelvis and abdomen, and electrocardiograms.

On evaluating the vascular system of pre-mellitic subjects, however, several deviations from normal were found. Firstly, the venule-arteriole ratio in the bulbar conjunctive was found to be significantly elevated and this venular dilation was found to be maximal during the morning and when the subject was relatively inactive. Venule-arteriole ratio in the fundus, on the other hand, was found to be normal.

Secondly, on examining biopsies of the ear lobes of pre-mellitics under the electron microscope, three deviations from normal were found. Most dermal capillaries from normal subjects were clearly patent. However, under identical biopsy and preparatory techniques, the dermal capillaries of the pre-mellitics were found to be constricted, this constriction was frequently quite marked and involved the dermal capillaries only, never those of the subcutaneous tissues or muscle beds examined.

The second change was found in the venules. Usually the venules of control subjects show close approximation of the endothelial cells to each other and to the basement membrane. However, the pre-mellitic venule shows some degree of separation between endothelial cells and expansion of the space between the basement membrane and the endothelial cells. Strictly speaking, both these vascular changes can be considered within the range of physiological variation, but their constancy among this group of subjects suggests a vascular liability not present in the normal controls.

The third change found in the earlobe was in the elastic tissue of dermal vessels. In pre-mellitic subjects this tended to be rather more electron-dense than normal, and to have a more fibrillar structure than the normal amorphous elastic tissue.

Perhaps the most interesting findings to come out of this early work on subjects in the pre-mellitic phase resulted from kidney biopsies done on two pre-mellitic girls, one seven and one eleven years of age. Both these youngsters fit the criteria of pre-mellitics. That is, both were offspring of two diabetic parents and both had normal glu-

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cose tolerance curves. Similarly, both had normal renal function and were entirely asymptomatic. Light microscopic studies of their renal tissue revealed irregular thickening of PAS - stained material in the glomerular basement membrane and parietal layer of Bowmans capsule. The glomerular basement membrane thickening was most prominent in the axial capillary loops but was occasionally observed in the peripheral loops as well. The irregular thickening of Bowmans capsule was somewhat less marked. Also there was thickening of PAS stained material in several afferent and efferent vessels consistent with premature arteriosclerosis and the basement membrane in certain tubules were also found to be thicker than normal.

Electron microscopy of the glomerular basement membrane showed considerable variation with widths of about twice normal in certain areas. These early changes as seen by the electron microscope are consistent with earlier observations of biopsy material from subjects with established diabetes. The early renal lesions demonstrated in these two pre-mellitic girls are by no means pathognomonic of overt diabetes, but they are similar to the changes observed to a more marked degree in later stages of the diabetic syndrome.

In summary then, what has been shown about persons in the pre-mellitic stage of diabetes:

Firstly, there was no significant difference found between these subjects and normal controls in carbohydrate tolerance, clinical evaluation of renal status, motor nerve conduction velocity, electrocardiograms and vasculature of the retina.

Changes thus far observed in pre-mellitic subjects not seen in controls were venular dilatation in the bulbar conjunctiva, elevated fasting insulin-like activity, probably incomplete dissociation of the "bound" insulin in serum after intravenous glucose, changes in the dermal vessels from ear lobe biopsies, and morphological changes in the basement membrane of Bowmans capsule, glomerular capillaries and proximal and distal renal tubules.

The significance of these findings and of the concept of a pre-mellitic phase in diabetes is probably obvious. No longer is it tenable to say that a person "becomes diabetic" when he manifests a decreased tolerance to carbohydrate, for this probably represents a late stage in the total syndrome of diabetes.

Contemporary thought makes it mandatory that we detect the patient with latent diabetes and treat him since it is hoped that by so doing diabetic angiopathy may be prevented or at least delayed. There is growing evidence however, that the vasculature has by this time already suffered an insult that will manifest itself in later years.

It is probably true that we are dealing with a damaged person by the time we are able to make the clinical diagnosis of diabetes, but we need not assume that he is irreversibly damaged at birth. We must regard as possible the proposition that the genetically transmitted abnormality might be susceptible in the pre-mellitic period to exogenous influences. Such influences might alter or even prevent the clinical manifestations of diabetes as we know them today.

From the patients view point, the development of methods for the diagnosis of Diabetes pre-mellitus and the discovery of exogenous factors which may prevent later stages of the syndrome, could usher in a new era of preventive medicine in diabetes.

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