EDITORIAL

Diabetes Mellitus

DIABETES MELLITUS is an enigma, best (yet poorly) described as a constellation of morphologic and metabolic sequelae to an underlying disorder which, itself, is almost always manifested by abnormalities in insulin and carbohydrate homeostasis. It is certainly inherited, but influenced strongly by environment, being more frequent in populations with caloric affluence and decreasing during times of deprivation. As discussed by Rimoin in the Specialty Conference which appears elsewhere in these pages, the precise mode of inheritance is complicated. Tattersall and Pyke,[1] in a recent and most provocative discussion of concordance for diabetes in identical twins, have noted environment to play a greater role beneath the age of 40, and, over 40, heredity the more important role. At first this appears to be a paradox for a supposedly inherited disease, but with the recent demonstrations of Beta cytotropic viruses causing diabetes in experimental animals and possibly in man[2,3] the paradox may be partially resolved, as follows.

The natural history of the Beta cell in man, let alone in experimental animals, is poorly understood. Do we have the same Beta cells given us at birth? Probably not. As we do with liver cells and possibly those of the exocrine pancreas and other endodermally derived tissues, we are always replacing old Beta cells with new ones. What controls this process? We know the cells arise by mitosis from already formed Beta cells,[4] but we know little of the initial stimulus to cell division, what it is or wherefrom it arises. It is even conceivable that diabetes may result from lack of the signal itself. This problem is analogous to what controls the mass of the liver and its regeneration after disease or partial resection.

As Bray notes in the Specialty Conference, obesity is associated with higher insulin levels, and both in experimental animals and man, with Beta cell hyperplasia. Thus "normals" can probably augment their insulin-secreting capacity in the presence of the increased needs induced by the peripheral insulin resistance of the obese state. What causes this resistance is another challenging problem awaiting solution. That the sequence can be simulated by promoting obesity in otherwise normal people has been shown by the classical studies of Sims and colleagues in Vermont, as discussed by Bray, in which force-feeding of human volunteers induced probable Beta cell hyperplasia, as manifested by higher basal and stimulated insulin levels; although morphologic confirmation is obviously lacking.

Why doesn't the obese maturity-onset type of diabetic increase his insulin reserve even more to overcome the diabetes, perhaps by even a greater degree of hyperplasia? It is tempting to speculate that the primary lesion may simply be a deficiency in Beta cell reproductivity. In youth a virus might cause loss of most of the Beta cells, and the inherited limited regenerative capacity may be associated with a temporary remission, followed by relapse and eventually by loss of all endogenous insulin production. The capacity to measure endogenous insulin production in insulin-treated juvenile diabetics by the detection of a byproduct (connecting peptide) in peripheral blood by Steiner's group[5] has confirmed this sequence of events. In the adult, the programmed Beta cell premature senescence may result in diabetes at age 70 or 80, but if in an obese individual, it may result in the mild maturity-onset type of diabetes at an earlier age, due to the increased insulin needs of the obese.

Although juvenile diabetics tend to breed juvenile diabetics as contrasted with maturity-onset diabetics (M. Gottlieb, unpublished, 1973), the association of the two types of diabetes with each other in a given family is much greater than the association of either type with diabetes in the general population. Thus the same heredity basis is common to both ends of the diabetes spectrum.

Goldstein et al[6] reported that fibroblasts from young diabetics exhibit an earlier senescence in tissue culture than do fibroblasts taken from older, normal, non-diabetic persons, and this same decreased *in vitro* longevity is shown by fibroblasts from offspring of two diabetic parents. The Beta cells may therefore be the Achilles heel of a decreased generalized mitotic potential; but this, at the moment, is very speculative. The numerous

other genetic diseases described by Rimoin, which are associated with diabetes, support the heterodisperse nature of the inherited defect, and, from a biochemical basis, demonstrate that any number of mutations resulting in a broad array of other inherited abnormalities may be associated with diabetes. This again suggests the Beta cell is more "fragile" or limited as far as its regenerative capacity is concerned.

One may ask why the Beta cell has been selected out as the weak link—why not the thyroid cell, or that in the adrenal cortex? The hair follicles in many males and some females and the ovarian cortex in all females also undergo an earlier senescence, but these are relatively dispensable tissues as compared with the Beta cell. The riddle cannot be answered as yet, unless mild diabetes might have offered at one time some degree of selective advantage.[7]

Finally, is the entire constellation, mentioned in the first sentence of this editorial, simply a result of the Beta cell deficiency? Many investigators feel it is, and there are recently published biochemical data in support,[8] but until long-term insulin and carbohydrate homeostasis is maintained by an artificial pancreas, or by successful long-term transplantation of Beta cells or even by rejuvenation of Beta cells remaining in the diabetic (all these possibilities are now being put to experimental test[9]), one cannot answer with confidence. The vast majority of those in the field, however, act as if the complications result from the disturbed insulin-carbohydrate homeostasis, and treat the disease accordingly.

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Some Caveats for the FDA

RECENT DECISIONS by the United States Supreme Court appear to give the Food and Drug Administration (FDA) very significant powers to decide what drugs and medicines can be marketed in the United States. A federal bureau will now have real power to decide which drugs a physician may prescribe for what purpose in caring for his patients, and those which he may not. This is a very considerable power which strikes very close to home for physicians and patients alike. And unless it is exercised wisely and with an understanding of human nature and human needs and the realities of clinical medicine, it may not be very popular.

The Supreme Court opinion itself, written by Associate Justice William O. Douglas, traces the growth of FDA authority and responsibility since 1906. The 1906 Food and Drug Act provided for criminal sanctions and seizure for condemnation of drugs found to be *adulterated* or *misbranded*. The Food, Drug and Cosmetic Act of 1938 established a system of pre-marketing clearance for drugs, the emphasis being upon the *safety* of the drug. The 1962 amendment of the 1938 Act directed the FDA to refuse approval of a new drug application if "substantial evidence" that the drug is *effective* for its intended use is lacking. The 1973 decisions of the Court now give the FDA the power to force drugs it deems to be ineffective off the market, to issue strict rules governing product effectiveness, to deny hearings to manufacturers on contested actions, and to proceed against entire product classes rather than individual drugs. These are significant and substantial powers.

While the distinction between a drug that is adulterated or misbranded and one that is not is clear enough, this clarity of distinction blurs somewhat when it comes to deciding upon safety and effectiveness. There are very few drugs that are entirely safe and always effective. There is nearly always some element of danger in the administration of any drug. Safety is therefore a matter of degree, and the degree is often a matter of conjecture since it depends upon effects of the drug which may not be known and upon the reaction or response of an individual patient which is never entirely predictable; and it is paradoxically true that