Diabetic Cataracts

A Review of Experimental Studies

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The complications which follow prolonged diabetes are a major concern of the physician who is responsible for the care of diabetics. The prevention of these complications is hampered by our ignorance of their cause. The exact etiology of diabetes is not known, and the syndrome may result from a variety of metabolic defects which are usually undetermined.[1–5] Thus, it is difficult to study complications in relationship to the cause of diabetes. Furthermore, the time required for the development of complications following a diagnosis of diabetes may be long and the acquisition of knowledge therefore slow. As a result of these difficulties, it is not surprising that there are two opposite viewpoints regarding the relationship of the control of diabetes with insulin to the development of complications. Some believe that complications can be prevented by good control;[6] others believe that complications develop in spite of good control.[7] Studies with animals may provide clues to the mechanism by which diabetic complications are produced.

Permanent diabetes may be produced in animals by pancreatectomy[8] or by the injection of alloxan,[9, 10] dehydroascorbic acid and related compounds,[11–13] certain chelating agents,[14–16] or pituitary extracts.[17] Temporary diabetes may be produced by the continued injection of pituitary[18] or adrenal hormones.[19] The production of diabetes in animals is followed by the development of a variety of complications.[20] All of the complications associated with human diabetes are not readily reproduced. Cataracts, however, do appear in diabetic animals and are probably similar to the cataracts associated with juvenile diabetes in man.[21] Diabetic cataracts in rats develop through certain stages.[22] At first vacuoles are observed around the periphery of the lens. Later fine crystalline opacities develop centrally, and still later the lens suddenly becomes opaque. The last of these changes occurs over a period of 24 to 48 hours and is readily seen with the unaided eye. This can be used as an excellent indicator of a metabolic end point. By relating various experimental conditions to the appearance of this end point, it is possible to gain an insight into the factors that may cause this complication of diabetes. It is the purpose of this paper to relate some of the experimental work that has been done in relation to the development of cataracts. This will be done by considering three points: (1) the relationship of the severity of diabetes to cataracts; (2) diabetic factors that influence cataracts; and (3) evidence for a theory concerning the development of cataracts.

DIABETES AND CATARACTS

Following the production of diabetes with alloxan or dehydroascorbic acid, rats have hyperglycemia, glycosuria, polyuria, polydipsia, and polyphagia.[23] They fail to gain weight at a normal rate. Any one of these findings might be used as an index of the severity of the diabetes. However, the environment of the lens is most closely represented by the blood sugar level. Furthermore, the other changes are secondary as indicated by the fact that all of the other signs of diabetes may be reproduced by increasing the blood sugar level with another sugar such as galactose.[24] The nonfasting blood sugar is readily measured. Although the hyperglycemia varies slightly from week to week, the average of several determinations on a single rat or group of rats remains constant and serves as a useful measure of the environment of the lens.[23]

The time required for diabetic cataract formation bears an inverse relationship to hyperglycemia[23, 25] (figure 1). The relationship is described by the equation for a hyperbola. Thus, a minimum time is required for the *maturation of a cataract regardless of the height of the* blood sugar, and minimum elevation of blood sugar is required for the formation of cataracts. The minimal blood sugar is about 250 mg. per 100 cc. At this level the renal tubular reabsorption mechanism for glucose is saturated with a resultant loss of sugar in the urine and a tendency to ketosis and neoglucogenesis.

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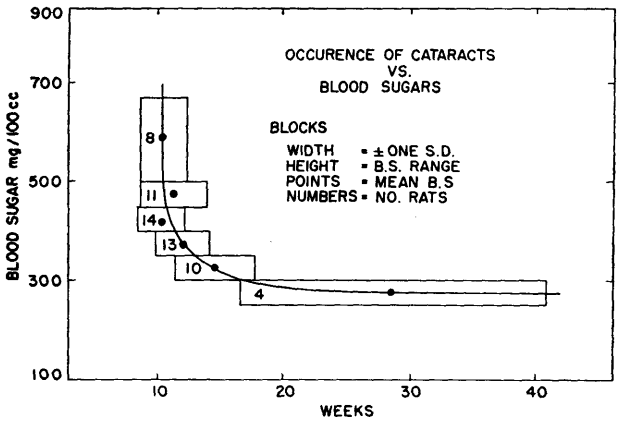

FIG. 1. Reprinted with permission of the "American Journal of Physiology."

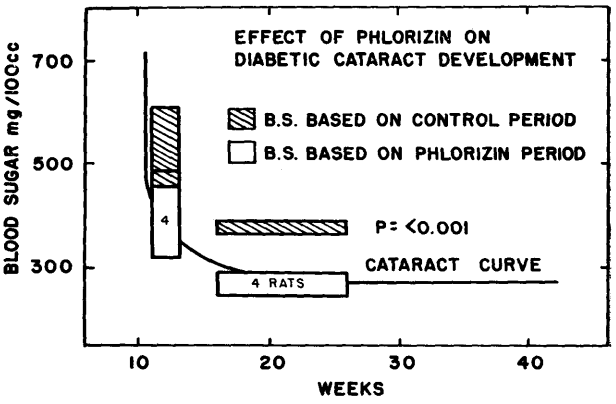

FIGURE 2

The relationship of the time required for the development of cataracts to the height of the blood sugar has led to the suggestion that the cataracts might be the result of one of the factors associated with diabetes. Hence, cataracts might be caused by the "toxic" effects of hyperglycemia or acidosis, by the destruction of proteins in neoglucogenesis, by the loss of an essential metabolite in the urine, or by the failure to absorb glucose in the absence of insulin. The fact that cataracts can be prevented by controlling these factors with insulin[25-28] supports the idea that one or more of them may play a mediating role in the production of cataracts.

DIABETIC FACTORS INFLUENCING CATARACTS

The possible mediating role of the various factors present in diabetes may be studied by changing the relative severity of the factors in diabetic animals and noting the effect on the time required for cataract formation. The administration of a high fat diet to diabetic rats is reported by Charalampous and Hegsted to eliminate glycosuria and prevent cataracts completely.[29] Fasting rats for a period of 40 hours each week lowers the blood sugar for the period of the fast and delays the formation of cataracts.[30] The administration of phlorizin to diabetic rats increases the loss of sugar through the kidney and hence lowers the blood sugar. The time required for cataract formation is significantly delayed in phlorizin-treated rats.[25] When the time required for cataract formation is related to the blood sugar level, the areas of cataract incidence fall on the expected cataract curve during the period of phlorizin administration. However, when related to the blood sugar values before phlorizin administration, the areas of cataract incidence do not fall on the expected cataract curve and thus demonstrate the delay produced by phlorizin (figure 2). Thus, the administration of a high fat diet, fasting, and the administration of phlorizin are beneficial in preventing cataracts. In each of these conditions, the blood sugar is lowered and the other metabolic changes of diabetes are aggravated. The general status as indicated by growth curves is not improved, and ketosis and neoglucogenesis are known to become worse in experiments of this type.[31, 32] Therefore, one is led to the conclusion that hyperglycemia must play a direct role in the production of diabetic cataracts.

If the high blood sugar level acts directly on the lens to produce cataracts, then the amount of sugar reaching the eye by the way of the blood stream should be of importance. This can be tested by altering the blood supply for one eye and using the second eye as a control.[33] Thus, in galactose-fed rats cataracts are first seen in the left eye in 56 per cent of the rats. However, when one of the carotid arteries is ligated and cut, 90 per cent of the cataracts are first observed on the side with the better blood supply and hence the better supply of galactose. In diabetic rats, however, the occurrence of cataracts is unrelated to the blood supply (figure 3). Since diabetic cataracts develop more slowly than galactose cataracts, the results might be explained on the basis of the development of collateral circulation. However, this is unlikely since rats with unilateral carotid ligation in which galactose feeding is delayed still develop cataracts preferentially on the side with the greater blood supply (figure 3). Since carotid ligation in normal rats does not cause cataracts and since carotid ligation in diabetic rats does not affect the side on which cataracts are first observed, one is led to the conclusion that cataracts in galactose-fed rats are related to the amount of blood and hence the amount of galactose reaching the eye. The failure of carotid ligation to influence cataract formation in diabetic rats leads one to question the hypothesis that hyperglycemia is directly responsible for the production of diabetic cataracts.

If diabetic cataracts are not the result of high levels of

EFFECT OF BLOOD SUPPLY ON DEVELOPMENT OF CATARACTS

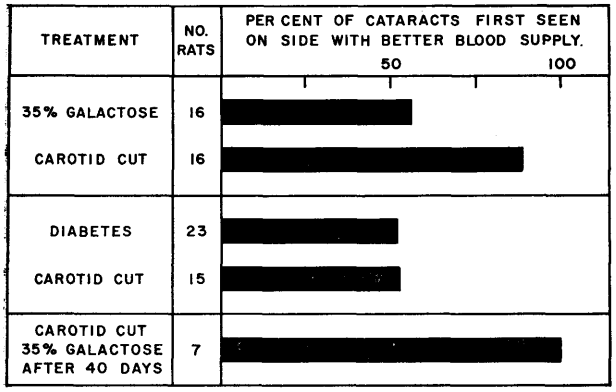

FIGURE 3

glucose working on the eye, then the role of hyperglycemia in producing cataracts needs to be re-evaluated. Hyperglycemia has been implicated as a factor in the production of cataracts because of the direct relationship between the height of the blood sugar and the rate at which cataracts appear and because cataracts can be prevented by lowering the blood sugar with phlorizin, a high fat diet, or fasting. The first point might be explained by assuming that some factor which parallels hyperglycemia is directly responsible for cataracts. A lack of insulin could be such a factor. If this is accepted as a possibility, then the second point may also be explained. If a lack of insulin produces cataracts, then cataracts are probably the result of an inability to obtain energy by utilizing glucose. Lowering the blood sugar with resulting ketosis would supply an alternate source of energy for the lens. If this raises the total energy supply above the "critical level," cataracts would be prevented (figure 4). Furthermore, if diabetic cataracts are the result of the inability of glucose, in the absence of insulin, to supply energy for the lens, the development

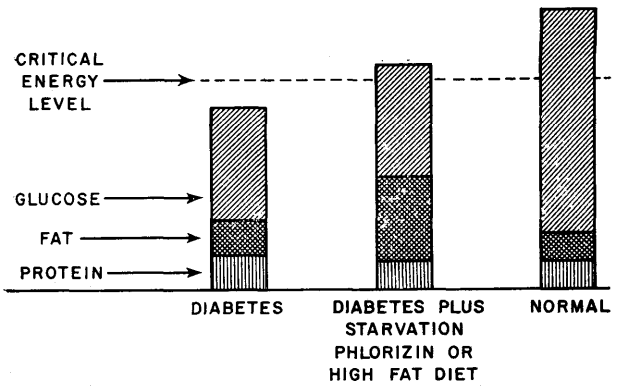

FIG. 4. Diagram of possible sources of energy for lens.

would be independent of the blood supply. Thus, the known facts can be explained by a mechanism that does not involve a direct action of hyperglycemia in the production of cataracts.

EVIDENCE FOR A THEORY

The following mechanism is proposed for the development of diabetic cataracts. In the absence of insulin, the uptake of glucose by the lens is impaired. Since the lens depends on glucose for a major portion of its energy, the total available energy is lowered beyond the critical point that is necessary for maintaining transparency. The lens is also dependent on the constituents in the blood for alternate sources of energy. Under ordinary circumstances, the quantity of these substances is determined by the other organs, notably the liver, and the amount in the blood is inadequate to supply the lens with energy. A decrease in available energy could produce cataracts by stopping the synthesis of glutathione,[34–38] enzymes,[39, 40] proteins,[41, 42] or other structural compounds,[43] or by blocking the maintenance of a water[44] and electrolyte balance.[45, 46] This hypothesis is supported by studies on glucose uptake on isolated lenses and by studies with diets that supply energy-yielding substances other than glucose.

Isolated rat lenses, which are washed and incubated at 37° in Tyrode's solution containing 100 mg. glucose per 100 cc., remove the glucose from the medium at a constant rate for a period of several hours.[47] Lenses obtained from rats with diabetes of one week's duration have an uptake of glucose that is less than half the normal value. This is a significant impairment in the uptake of glucose by the lenses of diabetic rats (figure 5). Ross[48] has reported that insulin will increase the uptake of glucose in isolated decapsulated lenses from normal rabbits. This has not been studied with rat lenses. Fasting the animals for a period of 16 hours prior to the removal of the eyes does not alter the glucose uptake of the normal or diabetic lenses. Thus, the beneficial effects of fasting on the prevention of cataracts may not be related to glucose uptake and may be associated with the production of ketone bodies as an alternate source of energy.

A diet consisting of 50 per cent fructose, 25 per cent casein and 25 per cent fat that is fortified with vitamins and minerals provides energy-yielding substances that can be utilized in the absence of insulin.[49] When this diet is fed to animals most of the fructose is rapidly converted to glucose[50] and the blood sugar level of fructose is between 10 and 20 mg. per 100 cc. of blood. Unlike other high fat diets, however, the hyperglycemia of diabetes is not lowered. The use of fructose as a source of carbohydrate makes it possible to maintain high blood sugar levels for an indefinite period. The fact that this diet also

EFFECT OF DIABETES ON GLUCOSE UPTAKE OF RAT LENS.

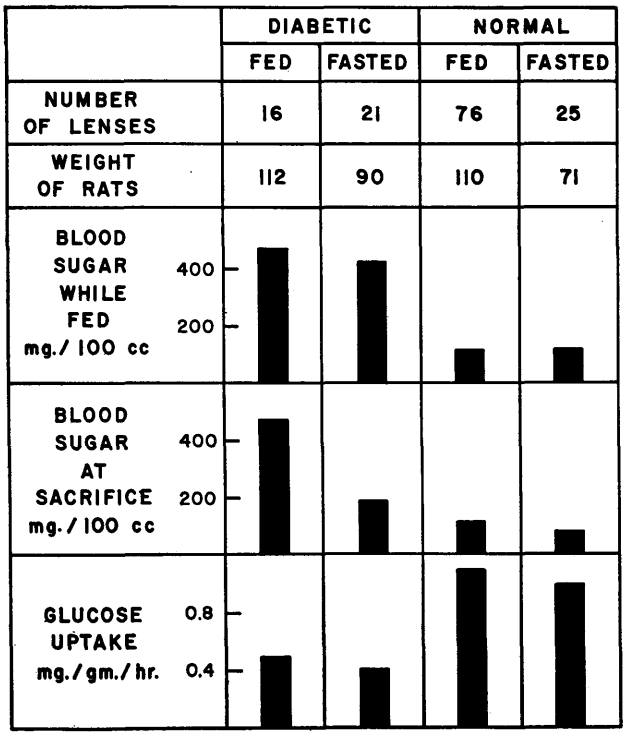

FIGURE 5

prevents the development of cataracts definitely rules out hyperglycemia as a direct mediator in the production of cataracts and demonstrates that the incidence of cataracts can be reduced with the special fructose-high fat diet to 20 per cent of that with a chow diet (figure 6).

EFFECT OF HIGH FRUCTOSE, FAT AND CASEIN DIET ON DEVELOPMENT OF DIABETIC CATARACTS.

DIET	NO. RATS	AVE. WT. gm.	BLOOD SUGAR mg./100 cc. CONTROL	BLOOD SUGAR mg./100 cc. ON DIET	PER CENT WITH CATARACTS AT 150 DAYS
SPECIAL	10	125	450	448	P <0.001
CHOW	10	129	490	475	

FIGURE 6

Growth curves of rats on this diet are also different from those of rats on other high fat diets. On a sucrose-high fat diet rats do not gain weight over a period of three months.[29] However, on a fructose-high fat diet the growth rate is accelerated. Thus, rats with apparently severe diabetes grow at a rate that would be expected for mild diabetes. It would appear that a diet which provides substances that do not require insulin for utilization has a beneficial effect on many tissues of the body.

SUMMARY

This study of one of the complications of diabetes provides evidence indicating that at least one tissue in the body degenerates in uncontrolled diabetes because it is unable to absorb glucose and because alternate nutrient substances are not available in adequate quantities. The provision of a diet containing substances that do not require insulin for utilization prevents this tissue degeneration.

SUMMARIO IN INTERLINGUA

Cataractas Diabetic: Un Revista de Studios Experimental

Iste studio de un del complicationes de diabete demonstra que al minus un del histos corporee se degenera in nonsubjugate diabete proque illo es incapace a absorber glucosa e proque substituibile substantias nutriente non es disponibile in adequate quantitates. Iste degeneration de histos es evitabile per le provision de un dieta que contine substantias que non require insulina pro lor utilisation.

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