OCULAR COMPLICATIONS OF DIABETES MELLITUS

ETIOLOGY-PREVENTION-TREATMENT

by

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The ocular complication of diabetes that is best known is undoubtedly cataract. On the whole, the importance of cataract in diabetes is probably overestimated rather than the contrary. For while a cataract observed in a diabetic is often considered a diabetic cataract, this is by no means always the case.

The observation is frequently made that senile cataract occurs more often in diabetics than in non-diabetics. Not only is the incidence greater, but the cataract occurs at a relatively earlier age. The variation in incidence of cataract from as high as 45% to as low as 16% of all diabetic patients, depends upon what degree of opacity is considered a cataract and the manner in which the lens is examined. However, it has been shown conclusively that in a comparison of a large series of non-diabetics above the age of forty with a large series of diabetic patients above the age of forty, the difference in the incidence of cataract is so slight as not to warrant consideration.

In most diabetics over forty the cataract is indistinguishable clinically from ordinary senile cataract. Therefore, considering the large number of cases of diabetes in patientsover forty years of age, we must necessarily expect a certain number of cataracts to occur and can hardly call a cataract a true diabetic cataract unless it conforms to the type occasionally seen in younger diabetics in whom cataract from natural causes is indeed rare.

The increased blood sugar level has been held to be the factor

responsible for the greater susceptibility to cataract formation. To it also are often ascribed the changes in refraction of the eye in diabetes mellitus and it has been shown that a return to a more nearly normal blood sugar level,brought about by the use of insulin therapy, at times may be accompanied by a decrease in the degree of myopia.

The deficiemt utilization of carbohydrate in diabetes is usually accompanied by a disturbance in fat metabolism which may lead to a constant more or less severe acidosis. Ketonemia and ketonuria are frequently present in the more severe, uncontrolled cases of diabetes mellitus. The oxidation of the fats and fatty acids is incomplete and the so-called ketone bodies, acetone, aceto-acetic acid and B-hydroxy-butyric acid circulate in the blood in greater than normal concentration. In similar fashion, such an acidosis has also been held responsible for the impairment in refraction so often seen in diabetes mellitus and which will later be described. The lipoids of the blood, of which cholesterol and lecithin are the chief representatives are often found increased in diabetes mellitus. It has been shown that insulin therapy tends to lower the concentration of these bodies in the blood. However, the part that these lipoid bodies play in the normal metabolic processes of the body is so imperfectly understood that it would be foolish to predict the role they play in the formation of cataract.

In order to estimate the etiologic importance of hyperglycaemia as a causative factor of so-called diabetic cataract, the ratio of sugar in the blood to sugar in the aquaeous humor in normals and in diabetics

under varying conditions should be known. For this purpose, the ratio in sugar concentration between the two fluids as well as the rate of increase in sugar concentration in the aquaeous humor as compared to the blood following ingestions in the form of glucose or in the form of a mixed meal was undertaken and the results published by D. S. Kirby and R. E. Wiener.[1] They found that the concentration of glucose in the aquaeous humor is less than in the capillary or the venous blood. The aquaeous humor glucose concentration approaches the blood sugar concentration most closely in the fasting condition. Following ingestion of carbohydrate material with a subsequent hyperglycaemia, the sugar concentration of the aquaeous humor rises, but the rise lags behind that of the blood, extends into the period when the blood sugar diminishes and is less pronounced than the glycaemia. The height of the rise of the aquaeous sugar depends more upon the duration of the hyperglycaemia than upon the height of the rise of the blood glucose. In cases of brief hyperglycemia there may be very little rise in the aquaeous sugar. In patients with mild diabetes or in those elderly patients who showed a diabetic type curve in their sugar tolerance tests, they found that there was no essential difference in this relationship between the blood sugar and the aquaeous humor sugar, except that coincident with the more pronounced and enduring hyperglycemia, following ingestion of carbohydrate, the glucose concentration of the aquaeous continues in its slow increase for a slightly longer period. Therefore, the rise in sugar concentration of the aquaeous humor in diabetes mellitus does not seem to be the etiologic factor of most importance in causing diabetic cataract. Other

pathologic changes such as the acidosis resulting from disturbances in fat metabolism and the decreased permeability of the tissues as well as abnormal water metabolism in this disease may play a more important role. Of great importance is the evidence of decreased permeability of the tissue barrier between the blood and the aquaeous in cataract and diabetes. Further investigation of this phase may ultimately lend a more plausible solution of the problem.

Before passing on to the subject of treatment of diabetic cataract, it is necessary that we have some conception of a true diabetic cataract if such exists. What may be called true diabetic cataract is characterized by the appearance of fluid vacuoles under the capsules of both lenses which progresses rapidly to complete opacity in periods of a few weeks to six months. This may occur at any age from that of eleven months as reported by Major and Curran.[2]

In the ordinary case of cataract occurring in a diabetic, the problem is purely one of treatment; the decision when to operate and what measures of pre and post operative care are necessary which would not be called for in a non-diabetic patient. While in the preaseptic days the well known lowered resistance of diabetics to infection caused some operators to refuse to operate on them. With modern aseptic technique and ordinary care to free the conjunctival sac from infectious organisms, the operation is attended by little more risk than in a non-diabetic. Yet, it is the practice in most modern hospitals, and I believe a wise practice, to have these patients made sugar-free, if possible, or at least

to have the amount of sugar in the blood reduced to an amount not over one per cent.

Patients with diabetes who require surgery are usually advanced in years. Such patients usually suffer from extensive degeneration and are consequently poorer risks. The outlook for the diabetic is, however, infinitely brighter than it was in the pre-insulin days. In the days prior to the introduction of insulin, as has been previously stated, operative procedures of even relatively minor importance on diabetic patients were contemplated with considerable trepidation.

The risk in the diabetic patient occurs not in connection with the actual operation itself, but arises as the result of untoward post-operative complications and sequelae. Probably no better instance of the necessity for the cooperation between the internist and the surgeon could be cited than occurs in connection with the diabetic patient, the surgeon being possessed of the specialized information concerning the incidence of complications and sequelae and the internist possessing a knowledge of how to apply therapy to counteract them. In fact, one can almost safely say that insulin has made operative procedures on the diabetic patient almost as safe as similar procedures on otherwise normal individuals of the same age and physical resistance.

In the pre-insulin days the complications most feared post-operatively were acidosis and coma; such complications occur occasionally even now, in spite of all that can be done with insulin.

In general, preoperative treatment is aimed at the accomplishment of four ends, namely -

1. The control of the blood sugar level at or near a normal figure as the exigencies of the case will permit.

2. The abolition of ketosis.

3. The maintenance of the body fluid volume at a sufficiently high level, and

4. The storage of a reserve supply of dextrose in the liver and elsewhere as glycogen.

Immediately following operation a sample of blood should be secured for blood sugar analysis and carbon dioxide determination, the analysis of which serves as a guide for subsequent dextrose and insulin administration. The efficacy of the intravenous method of administration of dextrose should never be forgotten in connection with such patients, who for one reason or another cannot be fed by mouth.

Some authorities advocate the administration of liquid carbohydrate, either by mouth or intravenously, as frequently as every two hours for the first several postoperative hours, regardless of the apparent general condition of the patient. Others given relatively large amounts of insulin properly buffered with dextrose to guard against the possible development of an unforseen acidosis. It should also be remem-

bered that the efficacy of insulin is greatly reduced in the presence of infection and, therefore, one must not expect to be able to calculate insulin dosage on the same basis as in the ordinary case of diabetes.

When the above care is observed the outcome of operation is usually favorable. There is somewhat more of a tendency to inflammation when, as often occurs, cortex is left within the eye. Also, one may be disappointed in the result of as uneventful cataract operation on a diabetic, by reason of the existence of a central retinitis which could not be diagnosed before the removal of the cataract.

A condition which is allied to diabetic cataract and which throws some light on its pathogenesis, is the occurrence of remarkable changes in refraction during the course of diabetes. Duke-Elder[3], who has done by far the most extensive and interesting work on this subject has described three typical cases in which the changes in blood sugar were recorded at the time of the refractive changes. One case with a very high blood sugar developed myopia of over thirteen diopters in each eye shortly before death. The other two cases developed hyperopia of over five diopters when the blood sugar was brought down from a high to a low level under treatment. When the sugar was allowed to go up, the hyperopia almost disappeared, only to reappear again when treatment was renewed and to remain until some time after a normal blood sugar had been established. These refractive changes are said to be due to disturbances in the content of the blood caused by the changes in blood sugar. When the blood sugar suddenly becomes high, the pressure of the blood is cor-

respondingly lowered through the pouring of fluid into the blood from the tissues, in order to dilute the increased sugar content of the blood. At the same time sodium chloride is lost from the blood. The resultant fluid of low osmotic pressure is able to penetrate the lens capsule, causing the lens to swell with the production of a state of myopia. It is fairly reasonable to assume that if enough fluid collects in the lens permanent changes in the form of cataract may develop. If the blood sugar is lowered before this occurs, the lens gives up water and becomes flatter than normal with hyperopia resulting.

These changes in refraction are often important as initial symptoms of diabetes. In statistics kept at the British University College Hospital it was found that 34% of the cases of diabetes gave a history of transient but rarely disturbing visual changes.[4] Because the visual changes are not very disturbing, the patient seldom consults a physician with this as a complaint, but instead complains of some of the other unpleasant and persistent symptoms. These are often sufficiently suggestive to enable the physician to make a provisional diagnosis without inquiring for further symptoms. In this manner this important symptom is often overlooked.

The history of the onset of diabetes usually obtained from a patient is that he became thirsty, and noticed that he was getting up to void. About this same time he noticed that his vision was becoming impaired, but returned to normal after a short period. This period may last anywhere from two to three days or two to three weeks, depending to some extent on whether the condition had been treated or not.

Under mild treatment, such as qualitative restriction of the diet, the condition disappeared rapidly, but even when the disease is neglected, the disability always gradually passes away.

The following may be cited as almost typical description of the visual symptoms given by patients already wearing glasses. Previously the patient had glasses fitted for both long and short distances, now the short distance glasses are practically useless, but he can still read with the long distance ones. Still others complain that they have obtained spectacles which enable them to see quite well for a few days, but that the spectacles then become useless. These are then taken back to the optician and changed for new ones. To the patient's annoyance the same performance is repeated. Another interesting complaint given by some is that they were unable to see with their own glasses, but obtained a pair from some relative of the family and saw perfectly with these.

Fortunately, this symptom is seldom noted in the absence of glycosuria, which is quite marked. However, it is invariably associated with one or more of the classical symptoms of diabetes mellitus. It disappears rapidly under treatment, and does not occur when the patient is in a satisfactory state of balance.

Probably more important than any of the ocular complications associated with diabetes mellitus are the retinal changes. A rough estimate of the occurrence of this complication can be said to be around twenty per cent. It is important because it seriously interferes with

vision in some cases, and because naturally it is not amenable to surgery.

Diabetic retinitis occurs in several forms, and is almost always bilateral, but both eyes need not necessarily be affected at the same time. In fact the lesion may be so pronounced in one eye, and so slight in the other, that the latter may escape detection. As a rule the retinitis associated with diabetes does not develop in the juvenile subjects of this disease.

Two varieties of diabetic retinitis are seen, often together; white patches which are usually small and single or in small groups, not tending to become confluent in large masses like the white spots of albuminuric retinitis and hemorrhages. Seldom are the white spots arranged in a star figure around the macula, as in albuminuric retinitis, but are frequently seen in the central region, and around the nerve.

The hemorrhages are found in all parts of the retina, but are most frequent along the large vessels not far from the nerve. Occasionally hemorrhages into the vitreous occur, producing the picture of retinitis proliferans and there seems to be more tendency for this to occur than in the hemorrhages of nephritic or arteriosclerotic origin. The extent to which vision is interfered with depends on whether or not the central area is involved.

The relation between diabetic retinitis and albuminuric retinitis is an interesting one and an important one. It is important because of the very different prognosis in that diabetic retinitis, from the

standpoint of the life of the individual, does not carry so grave an outlook as does albuminuric or renal retinitis. By this, I mean that the true basis of the renal retinitis, namely chronic nephritis is a far more serious condition than diabetes, especially since the introduction of insulin. It is an interesting one because of the frequency with which both conditions are found in the same individual. Thus, an albuminuric retinitis may complicate a diabetic picture, and vice versa. The best work on this particular phase of the subject was carried out by Wagener and Wilder of the Mayo Clinic.[5] They found that retinitis was not seen in the severe forms of pure diabetes, but always in mild, easily controlled cases, with some evidence of vascular disease. They described a retinitis characterized by superficial flame-shaped hemorrhages, which were seen in a number of cases with more severe vascular and renal complications. They believe so-called diabetic retinitis is due to arteriosclerosis, but modified by the presence of diabetes to a form which is ophthalmoscopically distinguishable from ordinary arteriosclerotic retinitis. Since Wagener and Wilder did not state in their article upon what they based their opinion that their particular cases were suffering from vascular disease, the question is still an open one.[6] Foster is convinced there is good reason for identifying a special form of diabetes due to retinitis.

The rapid loss of vision due to complicated cases is in marked contrast to the usual course in those without definite reno-vascular leions in which useful or even good vision may be retained for years.

Whether or not we believe with Wagener and Wilder that the retinitis of diabetes is always due to arteriosclerosis, and it must be remembered that there are some cases which show no other signs of vascular disease, it is true that it nearly always occurs at the age of vascular degeneration and that its lesions are the result of changes in the permeability of the retinal vessels, similar to those which cause arteriosclerotic retinitis.

Among the rarer ocular complications of diabetes mellitus, the condition known as lipemia retinalis occupies a prominent place, if not for its rareness, certainly for the striking ophthalmoscopic appearance it presents when found. No diseases except diabetes uncomplicated by treatment produces a lipemia of sufficient degree to be recognized ophthalmoscopically.

Diabetes mellitus is properly considered a disorder of the normal metabolism of the body. Usually the disturbance of the metabolism of carbohydrates is more evident than that of fat or protein. It is known that the fat metabolism is dependent in a large measure upon proper carbohydrate metabolism. Thus the fat of the body is handled abnormally in diabetes and consequently is present to excess in the blood stream.

Lipemia may be defined as a milkiness of the blood plasma due to an excessive amount of fat or to an altered physical state of the fat. It is not present in the blood of a normal individual when taken for examination in the post-absorptive period. Allen's conception of the

cause of lipemia in diabetes[7] is that a general cachectic condition of the whole organisms exists which affects all cellular functions including permeability. On the other hand, as long as we are hypothesizing, it is conceivable that the pancreas may secrete hormones which are specific in the removal of fat, just as it does for glucose. We know that insulin assists in the rapid removal of an excess of sugar from the blood, as well as of fat. However, the theory of Bloor's[8] sounds the most plausible to me. In short, he believes that the accumulation of fat in the blood causing the lipemia is due to the difficulty which the diabetic has in removing fat from the blood.

The employment of insulin therapy causes the salmon-colored appearance of the large vessels, and the cream-colored appearance of the peripheral vessels to clear up in about five to twelve days.

Rarely diabetes may be the cause of paralysis of the extrinsic muscles of the eye. This can be subdivided into two groups according to the site of the lesion. First, those in which the paralysis is the result of diabetes, directly or indirectly; second, those in which the ocular paralysis is due to a cerebral lesion which also gives rise to the diabetes. Paralysis of any of the ocular muscles may occur, but most frequently the sixth nerve is involved. Single branches of the oculo motor nerve may also be involved rather frequently. Rarely, the levator palpebrae superioris is affected, resulting in a unilateral ptosis.

These paralytic complications are seen in slight as well as in severe cases of diabetes.

The therapy recommended is the use of insulin plus dietary measures. In those cases which are due to the diabetes, satisfactory results are usually obtained in a few weeks.

Another somewhat rare affection of the eye arising in the course of diabetes is retrobulbar neuritis. This is in all probability the result of theliberation of an endogenous toxin or toxins which exercise a selective action on the papillo-macular bundle of the optic nerve. The condition is more common than generally recognized. This lack of recognition is in no small part due to the confusion which has arisen because of the striking similarity between diabetic retrobulbar neuritis and that occurring in tobacco-alcohol amblyopia. It is a well-known fact that diabetes increases the liability of the individual to tobacco amblyopia. While retrobulbar neuritis due to alcohol and tobacco often occurs in diabetic patients, there are sufficient instances in the literature in which alcohol and tobacco can be eliminated as accomplices in the production of this entity.

Diabetic retrobulbar neuritis is more frequent in middle age, and seems to favor the male sex. It is usually bilateral, but may involve only one eye. The usual complaint is that of failing vision, which comes on rather rapidly and sometimes even suddenly. The most persistent finding is a central scotomata for red and green. The amblyopia usually disappears in from three to eight months. The amelioration of

symptoms shows a definite relation to the disappearance of the ketone bodies from the urine.

In ones present state of knowledge, it is impossible to state the precise toxin which attacks the maculo-papular bundle. It may possibly be glucose, but of far more importance are the ketone bodies, B-oxybutyric acid, acetone, and diacetic acid. The presence of small amounts of these bodies is without apparent harm, but when the substances are formed in excess together with insufficient elimination, definite toxic symptoms arise.

As regards the treatment of this condition, by far the most important factor is prophylaxis. By the time it is recognized it usually is too far advanced to respond to the ordinary diabetic measures although there should, of course, be instituted. Proper control of the diabetic condition, through the cooperation of the patient and the physician, from the time the diagnosis of diabetes is established will prevent retrobulbar neuritis as well as most of the other ocular complications previously discussed. This is especially true of this condition, as ketonemia which is strongly suspected to be the causative factor, arises as the result of neglect on the part of the patient to follow his doctors instructions or due to poor regulation of the patient's condition by the physician.

Occasionally iritis, which may be purulent and sometimes associated with purulent keratitis and with hemorrhage in the anterior cham-

ber, develops in diabetic patients. It is ordinarily described as diabetic iritis, but more properly should be considered as an iritis which occurs in a diabetic subject. Iritis, following the operation of iridectomy, is not infrequent in diabetics.

The most important local drug in this as in other forms of iritis is one of the powerful mydriatics, preferably atropine sulfate. Mydriasis should be maintained until all ciliary irritation has subsided and during the period of refractive changes in the eye. In addition to this and dry heat the general principles of diet regulation and the use of insulin should be begun immediately, if the patient is not already under care.

Occasionally changes in the intra-ocular tension of the eyeball occur in diabetes. A few cases of glaucoma occur, usually as the result of a vascular lesion and accompanied by hemorrhages. In severe cases, with high blood sugar and acidosis, hypotonic bulbi is usually found, the globus becoming very soft in the terminal stages. Curiously enough, this condition is not found in comas other than diabetes, and therefore is of some diagnostic value. Though the sign is not constant, it occurs with considerable enough frequency to warrant observation, especially since it can usually be detected by digital palpation. It is most pronounced at the height of coma, but quickly recedes as the coma is overcome. Several theories exist as to the mechanism involved in this striking phenomenon, but the one that sounds most plausible to me is that it is due to a loss of vitreous and aqueous fluid in an

attempt to dilute the hypertonic blood.

Hemorrhages in the retina and vitreous are of rather common occurrence in diabetes. Ordinarily they disappear without leaving traces of connective tissue proliferation. However, occasionally following extensive and recurrent hemorrhages, the coagulated blood either becomes organized, or by virtue of the pressure of the unabsorbed blood, results in connective tissue proliferation, producing white masses, which conceal the optic discs and follow the direction of the blood vessels.

It conclusion it may be safe to add, that although the importance of diabetes as the causative factor of diabetic retinitis and diabetic cataract is undoubtedly overestimated, the decreased tissue permeability, the alterations in aqueous humor sugar, and the presence of acetone bodies at different times must necessarily have a deterimental effect upon the lens and retinal vessels just as they do on the other tissues of the body. Also, that the prevention and control of the ocular complications of diabetes must necessarily be the product of the type of control of the primary, generalized, metabolic disturbance, and only through this avenue can we hope to reduce the incidence of these complications.

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