SENILE CATARACT AND ITS RELATIONSHIP TO THE GLUCOSE-TOLERANCE CURVE

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'The essential chemical changes occurring in the lens in cataract involve a hydration followed by dehydration, an acidification followed by an alkalosis, a replacement of soluble by insoluble protein, an increase in calcium and lipoids and an averaging of the concentration of salts to correspond with those of the blood.' Thus Duke-Elder[1] sums up the complicated process resulting in the opacification of the lens—a process associated with diminished metabolism, decrease in capsular permeability and loss of substances active in oxidation.

When a tissue can no longer carry on the process of normal respiration resulting in the release of energy, such tissue starts to die. A cataractous lens is a dead lens incapable of normal metabolism; an asphyxiated organ whose capsule loses its free permeability to water, electrolytes and small-moleculed colloids; one whose ability to recover, if normal conditions once again prevail, is permanently destroyed.

We are all familiar with the congenital cataract of infants in which the foetal tissues, asphyxiated by anoxia during the first few weeks of intra-uterine life, become enclosed by normal clear lens material, laid down once the anoxic state has ceased. Here the ability to recover is re-established and normal metabolism, normal oxidation and normal activity of the cells is resumed. Not so in the case of the adult lens. Cataract in the adult represents, as a rule, gradual but inevitable inability on the part of the lens tissue to carry on the normal metabolism, with resultant decrease in the release of energy and gradual death of the tissue by asphyxia. At what stage the ability to recover from the asphyxiated state is passed is difficult to establish, but from the clinical point of view what does this gradual asphyxiation involve?

Firstly, it should be recalled that the lens consists of protein (under normal circumstances completely soluble) comprising about 35% by weight of the organ. The classical work of Mörner[2] showed that this protein comprises 3 principle components, viz. alpha, beta and gamma crystallins. The process of ageing involves the alteration of these proteins from their soluble to an insoluble form, this process becoming clinically manifest at first by the onset of presbyopia with a loss of elasticity of the lens and ending with the total cessation of metabolic activity in a mature senile cataract.

Secondly, lipoids, particularly in the form of cholesterol and phospholipoids—substances essential to the life of the cell—as in other tissues tend to accumulate with increasing age.

Thirdly, despite normal calcium metabolism, secondary calcium deposition occurs in the dying lens, a reaction probably secondary to the death of the tissue as occurs in its deposition in an atheromatous artery.

Fourthly, the potassium content of the normal lens is high (40%). This steadily decreases with age, being about 9% in cataractous lenses. The potassium/calcium ratio is normally about 380:1, but this evens out steadily in the cataractous lens until it becomes reduced to 2:3 or less.

Fifthly, the sodium content is greatly increased in cataract probably as a result of a diffusion phenomenon in an attempt to maintain the sodium:potassium balance. Likewise, there is an increase in magnesium and, as would be anticipated with the increasing sodium, chlorides accumulate. Contrariwise, the phosphates associated with the potassium decrease, probably also as a diffusion phenomenon.

Sixthly, the ageing process involves an accumulation of extracellular water, often exhibited as vacuoles between the cells, and a loss of intracellular water as a result of prote-

olysis which increases, initially at any rate, the osmotic activity by the fragmentation of the large protein molecules into smaller ones.

Seventhly, the normal lens contains glucose in the same form as it occurs in the blood. It increases with age and in diabetes, and represents the source of energy required for active metabolism and maintenance of normality. This glucose is derived from the aqueous, and in aphakia the glucose content of the aqueous increases.[3] It is always, however, lower than that in the plasma. According to Harris *et al.*[4] under no circumstances can a higher level of glucose occur in the lens than in the aqueous, and penetration into the lens is dependent upon the metabolism occurring in the lens capsule. Until recently[5] it was believed that the lens energy was derived either from direct oxidation (10%) or from the anaerobic process known as glycolysis (90%), the enzymes lactoflavin and aneurin being intimately concerned in the process. By this process the resultant pyruvic acid in the presence of oxygen is reduced to carbon dioxide and water, or if oxygen is deficient, to lactic acid. Van Heyningen[6] has recently demonstrated the presence of fructose in the lens, which represents an incomplete anaerobic breakdown of glucose to produce energy via the sorbitol pathway. Until recently it was thought that this sorbitol pathway was only active in the accessory sexual tissues such as the placenta and seminal vesicles, where the fructose formed there is broken down as the principal fuel of the sperm cells. It is likely that, with low concentrations of glucose in the lens, this primitive energy-producing pathway is unlikely to be used, as most of the glucose will be phosphorylated.[7] Kuck[8] has shown, however, that if the blood level of glucose rises beyond 200 mg./100 ml., more fructose than glucose accumulated in the lens in experimental animals, and that at 350 mg./100 ml. the ratio of fructose to glucose is about 2:1. This suggests that with higher concentrations of glucose in the lens the sorbitol pathway for the production of energy may be increasingly called upon. The accumulation of sorbitol, which is a sugar alcohol, will then tend to occur, furthering proteolysis and consequently the formation of cataract. Van Heyningen[6] has demonstrated this accumulation in diabetic cataract and similarly, dulcitol in galactose cataract and xylol in xylose cataract.

Whatever the mechanism of production of proteolysis, there are 3 changes which are consistently observed early in sugar cataracts, viz. a decrease in amino acids, an increase in sugar alcohol and a drop in the activity of the shunt mechanism which provides reduced TPN for the production of sugar alcohol. It would appear, therefore, that the higher the concentration of glucose in the lens, the more likelihood there is of a more primitive mechanism of energy production being brought into play.

In the established diabetic, the response to a high level of serum glucose differs from the normal in that the insulin response is slower and less effective, and the reabsorbtive power for glucose by the renal tubules is exceeded. This results in a raised fasting serum level of glucose, a delayed peak in the glucose-tolerance curve, and the fall to normal is long delayed and may, in fact, never occur. Normally, at a level of 150 mg./100 ml., glucose (as detected by ordinary clinical tests) starts to appear in the urine. Commonly in elderly people this level is raised so that, even with relatively high serum glucose levels, the urine remains sugar free.

What is, then, a normal response to ingested glucose? If 50 G of glucose is given to a normal healthy individual who has been starved for 12 hours, what should the response be? Ordinarily the fasting level should be below 110 mg./100 ml., after half an hour, less than 160 mg./100 ml., and after two and a half hours, it should have returned to the fasting level or below.[9] With normal renal function sugar should not appear in the urine.

According to Fajans[10] a delayed peak and a delayed return to the fasting level raises the suspicion of pre-diabetes, and a fasting level of 125 mg./100 ml. or higher (venous blood) with a delayed peak is diagnostic of the disease. A fasting level of 150 mg./100 ml. or more makes a glucose-tolerance curve unnecessary, as this level on its own is diagnostic.

On reviewing the serum response to ingestion of glucose of patients presenting with incipient cataract over the past few years, several interesting facts have been brought to light. It should be noted that no attempt has been made to classify the type of cataract occurring in these patients, and also that all patients who have been known to have diabetes before the diagnosis of their cataract being made, have been excluded from this series. In other words, of those patients who have frank diabetes, cataract was the presenting sign.

The total number of cases reviewed is 183 private patients, of which about two-thirds were females. The youngest investigated was 18 years old and the eldest 92. Of these patients, at original examination, 61 had normal glucose-tolerance curves, but 17 who have been re-examined subsequently have developed an abnormal response to ingested glucose. In every case of these 17 there was a family history of diabetes. The remaining 122 all had abnormal curves at the first investigation, either in the form of a frank diabetic curve with a fasting level of 150 mg./100 ml. or higher (in one case 339 mg./100 ml.) or, more commonly, with a normal fasting level but a decreased insulin response either in the form of a delayed peak, a rise above 180 mg./100 ml. or a delayed return to the fasting level. One was struck by the fact that only 31 showed glycosuria during the test and that of these, only 10 had glycosuria in the fasting urine specimen. The great majority, therefore, had a raised threshold for sugar. One case with a peak of curve at 280 mg./100 ml. had a fasting level of 113 mg./100 ml. and well-developed diabetic retinopathy. In this case the level after 2½ hours was within normal limits, being 68 mg./100 ml. Subsequent follow-up has shown that this patient has developed full-blown diabetes.

The unreliability of a single fasting level estimation of serum glucose is illustrated by the fact that 90 of these patients had normal fasting levels, and of these only 61 had normal curves. Even those with normal curves, when followed up over a period of time, have developed true diabetes, e.g. one of these patients who originally presented with a fasting level of 107 mg./100 ml., a peak of 160 mg./100 ml. and a return to 90 mg./100 ml. after 2½ hours was found 7 years later, to have a fasting level of 302 mg./100 ml., a peak of 471 mg./100 ml. and a return to 397 mg./100 ml. at the end of 2½ hours. Yet another pre-

sented with a fasting level of 98 mg./100 ml. with a peak of 173 mg./100 ml. after one hour and 114 mg./100 ml. after 2½ hours. Four years later these figures had risen to 128 mg./100 ml., 228 mg./100 ml. and 148 mg./100 ml. respectively. Yet another patient had the serum figures of 18 mg./100 ml., 182 mg./100 ml. and 108 mg./100 ml., but 8 years later the figures had risen to 122 mg./100 ml., 230 mg./100 ml. and 124 mg./100 ml.

It should be noted that even in frank diabetics not a single case presented with the classical symptoms of loss of weight, polyuria or polydypsia. On the contrary many, if not most, were obese and overnourished.

DISCUSSION

The suggestion that the causative factor of cataract in the adult should be looked for in generalized faulty metabolism is not a new one. Langdon,[11] in 1925, reviewed 100 cases of cataract which had been subjected to physical examination, urine analysis and the investigation of blood chemistry, including a tolerance curve; 'where a diagnosis of diabetes was indicated'.

Unfortunately the figures were not clearly set out. He does state, however, that 'fully 5 cases showed inability to digest the sugar meal in the normal fashion, making it seem possible that it would be well advised to warn them against excessive ingestion of carbohydrates'. In the same article he quotes Corson-White concerning observations made on the changes of the blood-sugar content of lower animals. Dogs, for example, with clear lenses, averaged 112 mg./100 ml., while those with cataract averaged 222 mg./100 ml. In parrots with normal lenses the average was 114 mg./100 ml. and those with cataract 168 mg./100 ml. In owls the figures were 118 mg./100 ml. and 189 mg./100 ml. respectively.

It is not the intention of this paper to suggest that all cases of incipient cataract are due to an inability on the part of the body to deal with its circulating glucose, whether the primary factor is associated with excessive ingestion, decreased insulin sensitivity or secretion, or imbalance associated with anterior pituitary, adrenal or thyroid glands, but it appears to be significant that over 60% of the cases investigated show an abnormality in their ability to metabolize glucose efficiently. Even more significant is the fact that 17 cases which presented with quite normal glucose-tolerance curves, but with a strong family history of diabetes, showed true diabetes after the passage of some years.

It is well known that increasing age is usually associated with an increasing 'tolerance to glucose' as evidenced by the curve, and one wonders whether this inability to deal with the intake and manufacture of carbohydrate is not, in itself, an accurate guide to the ageing process. Much has been written in recent years about the accumulation of tissue cholesterol in old age, but one wonders whether this is a cause or effect, and how much it can be related to the inefficient utilization of glucose.

It is interesting to speculate at what stage and at what level the more primitive mechanisms such as the sorbitol pathway become operative in producing energy and whether the decreased glucose metabolism as evidenced by the abnormal curves illustrated here is sufficient to trigger off such a mechanism in an ageing lens. This might explain the onset of cataract in otherwise clinically-normal individuals. Whether the restriction of carbohydrate intake, the use of antidiabetic oral therapy or of insulin will effect the progress of the lens opacities is something to be sought for in the future. Most physicians seem loath to subject patients of this group to strict control, but 1 case I have followed for 9 years still retains 6/9 vision in the better eye either because of, or in spite of, such a regime.

Dunlop,[12] writing on 'Principles of treatment of diabetes', states: 'It is insufficiently realized that some 45% of all diabetic patients can and should be controlled by dietary measures alone without recourse to insulin or oral hypoglycaemic agents. Furthermore, good diabetic control is impossible for diabetics requiring insulin or oral drugs unless they are meticulously educated in the principles of dieting. There is a substantial body of evidence to suggest that good control will do something to prevent or at least delay the onset of complications (retinopathy, nephropathy, cardiopathy, etc.). There is, therefore, no justification for a *laissez faire* attitude to the careful dietetic treatment of diabetics.'

Perhaps the cases presented represent a state of pre-diabetes and perhaps the development of lens opacities could be used as an index of pre-diabetes in the population. It has been estimated that in the USA there are over a million undetected diabetics who should be under some programme of therapeutic management. It is further claimed that 30% of diabetics are discovered, on routine examination for insurance, by urine examination alone and that less than 2% of diabetics present with classical symptoms of polydypsia and polyuria.[13]

What emerges clearly from this study is the fact that urine examination, particularly in the older age-group, is unreliable in detecting even the established diabetic, and that a normal fasting level of glucose does not necessarily mean a normal glucose-tolerance curve. Furthermore, a patient with a normal curve and cataract should be followed up over the years as a significant number develop frank diabetes, particularly if there is a family history of such disease.

Many questions are left unanswered and many avenues unexplored. I should suggest, however, that the presence of incipient cataract—particularly in the younger age-group—should arouse one's suspicion either of established and undetected diabetes or pre-diabetes, particularly in the presence of a positive family history. Furthermore, a normal fasting blood sugar and negative urine examination cannot rule out diabetes as an aetiological factor. Prompt and early control of the disease may not only slow down the process of lenticular sclerosis, but the other complications of diabetes may likewise be aborted.

SUMMARY

183 cases of incipient cataract were investigated by means of the standard glucose-tolerance curve. 60% were found at first examination to have some abnormality of the curve. Of the remaining 61 cases, 17 or 28%, were found to have diabetic curves on follow up over a period of seven years or less.

The factors associated with the formation of cataract are briefly reviewed.

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