The Micro-angiopathy in Diabetes Mellitus

A Concept regarding the Mechanism of its Origin

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Our knowledge of the various causative factors and the mechanism which leads to the generalized micro-angiopathy (retinopathy, intercapillary glomerulosclerosis, and probably neuropathy) in diabetes mellitus is at present insufficient, and a better understanding of this problem is urgent.

Recent research in the field of microbiology of the circulation and in the study of the pathogenesis of retrolental fibroplasia has emphasized the importance of vasomotor reactions in the smaller blood vessels in response to variations in oxygen and carbon dioxide tensions in blood and tissues. The similarities in the clinical pictures and in the patho-anatomic changes between diabetic retinopathy and retrolental fibroplasia are evident. In both conditions the main changes in the retina are vascular in origin and are characterized by engorged and tortuous veins, hemorrhages, and exudates. In some cases of both retrolental fibroplasia and diabetic retinopathy there appear new formation of vessels, vitreous clouding, opacities, and proliferation of connective tissue into the vitreous body. The capillary micro-aneurysms which are the characteristic lesion in diabetic retinopathy have not been demonstrated in the retina of infants with retrolental fibroplasia. This might be explained by the fact that the basement membrane, which is necessary for the formation of the retinal capillary micro-aneurysms, is not developed in the newborn infant.[1] Not only are the above structural similarities present, but the progression of the lesions from mild into severe stages follows the same pathways in both conditions.

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Although not all the details in the mechanism of the production of retrolental fibroplasia are yet known, extensive clinical[2-4] and experimental[5-7] investigations have shown that the most important causative factor is the high concentration of oxygen formerly administered to premature infants placed in incubators. The increase in oxygen tension in the arterial blood of newborn hypoxic infants placed in 40 per cent oxygen is tenfold.[8] Ophthalmoscopic observations have demonstrated that the retinal vessels constrict if the oxygen tension in the circulating blood is increased and that vasodilatation occurs if the oxygen tension is lowered. The same vasomotor reactions to variations in the oxygen tension have been observed in the skin of newborn infants and are known to occur in the smaller vessels of the brain.[9] Identical vasomotor reactions, although in the reverse direction, are caused by variations in the carbon dioxide tension in the circulating blood; that is, an increase in carbon dioxide tension causes a vasodilatation and a decrease in carbon dioxide tension causes a vasoconstriction.[10] In addition, low oxygen tension not only determines the caliber of the retinal vessels but is also the only known incitement for new formation of small vessels.[5]

The vasomotor reactions in the smaller blood vessels (arterioles, capillaries, venules) in response to the variations in oxygen and carbon dioxide tension are not confined to the newborn infant but occur in adult nondiabetic as well as diabetic individuals.[11-14]

In diabetes mellitus the reactions of the smaller blood vessels in the bulbar conjunctiva have been intensively investigated at this laboratory[15-18] with Knisely's technic.[19] In diabetic individuals there were observed pathophysiologic responses of the smaller blood vessels similar to those in subjects exposed to varying oxygen or carbon dioxide concentrations. Two main pattern deviations, which varied quantitatively from time to time, could be recognized in the diabetics. In the vast majority of cases Vascular Pattern Change 1 was found. This is characterized by a slight constriction of the terminal arterioles and a marked loss of tone in the venous part of the peripheral vascular bed, accompanied by aggregation of the blood cells, a decreased rate of blood flow, and ab-

normal permeability. In some cases Vascular Pattern Change 2 was observed. This is characterized by an increase in the vascular tone, since both the arterioles and the venules are tightly constricted and many of the capillaries are completely closed. By serial observations and by statistical evaluation of single observations in diabetic children[17, 18] causative links were demonstrated between the reversible response changes and the irreversible degenerative changes in the bulbar conjunctiva. It therefore appears that the pathophysiologic vasomotor responses over a period of years lead to the permanent clinical micro-angiopathy in diabetes.

In well controlled diabetic persons there is evidence that the partial tension of carbon dioxide (pCO_2) varies concomitantly with insulin administration.[20-22] In the first hours after the administration of insulin the pCO_2 increases and then decreases slowly as the insulin action disappears. More marked changes in pCO_2 occur in acidosis. In this condition the expected sequence of vasomotor reactions was observed; that is, when the pCO_2 was reduced, Vascular Pattern Change 2 was found, and as the patients improved and their pCO_2 increased, the caliber of the vessels reversed through Vascular Pattern Change 1 (dilatation), to resume finally the same condition as they had prior to acidosis.[23] It is a general clinical impression that diabetics who frequently become acidotic are more prone to develop early and severe diabetic micro-angiopathy than are well regulated diabetic patients.

Far less is known about the variations in oxygen tension in diabetics. There is some evidence that oxygen is better utilized at high glucose levels, which suggests the possibility that the oxygen tension in the tissues of diabetics may also change concomitantly with glucose levels and insulin administration.[24] In this regard it might be mentioned that prolonged hyperglycemia has been suggested as a cause of venous distension in the retina.[25] In the diabetics the vasomotor reactions due to changes in oxygen and carbon dioxide tensions in the blood may be aggravated because of the strong tendency of the circulating red cells to aggregate in these patients. These aggregates, which can periodically plug the terminal arterioles or cause the formation of microthromboses in the smaller venules and in the venous part of the capillaries, contribute to the development of stagnant hypoxia.[15]

SUMMARY

It has been pointed out that a comparison between the vascular changes in retrolental fibroplasia and in diabetes mellitus suggest a mechanism leading to the micro-angiopathy in diabetes mellitus. The concept of this mechanism is based on the pathophysiologic vasomotor reactions in response to variations in the oxygen and carbon dioxide tensions over a period of years.

SUMMARIO IN INTERLINGUA

Le Micro-Angiopathia in Diabete Mellite: Un Nove Concepto Relative al Mechanismo de su Origine

Es signalate que le comparation del alterationes vascular in fibroplasia retrolental con le alterationes vascular in diabete mellite suggere le existentia de un mechanismo que effectua le micro-angiopathia de diabete mellite. Le concepto de iste mechanismo es basate super le pathophysiologic reactiones vasomotor a variationes observabile in le curso de plure annos in le tensiones de oxygeno e dioxydo de carbon.

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The Basis for the Satisfaction Derived from Eating

Man eats in order to feel satisfied. He thinks little about the nutritive value of his food, in the selection of which the main question, unconsciously asked, is: "Is this food satisfying?"

Several factors no doubt combine to give this sense of satiety; chief among them is the physiologic activity of the digestive tract. Lack of food, with the accompanying rhythmic gastric contractions, gives rise to the sensation which is interpreted as hunger—even to hunger pains; while a full stomach, physiologically active, with its muscular and secretory functions fully unfolded, produces the opposite feeling, a sense of satisfaction. The food which gives this sensation in highest degree and longest is that which remains longest in the stomach and small intestine and demands of these organs greatest functional activity. Foods as a rule show the same behavior in this respect in both the stomach and the intestine, for those foods which remain longest in the stomach and call forth the greatest secretion of hydrochloric acid also remain longest in the intestine. For such foods a greater length of time is required in the intestine for the neutralization of the acid which comes from the stomach and therefore a longer time for the completion of digestion. The satiety value of an article of diet can therefore be measured in two ways: (a) by the length of time the food remains in the stomach and (b) by the amount of gastric juice stimulated by it.

From the book *Nutrition and Diet in Health and Disease* by James S. McLester, M.D., and William J. Darby, M.D., Ph.D. Philadelphia, W. B. Saunders Co., 1952, 6th ed., p. 130.

The Digestibility of Fats

Contrary to the lay opinion, fats are not poorly digested as is indicated by the high coefficient of digestibility of fat. Langworthy, in his studies on animals fats, found that the coefficients of digestibility range from 97 per cent for butter to 88 per cent for mutton fat. He observed that the presence of considerable quantities of fat in the diet (about 100 gm.) did not alter the digestibility of the other foodstuffs. For instance, the digestibility of the carbohydrate quota, independent of the kind of fat and of its amount, remained practically the same, about 97 per cent. The average coefficient of available energy from all sources was approximately the same (91 to 93 per cent), no matter what the kind of fat, or within the limits of the experiment, its amount. He concluded that fats do not appreciably influence the digestibility of the other food.

The interesting observation was made that beef fat differed from the other fats tested (lard, mutton fat, and butter) in that it often produced diarrhea when as much as 140 gm. were taken, whereas the other fats taken in like amounts did not show such a tendency.

These studies by Langworthy led to the generally accepted conclusion that fats of low melting point are more completely assimilated than those which are fluid only at higher temperature. A similar conclusion was reached in the studies of Matill and Higgins, but these authors, like Holt and his associates, pointed out that other factors also are of influence. They state that the type of glyceride in which this fat occurs in the food is an equally important factor in determining its digestibility.

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