EDITORIALS

THE RESPONSES OF THE SMALLER BLOOD VESSELS AND THE SERUM PROTEINS IN PREGNANT DIABETIC SUBJECTS

Conjunctival vessels have been under scrutiny for many years. They have been studied anatomically in an effort to learn more of the role of the capillaries in human disease. The conjunctiva represents a unique area of the body in which it is possible to study and trace the capillary bed from the arteriolar to the venular end. This observation can be made with a minimum of trauma so that the normal activity of the functioning components of the bed will not be disturbed. Recent anatomical studies have been reported by Grafflin and Corddry (1953), Bloch (1954) and Meighan (1956).

Bloch (1956) believes that some of the changes which take place in other small vessels of the body are similar to those which are observed in the conjunctival vessels.

The conjunctival vessels have been studied in patients with systemic hypertension (Lee and co-workers, 1951), (Glack and co-workers, 1949). Lee (1955), for example, noted changes in hypertension associated with vasoconstriction, abnormal reactivity to locally instilled epinephrine and permanent change in vascular topography in the form of elongation, coiling and tortuosity of the tissue capillaries. He also described vasoconstriction of the minute terminal arterioles and metarterioles.

According to earlier workers, Rollin (1934), Pletnava (1938) and Sedan-Bauby (1949), the condition of the conjunctival vessels is a reliable guide to the state of the circulatory system in individuals with systemic hypertension.

The conjunctival vessels in diabetics have been under close study for many years. The first reference to the occurrence of aneurysmal dilatations in the conjunctival vessels in diabetes is that of Bajardi (1901). He stressed their significance only when they were present in large numbers. A similar conclusion was reached by Keller in 1920 and Streiff in 1914. Keller (1920) also noted the presence of arteriolar constriction, venular dilatation and congestion of the conjunctival vessels. Ruedeman (1933) found no diagnostic changes in the diabetic conjunctiva and Waite and Beetham (1933) reported the results of an examination with a slit lamp of the conjunctiva of over 2,000 diabetic subjects and made no mention of microaneurysms. Koby (1930) noted considerable dilatation of the conjunctival veins in diabetics. Along the same line, Janert and Olbert (1955) found changes in the conjunctival veins which were significantly more frequent in diabetics than in normal subjects.

Ashton (1949) made preparations of post-mortem conjunctiva and found no evidence of microaneurysms while Friedenwald in 1952 concluded that about 5 per cent of diabetics with retinopathy showed saccular aneurysms in the conjunctival capillaries, an incidence which he considered to be somewhat higher than in nondiabetics. McCulloch and Pashby (1950) noted a very high incidence of conjunctival aneurysms in diabetics as did Weinstein and Forgacs (1951).

Conjunctival aneurysms do occur occasionally in healthy subjects but more frequently with advancing age in otherwise healthy elderly people. They have been described in many other nondiabetic diseases including syphilis, anemia, leukemia, renal disease and gout and particularly in patients with marked arteriosclerosis.

Cook reinvestigated this problem in 1954 and noted an increased incidence of saccular conjunctival aneurysms in the hypertensive patients in the diabetic group as compared to those without hypertension. He believes that the greater incidence of aneurysms in the diabetic as compared to the nondiabetic subjects may be explained by the greater incidence of hypertension in the diabetic group. Therefore he did not believe that one could postulate a specific conjunctival vascular lesion in diabetes analogous to that occurring in the retina.

Hoffmann and Kruger (1955) applied suction in measured quantity to the bulbar conjunctiva and found variations in capillary fragility, particularly in patients with hypertension. An astonishingly low abnormality of conjunctival capillary fragility in patients with diabetes was reported.

Ditzel and Moinat (see pages 307-23) have reinvestigated the changes which may take place in conjunctival vessels in normal patients during pregnancy and compared those with the alterations which occur in diabetics going through pregnancy. These investigators were aware of the earlier work of Landesman and his co-workers (1953, 1954) who had reported progressive constriction of the arterioles, reduction in blood flow, during pregnancy in normal individuals, particularly in the third

trimester. They were also stimulated to carry out this investigation by the earlier reports of Odell and his coworkers (1947) who had attempted to correlate intravascular erythrocyte aggregation as seen in the conjunctival vessels with changes in plasma protein which had been shown to occur during pregnancy. Ditzel and Moinat's studies are of particular interest because they show a definite association in protein changes during pregnancy and vascular and intravascular responses of the conjunctival vascular bed. Ditzel and Moinat observed the lateral bulbar conjunctiva with a stereo binocular ophthalmoscope. Usually they employed a magnification of forty-eight to sixty-four times. Occasionally, for short observations, they used a magnification of 144 times. The vessels were photographed, the speed of the linear velocity of the blood cells and the diameter of the vessels were measured. They graded the changes in the caliber of the arterioles, capillaries and venules and also observed intravascular erythrocyte aggregation as well as perivascular changes.

All of the alterations which Ditzel and Moinat observed in diabetics during pregnancy occurred also in normal pregnancies uncomplicated by diabetes. However, the changes took place earlier and with greater frequency in the diabetics than in the nondiabetics. The changes they noted included arteriolar constriction, venular distention, capillary tortuosity, edema, hyaline infiltration and erythrocyte aggregation. In normal pregnancy there was a definite alteration in blood proteins characterized by lowering of the total protein content, a progressive decrease of albumen and a slight increase in alpha-2 globulin. The most consistent change noted in the globulins appeared to be an increase in the beta lipoproteins during the last weeks of pregnancy. The same changes took place in the diabetic pregnancy, but the major fluctuations in the serum protein pattern occurred earlier in the pregnancy. Lipoproteins were involved particularly. These changes may have been related to the periods of poor control of the diabetes. After delivery, the different factions tended to return to their prepregnant level.

These results are quite stimulating. They may be related to altered hormone equilibrium occurring in pregnancy. It is possible that the conjunctival vessel changes may be reflecting alterations that are occurring in vessels of similar size elsewhere in the body. It may be that the vasomotor changes observed in the conjunctiva are the initial step leading to vascular degeneration in the vessels of similar size throughout the body.

Although earlier workers had observed an increase in severity of diabetic retinopathy during pregnancy, in the present series Ditzel and Moinat were unable to detect any significant increase in retinopathy associated with changes observed in the conjunctiva. It may be that the conjunctival changes are earlier ones and similar alterations cannot be picked up in the retina due to the lack of adequate magnification by the presently available methods for studying the retinal vessels and periretinal vessel tissue.

It may be that the vascular changes noted in the conjunctival vessels in pregnant diabetics are closely related to the protein changes studied. Possibly they are related to some other factors such as alterations in systemic blood pressure. Regardless, the technic employed by Dr. Ditzel and Dr. Moinat and their predecessors affords an opportunity to study the predisposing and disposing factors for the vascular degenerations that are responsible for some of the most serious complications of diabetes.

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MECHANICAL FACTORS IN THE LOCALIZATION OF ATHEROSCLEROSIS

No single cause has been found which adequately explains the complexity of the atherosclerotic process. Attention has been given to possible etiologic factors such as: race, heredity, age, sex, climate, diet, living standard, occupation, emotional stress, composition of the blood and mechanical factors. The demonstrable predilection of atherosclerotic plaques for certain fairly well-defined areas of the arterial system has given rise to many theories to explain this localization. The present paper proposes to review current progress in this area.

Among the regions with high incidence of arterial lesions are: the left middle cerebral, the left coronary, the splenic, and the aortic at four levels (at the coronary orifices, at the intercostal orifices, at the lumbar orifices and at the bifurcation).

A widely accepted explanation of the localization of tissue change is derived from its occurrence in regions subjected to extremes of pressure and stress. Leary[1] noted that the ascending aorta is momentarily subjected to greater stress than any other part of the arterial system with the closure of the aortic cusps. The pressure is then generalized and reduced by the elastic aorta. Leary believes that the stress on the proximal portions of the coronary arteries probably accounts for the apparently selective frequency of coronary sclerosis, though the systolic pressure occurring while their muscular branches are compressed is also an important factor. In his comprehensive review of the literature on arteriosclerosis in 1944, Hueper[2] cites other stress and strain hypotheses, such as the impact of the pulse wave causing a longitudinal and transverse stress while the action of the blood current creates oblique pressure. These antagonistic forces are supposed to cause primary intimal sclerosis. Sudden and marked fluctuations in pulse pressure have been suggsted as causing vascular tortuosities by producing excessive longitudinal tensions in the vascular wall.

Regions of arterial branching are frequent sites of pathologic change. Winternitz[3] has noted the frequency of intramural intimal circulation which anastomoses with the adventitial vasa in such areas. He showed that this development is accelerated in atherosclerosis. Duguid[4] suggested that the branches of a vessel drag on the main vessels during systolic lengthening causing splits and chinks and separation of the intima from the media.

In a recent article J. B. Duguid and W. B. Robertson[5] emphasize that the mechanical factors concerned in arterial function must be taken into account in the search for the genesis of atherosclerosis. The arteries are elastic tubes with muscle, elastic tissue and fibrous tissue. The arteries dilate with each pulse beat; the recoil is a function of the three elastic tissues, but the muscle tissue is mainly responsible for the contraction. These authors maintain that the muscle of the arterial wall has a greater degree of elasticity than the elastic and fibrous tissue cells. Impairment of the flexibility of the intima leads to the kind of structural disorganization seen in atherosclerosis.

Since thrombi of all sizes and kinds occur with astonishing frequency in the intimal and subintimal tissues, repair produces a fibrous overgrowth within the wall which interferes with ability to recoil. Cholesterol and other fatty debris are products of blood destruction. These can be accounted for by small hemorrhages recurring over long periods.

These authors insist that movement is the crucial factor in the cause of atherosclerosis. They agree with Harrison who has shown that cholesterol is merely an effective "marker" of structural damage. This interpretation likewise supports that of Aschoff, who believed that fat concentration in the food does not cause atheroma but modi-

fies the patches by determining the presence or absence of fatty change.

Points of fixation and surrounding tissue pressure have been variously interpreted as causative and inhibiting factors. Moschcowitz[5a] postulates a relation between impaired expansile mobility of vessels and the localization of lesions. His examples of such areas include: the intercostal vessels which fix the posterior wall of the aorta, sections of the abdominal aorta fixed against the rigid vertebral column, the portions of the dural vessels which lie within the bony framework, that portion of the carotid artery which traverses the canal in the temporal bone and along the cavernous sinus, the left coronary artery which is imbedded in firmer muscular wall than the right, and retinal vessels which are enveloped by the tension of the eyeball.

Other instances have been cited in which firm support of the arterial wall is credited with reducing the incidence of lesions. The internal carotid artery in the base of the skull is very rarely affected by atherosclerosis while the portions lying proximally and distally are notoriously prone to involvement (Hultquist[6] cited by Hueper[2] and Willis[7]). The portion of the anterior descending coronary artery which lies buried in the myocardium is spared from atherosclerosis while branches of the same artery lying in epicardial fat, and therefore not surrounded by appreciable tissue pressure, are affected by atherosclerosis (Geringer[8] cited by Willis[7]).

It becomes obvious that if these mechanical theories of causation are to be properly evaluated, mathematical means of calculating pressures at various points in the arterial system must be developed. This in turn would seem to be contingent upon the nature of the fluid transmitting the pressure and the characteristics of its flow.

Some of the fundamentals involved in any such systematization are presented by L. E. Bayliss[9] in his chapter on rheology of blood and lymph in *Deformation and Flow in Biological Systems* by A. Frey-Wyssling in 1952. Bayliss reminds us of Poiseuille's work in 1836. The variable factor of viscosity has required certain modifications in Poiseuille's law but in cases where the sheer stress is strong enough and in vessels with a radius greater than .01 cm., the flow obeys the law. This early law, which relates the amount of flow proportionately to the fourth power of the radius of the tube, contributes materially to an understanding of how the smallest arterioles and capillaries are able to withstand the pressures to which they are subjected and perhaps thereby to their ability to remain free of atherosclerotic manifestations.

Bayliss's chapter describes enough of the variable factors requiring compensatory calculations to justify his conclusion that "the whole problem of pressure-flow relation of blood needs much further investigation." Even sharper doubts are raised more recently by Jeffords[10] who attributes a cone-shaped form to the arteries instead of the cylindrical shape upon which Poiseuille's equation is based. The fact that blood is not a simple Newtonian or viscous fluid is also counted against the applicability of Poiseuille's equations.

Another pioneer in the reduction of physiological components to measurable terms is R. H. Woods[11] who applied the classical law of Laplace to hemodynamics in 1892. This law's applicability has recently been developed further by A. C. Burton.[12] The total tension in the blood vessel wall is given by Laplace's law as the hydrostatic pressure within it multiplied by the radius. Since the radius changes by a factor of 10,000 times as we pass from the aorta to the capillaries, its importance in determining the maintenance tension within the wall is apparent. Burton correlates the amount of elastic tension in the vessel wall to the amount of elastic tension required to hold the wall of the vessels against prevailing hydrostatic pressure of the blood. He sees the elastic tension in the vessel wall as the factor which makes possible the establishment of an equilibrium between active tension supplied by smooth muscle fiber and the pressure generated within the vessel. A third component of total tension suggested by Burton is the interfacial tension which could result from friction between the vessel wall and the fluid flowing through it.

Elastic diagrams of the aorta and the vena cava are produced by Burton by plotting the tension as the ordinate against the radius (or circumference) of the vessel using data on volumes at different pressures and Laplace's law. A further suggested application of Laplace's law is the calculation of the critical closing pressure of vessels as the active tension in dynes per centimeter divided by the unstretched radius of the vessel.

The application of Burton's development of Laplace's law to curved and branching vessels has been suggested by G. C. Willis[7] with the following modification of the law to meet these conditions:

$$T = \frac{P}{\frac{1}{R} + \frac{1}{r}}$$

(Where T is tension in dynes per centimeter, P is

excessive hydrostatic pressure inside the vessel over and above local surrounding tissue pressure in dynes per square centimeter, R is the radius of the arc made by a curved vessel in centimeters, and r is the radius of the vessel in centimeters.) Willis suggests that the calculation of increased tension T at various sites under experimental conditions, vascular anomalies, and in the ordinary atherosclerotic subject corresponds remarkably well with the localization of atherosclerosis.

Willis discusses the relation of the factors influencing the operation of this formula with respect to the mechanical factors influencing the localization of atherosclerotic plaques. (1) *Blood pressure within the artery.* Sites of localized hypertension have a high incidence of atherosclerosis. (2) *Surrounding tissue pressure.* Arterial segments supported by surrounding tissue pressure are sometimes spared. (3) *Radius of the artery.* Increase in radius resulting from dilation increases tension in the wall facilitating atherosclerosis. (4) *Curving of the artery.* The elongation of the outer curves of such arteries, occurring simultaneously with tangential stretching of the inner curves during the recoil following the cardiac systole, may account for the frequency of atherosclerosis in curved arterial segments.

Rodbard and co-workers[13] have studied the relationship of diameter of the vessel and stretching force to dilation. By measuring the force required to balloon segments of Penrose tubing under varying conditions they claim to have confirmed the principles set forth above by Burton. It is recognized by these investigators that their model departs in many ways from the situation which holds for blood vessels but confirms the fact that external support inhibits dilation and that increased radius caused by stretching facilitates further dilation.

Evidence which would seem to contradict the validity of the Penrose tube findings was compiled by Roy[14] whose tests with aortic segments showed that the degree of distensibility decreased in proportion to the weight applied. The studies of Roy and others on the elastic properties of different tissues and possible relationships of elasticity to structure and function are reviewed in another article by Burton.[15] He compares the varying structure of blood vessel walls in different parts of the body. Graduations of elasticity or distensibility appear to be achieved by variations in the proportions of endothelial cells, elastic tissue, smooth muscle, and collagenous fibers. This variety recommends a cautious use of any formulae designed to apply to all parts of the vascular system.

Discussion. Just as there are widely conflicting theories concerning the pathogenesis of atherosclerosis, there are divergent opinions concerning the importance of the mechanical factors and the methods of measuring them. Recent developments in the fields of biophysics have led to a rediscovery and re-evaluation of the laws and formulae of such physicists as Poiseuille, Laplace, and Hooke. The applicability of their theories to conditions within the walls of living arteries still remains to be convincingly demonstrated. Under normal conditions much still remains to be learned concerning the influence of the viscosity of the blood, the relation of actual shape of the blood vessel to the cone or the cylinder, the effect of the varying relation of potential and kinetic energy in various parts of the arterial system, and varieties of morphology of the blood vessel itself in different parts of the body. Pathologic conditions would introduce new factors including changes in the viscosity of the blood and muscle tone.

In spite of these imponderables and others yet undiscovered the high mortality from cardiovascular disorders places increasing urgency upon further research in this field. The demonstrable patterns of localization of the atherosclerotic process especially under hypertensive conditions suggest that the accumulation of further experimental and clinical evidence in confirmation or contradiction of mathematical laws and formulae will be highly desirable. Accumulations of experimental evidence may eventually lead to the discovery of new laws which could contribute materially to our understanding of the atherosclerotic process.

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IDIOPATHIC HYPOGLYCEMOSIS IN CHILDREN AND CENTRAL NERVOUS SYSTEM DAMAGE

McQuarrie and co-workers,[1, 2] in their reports of 1949 and 1953, called attention to a syndrome noted in children consisting of hypoglycemic episodes and convulsions. While they reported on thirty-eight cases with episodes of spontaneous hypoglycemia from various causes, the most fascinating of the group were twenty-five children with the condition that these authors referred to as "idiopathic hypoglycemosis." Investigation of this group of children revealed no specific organ, system or hormonal etiology, but the children were found to have increased sensitivity to injected insulin or impairment of the normal response to hypoglycemia. Some children had undergone partial or subtotal pancreatectomy without relief of symptoms. Nor did the histologic examination of the pancreas provide a clue to the disorder. An alpha cell abnormality, once suspected to be the etiologic factor, has as yet to be proved.

Eleven of the twenty-five patients included as idiopathic hypoglycemics showed a familial or hereditary factor in the etiology. Twenty-one of the twenty-five patients had the onset of clinical hypoglycemia under two years of age. There were eighteen boys and seven girls in the group. McQuarrie and co-workers stated that they saw only children who had the severest conditions, and undoubtedly a far greater number of children who have the less severe type are never diagnosed properly, recover spontaneously, or automatically adjust their own diets by voluntary food selection.

The presenting complaint in nineteen cases was convulsions, coma with convulsions in three, and staring, pallor, strabismus, tremulousness, and so forth in three. Fasting blood sugar levels as low as 10 to 15 mg. per 100 ml. of blood (macro) were noted. On corticotropin, 10 mg. every six hours, the fasting blood sugar levels could be maintained in the range of 50 to 90 mg. per 100 ml. and convulsions could be prevented. The nondiabetic type of curve was noted on the epinephrine and glucose tolerance tests.

While mental retardation and obvious brain damage were present in many of McQuarrie's patients, there were a few who were normal and later normoglycemic without treatment. In some instances the severely damaged infants were known to have developed normally before the onset of the convulsions.

Gall and Burke[3] reported two additional cases of hypoglycemosis, one in which the patient was a four and a half-month-old boy in whom a severe degree of cortical atrophy was demonstrated, and a second in which the patient was a severely damaged eight-month-old child in whom convulsions had been noted from the second day of life.

The beneficial effects of corticotropin therapy did not appear to be temporary in some of McQuarrie's cases. Of the cases reported by Gall and Burke, one child succumbed following progressive deterioration and convulsions at four and a half years of age, while the other child was severely damaged mentally though continually receiving corticotropin therapy.

All of the authors cited above call attention to the importance of obtaining fasting blood sugars in infants having convulsions, because salvation from severe damage of the central nervous system could be effected by corticotropin therapy. It is apropos to mention dangers to the brain of hypoglycemic episodes from overdosage of insulin inasmuch as resultant damage to the brain would be the same.

Though no protocols have been published in any of these above-cited cases many authors have demonstrated changes in the brain consequent to insulin shock therapy or hypoglycemic episodes.

Baker[4] in 1939 subjected rabbits to repeated insulin shock insults and killed the animals at various time intervals during the study. He noted that nerve cell damage did occur, but was by no means as striking as cerebral hemorrhage, areas of demyelinization, encephalomalacia and glial reaction. The changes were thought likely to be only temporary in the brains of animals subjected to one or several hypoglycemic episodes. Baker suggested that cerebral damage in hypo-

glycemia might be due to qualitative circulatory disturbance, inasmuch as blood reaching the brain is deficient in the proper nutritive materials.

Heberden and Friedlander[5] in 1955 reported pathologic changes in the brain of a two-year-old diabetic child who had suffered from prolonged overdosage with insulin and who finally succumbed to convulsions many months later. In this same child ventricular dilatation and cortical atrophy were suspected following neurologic, electro-encephalographic and pneumo-encephalographic studies.

Numerous authors were cited by Heberden and Friedlander in a discussion of the histopathologic changes in the brain associated with recurrent and prolonged hypoglycemic episodes. Gross vascular lesions, complete necrosis of nerve cells, and encephalomalacia of the cortex, thalamus, and caudate and lenticular nuclei occurred. Lesions of the basal ganglia similar to effects of severe anoxia, carbon monoxide poisoning, cardiac arrest and status epilepticus have also been described as neuropathologic changes in hypoglycemic deaths.

Heberden and Friedlander concluded that coma up to three hours can be associated with a lack of demonstrable brain damage and that the level of blood sugar seems to bear little relationship to the duration of coma. A progressive rise of the blood sugar is not necessarily accompanied by a return to consciousness.

In diabetics, use of the long-acting insulins has, in a sense, added a further threat of hypoglycemic coma because of the insidious approach of the coma and the sustained action of the agent.

Experimentally, hypothermia and barbiturates have been noted to protect animal brains from hypoglycemic damage. Cortisone and corticotropin have been recommended to alleviate the prolonged hypoglycemia.

It is generally accepted that nerve cells require glucose for oxidative processes and that the cells themselves have meager glucose reserves. Hence, the cells depend on blood glucose to a large extent.

Those of us treating children, therefore, must be particularly alert to the hazards of hypoglycemic episodes, whether from administration of insulin or from other causes, because the immature central nervous system is more susceptible to convulsions and perhaps to permanent brain damage than the mature central nervous system.

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Max Rubner
1854-1932

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Few people have made contributions to the field of metabolism comparable to those of Max Rubner. His development of the Isodynamic Law and the Law of Surface Area, and the determination of the calorie equivalents of foodstuffs along with other fundamental work, gave impetus to studies of energy metabolism.

Max Rubner was born in Munich on June 2, 1854. He received his early training under Carl Voit in Munich. During this time he was associated also with Pettenkofer. Voit and Pettenkofer had recently developed a method of estimating carbon dioxide, and this procedure enabled Rubner to carry out his studies. He also spent a year with Carl Ludwig at Leipzig.

When Rubner was twenty-four he embarked on experi-