COMMUNICATIONS

HAEMORHEOLOGICAL FACTORS IN THE DEVELOPMENT OF DIABETIC MICROANGIOPATHY*†‡

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THERE is good supporting evidence that haemorheological changes in the microvasculature play a major and important role in the development of diabetic microangiopathy.

(1) *The microaneurysms*—the most characteristic lesion in the diabetic retinopathy—are almost exclusively confined to the venous part of capillaries and small venules (Ballantyne and Loewenstein, 1943, 1944; Friedenwald, 1948, 1950; Ashton, 1949, 1950).

(2) *Venous changes occur before arteriolar changes in the retina of diabetics* (Ballantyne and Loewenstein, 1943, 1944; Ballantyne, 1945, 1946; Jensen, 1949; Walker, 1950; Lundbaek, 1953).

This means that the initial changes in diabetic retinopathy take place in that part of the microvasculature which has the slowest linear rate of flow and in which the shearing forces are the least.

(3) *The microaneurysms are by no means specific to diabetes.* Identical microaneurysms with similar hyaline thickening, lipid and mucopolysaccharide staining may be found in a variety of unrelated conditions associated with prolonged periods of retinal venous stasis (Ashton, 1951, 1962).

In cases of central retinal venous occlusion the microaneurysms are particularly numerous (Loewenstein and Garrow, 1945; Ballantyne and Michaelson, 1947; Becker and Post, 1951; Ashton, 1951; Wise, 1956, 1957). In a case of macroglobulinaemia, Ashton (1962) found more microaneurysms in the retina than in any previous study he had made.

The mechanisms of formation of microaneurysms in retinal vein occlusion and in macroglobulinaemia appear fairly clear and differ only slightly from each other. In retinal vein occlusion the intravascular rise in venous tension produces stasis and dilatation of the veins above the obstruction, which in turn causes anoxia of the venular and capillary walls, focal mural degenerative changes of the basement membrane, microaneurysm formation on the venous side, and a breakdown of the blood-retinal barrier (Ashton, 1951; Wise, 1956). Thus the two factors, increased capillary pressure and anoxia, appear to be responsible for the capillary injury.

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In macroglobulinaemia the mechanism of the microaneurysm formation is related to the presence of macroglobulins in the circulation. The plasma macroglobulins (with sedimentation constants of 19S or more and molecular weights about 1 million) make the blood highly viscous, and produce marked aggregation of red cells, extreme decrease in linear rate of flow and stasis in the periphery of the retina, anoxia of the venular and capillary walls, focal mural degenerative changes, and microaneurysm formation. The increase in viscosity probably leads to a rise in pressure within the retinal circulation and again the combination of increased capillary pressure and anoxia appears to be the factor responsible for microaneurysm formation (Ashton, Kok, and Foulds, 1963). That the retinopathy thus formed is due to the presence of macroglobulins is strongly supported by the repeated observation of reversibility of the retinopathy after plasmapheresis (Schwab, Okun, and Fahey, 1960; Coyle, Frank, Leonard, and Weiner, 1961; Conway and Walker, 1962; Kok, Whitmore, and Ainsworth, 1963).

The earliest possible change observed in the retina of young diabetics is a general dilatation or fullness of the veins (Ballantyne and Loewenstein, 1943, 1944; Ballantyne, 1945, 1946; Jensen, 1949; Ashton, 1953; Lundbaek, 1953; Larsen, 1960). Walker (1950) and Hardin, Jackson, Johnston, and Kelly (1956) found venous engorgement without other signs of retinopathy in 13.3 and 10 per cent. respectively. Since venous dilatation and evidence of venous stasis also appear to precede the formation of microaneurysms, exudates, haemorrhages, and neovascularization in diabetes, it is of importance to elucidate the mechanism for this early change. Histological studies have not revealed changes in the larger or central retinal vein which can explain the venous stasis (Larsen, 1960).

In 1952, while working at the Joslin Clinic in Boston, I had the opportunity to observe an exceptional case.

In a 15-year-old, poorly-regulated diabetic boy, I observed the development of early diabetic retinopathy (*i.e.* dilatation of venules and microaneurysms) in one eye in immediate time-relationship to the occurrence of central retinal vein occlusion in the other eye and again suggesting venous stasis in the retinal circulation as a common pathogenetic factor in these two conditions (Ditzel and White, 1956). It was observed, however, that the veins and venules were dilated not only in the retina but also in the bulbar conjunctiva. In this tissue the small blood vessels and the microcirculation can be studied under a magnification of $100\times$ in contrast to the $15\times$ magnification provided by the ophthalmoscope. As the diabetes became regulated, it was observed that the venous changes both in the retina and in the bulbar conjunctiva slowly reversed.

These observations suggested that the dilatation of the venules and veins in diabetes was a functional change, possibly a loss of tone leading to marked slowing of venous flow. We found this observation of significance and it gave impetus to a series of haemorheological investigations designed to elucidate the mechanism of prolonged venous stasis in the microcirculation of diabetics. These studies have shown that the venous stasis and impaired capillary-venous flow are produced mainly by three factors:

- (i) Pathophysiological functional changes of the vessel walls, leading to a redistribution of flow and leakage of plasma components through the small venules;
- (ii) Aggregation of erythrocytes;
- (iii) Increased whole blood viscosity.

(i) *Pathophysiological Functional Changes in the Vessel Walls.*—Although considerable variation exists in the arrangement of the smaller blood vessels in the bulbar conjunctiva from subject to subject, certain characteristics of the vessel walls and the blood flow are invariably the same. The picture of the combined vascular and haemorheological pattern of healthy children or young individuals can be fairly well defined by these characteristics. The arterioles are often found to enter the conjunctiva parallel to larger venules. The capillaries can be seen to branch from the tip of the arterioles. Besides the “true” capillaries it is often possible to follow a terminal arteriole more directly into a venule through a non-anastomosing vascular channel, an arteriolar-venular communication, which should not be mistaken for the so-called arterio-venous anastomoses (Fig. 1). Under normal conditions the ratio between the diameter of the arteriole and that of the accompanying venules is relatively constant at 1 : 3 to 1 : 2 (Grafflin and Corddry, 1953; Ditzel and Sagild, 1954; Meighan, 1956; Bloch, 1956; Ditzel and Duckers, 1957; Ditzel and Moinat, 1957; Ditzel, 1962).

FIG. 1.—“Arteriolar-venular communication” and arterio-venous anastomosis. The latter is a rare finding in the vascular bed.

In young diabetics, besides the normal vascular pattern, two fairly well-defined functional deviations from the normal could be observed; these are designated Vascular Pattern-Change I and Vascular Pattern-Change II (Figs 2 and 3, overleaf). These responses apparently manifest themselves as different stages in a complex reaction maintained by some blood- or tissue-borne factor in the diabetic metabolic disturbance (insulin deficiency ? lactic acid ? $p\text{CO}_2$? pH ? growth hormone ?).

Most often (approximately 45 per cent.) Vascular Pattern-Change I occurs; this is characterized by a general but not universal engorgement of the venules, occasionally with fusiform sacculations in collecting venules. There occurs some redistribution of flow from the “true” capillaries to the arteriolar-venular shunts.

The arteriolar/venular diameter ratio decreases. Concentration of the passing blood can occasionally be observed in smaller venules, the linear rate of blood flow decreases. As the venules become engorged, evidence of microscopic oedema is observed (Ditzel and Sagild, 1954; Ditzel and Duckers, 1957; Labram, 1959; Ditzel, 1962).

Other cases show Vascular Pattern-Change II, which is characterized by arteriolar constriction. The direct arteriolar-venular communications are open and much blood appears to be shunted through these channels (Ditzel and Duckers, 1957). Most “true” capillaries appear free of circulating red cells, leaving the tissue ischaemic. The most harmful effects of the loss of venular tone are a decrease in the linear rate of blood flow

FIG. 2.—Change from Vascular Pattern-Change I to Normal Vascular Pattern in a juvenile diabetic. Note disappearance of venous congestion. (Magnification approx. $45\times$.)

FIG. 3.—Conjunctival vascular bed, showing Vascular Pattern-Change II in a young diabetic. Note tissue ischaemia. Most true capillaries are closed, but the arteriolar-venular communications are open (pc). (Magnification approx. $70\times$.)

through the venules and the development of pathological permeability. The continuous seepage of plasma components through endothelium leads to oedema and after some time to hyaline-mucoid changes in the tissue (Ditzel and Duckers, 1957; Ditzel and Moinat, 1957). The most harmful consequence of the prolonged constriction of arterioles and capillaries and shunting of blood would be hypoxia and malnutrition. Because the small blood vessels, beyond the branched arterioles, are an integral part of the tissue in which they are embedded, the degeneration may vary in intensity and appearance from tissue to tissue. It is conceivable that the vascular damage, the functional impairment, and the subsequent tissue response are greatest in tissues with high cellular metabolism (retina),

in tissues in which damaged small blood vessels cannot be replaced (kidney glomeruli), and in tissues in which the capillaries form the only vascular component (kidney glomeruli, inner nuclear layer of the retina). Although the small vessel degeneration might be general, the kidneys and the retina would be more strongly affected. In diabetes, the "complications" which appear after long duration of the condition are those affecting the kidney and the retina. Not until recently has the similarity in the changes taking place in these and other tissues been recognized.*

If these deviations are important in the pathogenesis of diabetic microangiopathy, the following requirements must be satisfied:

- (1) The pattern changes must occur more frequently in diabetics than in a comparable group of non-diabetics.
- (2) Their incidence must increase with the duration of the diabetes.
- (3) Their incidence must be greater in diabetics with retinopathy and nephropathy.

All three requirements have been shown to be fulfilled for the pathophysiological response changes (Ditzel, 1956; Ditzel and Duckers, 1957; Ditzel, Sargeant, and Hadley, 1958; Labram, 1959; Rees, Camerini-Davalos, Caulfield, Lozano-Castañeda, Cervantes-Amezcus, Taton, Pometta, Krauthammer, and Marble, 1964).

These response changes could be seen even in cases of recent onset. In a selected group of children of young diabetic mothers there was a correlation between the vascular change in the bulbar conjunctiva and the abnormality of the glucose tolerance test (Ditzel, White, and Duckers, 1954; Ditzel and Duckers, 1957). This same group of children was re-examined 3 years later, and among sixteen cases which had previously shown Vascular Pattern-Change I, three had developed symptomatic diabetes (Ditzel, White, and Sargeant, 1957). Rees and others (1964) demonstrated reversibility of the venular dilatation in the conjunctiva of young newly-diagnosed diabetics after insulin and dietary treatment had been started. By measuring the same vessel segments over the day in 100 young diabetic and non-diabetic subjects, we have shown that the diurnal variations in venule diameter were far greater among the diabetics than among the non-diabetics (Ditzel and Camerini-Davalos, 1958; Ditzel, Beaven, and Renold, 1960; Ditzel, 1962; Rees and others, 1964). With increasing duration of diabetes, the venular anomaly tended to become fixed, and it was essentially irreversible in the majority of diabetics of 15 years' standing or more (Ditzel and others, 1960).

With these new observations at hand, ophthalmologists have started to make more exact studies of the retina in young people with diabetes of recent onset, patients whom previously they rarely saw. By so doing, Larsen (1960) reported that fullness or dilatation

* For functional circulatory studies of the skin of diabetics: see Megibow, Pollack, Megibow, Bookman, and Osserman (1949); Megibow, Megibow, Pollack, Bookman, and Osserman (1953); Mendlowitz, Grossman, and Alpert (1953); Bárány (1955); Sigroth (1957).

Vessel pathology of the conjunctiva: Funahaski and Fink (1963); Pieri and Scarpelli (1966).

Peripheral nerves: Fagerberg (1959).

Heart: Blumenthal, Alex, and Goldenberg (1960).

Skin and muscles: Goldenberg, Alex, Joshi, and Blumenthal (1959); Aagaens and Moe (1961), Pedersen and Olsen (1962); Handelsman, Morrione, and Ghitman (1962), Zacks, Pegues, and Elliott (1962).

Inner ear: Jørgensen (1961).

Placenta: Burstein, Berns, Hirata, and Blumenthal (1963).

Mucosa of the stomach: Angervall, Dotevall, and Lehmann (1961).

Pancreas: Lazarus and Volk (1961).

Gingiva: Stahl, Witkin, and Scopp (1962).

Retina: Ashton (1958).

Kidney: Thomsen (1965).

of the retinal veins might be seen, even from the onset of diabetes. During the first years of the disease the fullness of the retinal veins seems to be related to the degree of regulation, but venous dilatation is later apt to be more permanent. Jütte (1960, 1964) carefully measured the retinal veins by the method of Lobeck and found them to be dilated in 43 per cent. of 100 juvenile diabetics. The dilatation increased with the duration of diabetes over the first 10 years. An increase in vein diameter occurred during periods of poor regulation, but was reversible. In many juvenile diabetics, Jütte as well as Thiel (1956, 1959), also observed dilatation of the smaller venules (rubeosis retinae). Both Larsen and Jütte agreed that the venous dilatation appeared to be due to a pathophysiological response and that it led to prolonged venous stasis. Thus these response changes appear to be of a more generalized nature.

One may ask whether similar response changes take place in the kidney glomeruli, but for obvious reasons such changes are not observable. Indirect evidence for a functional disturbance in permeability might be obtained by measuring the glomerular filtration rates in young diabetics with Vascular Pattern-Change I in the conjunctival vascular bed. We have recently reported such a study, using the radio-vitamin B₁₂ method of measuring glomerular filtration rates and have found that those in young diabetics without evidence of nephropathy were abnormally high in comparison with a group of healthy subjects (Ditzel, Schwartz, and Skovborg, 1966) (Fig. 4). Further studies using this technique are in progress.

FIG. 4.—Glomerular filtration rate measured by the radio-active vitamin B₁₂-method in twelve control subjects and eighteen young diabetics without evidence of diabetic nephropathy and short duration of disease. The difference in distribution is highly significant ($P < 0.01$).

If similar vascular response patterns are more generalized in distribution, it becomes necessary to explain why no microaneurysms develop in the bulbar conjunctiva. As was pointed out by Ashton (1949), capillary microaneurysms are seen only in the retina and possibly the glomeruli of the kidneys (Ashton, 1958); this

suggests that their formation is related to local factors in the retina, such as high cellular metabolism, absence of lymphatics and perivascular connective tissue, high capillary pressure, and fluctuating ocular tension (Poulsen and Larsen, 1961). It also has to be explained why no retinopathy is seen in all cases showing Vascular Pattern-Change I. Here the duration of diabetes is important, because it allows more time for the harmful influence of venous stasis to take place. Two additional changes in flow properties appear to add to the decrease in venous-capillary flow, namely intravascular erythrocyte aggregation and the blood viscosity.

(ii) *Erythrocyte Aggregation*.—The presence of prolonged significant erythrocyte aggregation in diabetic subjects has been described by several workers (Bloch, 1956; Ditzel, 1956; Weis-Fogh, 1957; Ditzel, 1959; Ditzel and Moinat, 1959; Rees and others, 1964). In short-term diabetes the degree of aggregation varies according to the disturbance in the carbohydrate metabolism or complicating factors (infections), and in long-term diabetes it is persistent. It is associated with a significant decrease in the linear rate of flow particularly in the post-capillary venules. Large heavy aggregates in static venous channels tend to sediment to the lower side of the vessels (Fig. 5).

FIG. 5.—Heavily aggregated flow with settling of blood cell masses in collecting venules in a 30-year-old man who has suffered from diabetes for 19 years. (Magnification approx. $45\times$.)

The intravascular erythrocyte aggregation is formed by an interaction between the red cell membrane and an increase in the content of α_1 -, α_2 -, and beta-globulins as well as fibrinogen. We have also found a correlation between the degree of aggregation and the total amount of lipoproteins (Ditzel and Moinat, 1959). Evidence for a coating of the erythrocytes consisting of α_2 -globulin and fibrinogen has been found in diabetic subjects with a markedly altered plasma protein pattern and marked aggregation, but not in cases with smaller deviations in protein patterns (Ditzel, 1955, 1959).

In 145 young diabetics a relationship was found between the incidence and degree of severe intravascular erythrocyte aggregation and the degree of microangiopathy. Since 20 per cent. of the diabetics showing no clinical evidence of retinopathy or nephropathy

had intravascular erythrocyte aggregation, the rheological effect of this change may be important in the development of diabetic microangiopathy (Fig. 6).

FIG. 6.—Relationship between intra-arteriolar erythrocyte aggregation *in vivo* and diabetic microangiopathy.

(iii) *Blood Viscosity*.—Because of the evident similarity of venous-capillary changes in the retina of macroglobulinaemia and diabetes, Skovborg has begun a study of blood viscosity in diabetics. Skovborg, Nielsen, Schlichtkrull, and Ditzel (1966a, b) found increased viscosity in forty non-acidotic long-term diabetics as compared with 25 normal controls. The haematocrit-corrected full-blood viscosity (measured with the Wells-Brookfield viscometer) was 20 per cent. higher in the diabetics, and was significantly correlated with the α_1 , α_2 , and β -globulins and fibrinogen concentration. In short-term diabetics without evidence of retinopathy and nephropathy, the haematocrit-corrected viscosity is not greater than in normal subjects in the present study (Fig. 7). The series is still rather small but these findings indicate that high blood viscosity is a late phenomenon, which may assist the progress of already-established retinopathy.

FIG. 7.—Shear-stress and haematocrit in diabetics and control subjects at shear rate 23 sec.⁻¹.

Summary

Haemorheological changes appear to play an important role in the development of diabetic microangiopathy. The importance of pathophysiological response changes leading to slowing of venous flow and the redistribution of flow in the microvasculature is emphasized. Intravascular erythrocyte aggregation and increased blood viscosity both aggravate the tendency to stasis in the venous microcirculation of diabetics.

This emphasis on haemorheological factors should not detract from the importance of other intracellular changes which occur in the altered metabolic-hormonal environment. The pathogenesis of diabetic angiopathy is a problem of great complexity.

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