Pathogenesis of diabetic microangiopathy

Neither retinopathy nor nephropathy is found at the onset of diabetes. Thickening of the capillary basement membrane, an early change, is first detectable by electronmicroscopy of the glomerulus after 1–2 years of juvenile-onset diabetes. Similar changes have been described in skeletal muscle and in myocardial and retinal capillaries in diabetic animals and man.

As these microangiopathic changes advance capillary microaneurysms develop in the retina, endothelial cells and pericytes are lost, and later new vessels and connective tissue form and extend into the vitreous fluid (retinitis proliferans). In the kidney the glomeruli become distorted, with proliferation of the mesangial connective tissue; Kimmelstiel-Wilson nodular lesions form; and there is sclerosis and narrowing of the afferent and efferent arterioles. Sclerotic changes also occur in the vessels in nervous tissue, with segmental demyelination, but the precise link between the two is uncertain. Microvascular changes in the legs predispose directly to gangrene; microangiopathy of the vasa vasmorum may also be important in producing large artery disease. Myocardial microangiopathy leads to scattered myocardial fibrosis, and when blood flow is also impaired by atheroma it may predispose to myocardial infarction.

The evidence that all these lesions are secondary to dys- function of the islet cells is overwhelming. The same lesions are found in secondary diabetes in animals and man, and in the latter improved metabolic control from treatment slows their development. In inbred rats made diabetic with alloxan or streptozotocin the glomerular changes can be reversed by transplanting the diabetic kidney into a normal host or by curing the diabetic state by transplantation of pancreatic islet cells.

How does diabetes predispose to all these microvascular diseases? The answer is still uncertain, but the proceedings of a recent conference have helped in piecing together a fascinating if complicated jigsaw. The normal basement membrane is composed of collagen-like glycoproteins with the carbohydrate subunits linked to hydroxylsine and asparagine residues. Hyperglycaemia probably leads directly to increased enzymatic incorporation of carbohydrate into the basement membranes, but whether other chemical changes occur is still disputed. Westberg has suggested that a reduction in (cross-linking) cystine residues may make these membranes leakier than normal. Diabetic capillaries undoubtedly leak plasma proteins excessively, and the size of the leak seems to depend on both the duration and quality of diabetic control. Poor control in previously well-controlled diabetics increases the leakage-rate of plasma proteins from the circulation and doubles the secretion of albumin in the urine. The passage of plasma proteins into and through the capillary wall depends both on the capillary structure and on the hydrostatic pressure. In diabetic rats if the filtration rate per nephron in one kidney is increased by removing the other, protein leakage rises and glomerular damage accelerates rapidly. Conversely, constriction of the renal artery in diabetic rats and fortuitous stenosis in a patient retarded the glomerular disease on the affected side. Systemic hypertension increases vascular leakiness in non-diabetics and may well accelerate the progression of diabetic microangiopathy. Conversely, in diabetics with proteinuria antihypertensive treatment may delay the development of renal failure.

Even when the systemic arterial pressure is normal, overall blood flow (and therefore capillary hydrostatic pressure) is raised in the resting forearm, kidney, and retina of diabetic patients. This increased flow through the capillary bed is patchy: in some areas of the retina (which is most open to study) the arteries, capillaries, and veins are all dilated, while in others perfusion is apparently grossly reduced. The explanation lies in part in the absence of any sympathetic nerve supply to the retinal vessels: blood flow depends on the calibre of the ophthalmic artery and on vascular responses to changes in the blood gases. A local fall in PO2 and rise in PCO2 leads to local dilatation and increased flow. Normally this ensures adequate and homogeneous perfusion of the capillary bed. Nevertheless, in diabetic patients neither the endothelium nor the perfusing blood is normal and such local responses are therefore impaired.

As with the retina, the anatomy of the glomerulus partly determines the type of damage that it suffers in diabetes. The glomerular endothelium lies on one side of the basement membrane, which on the other side is covered by the foot processes of the epithelial cells. A third type of cell, the mesenchymal mesangial cell, also lies on the endothelial side of the basement membrane and bears the brunt of the vascular...
damage. In rats after 10-16 months of diabetes progressive thickening of the mesangium leads to sclerosis of the glomerular tufts. Using human IgG aggregates Mauer et al.24 found that the mesangial cells were unable to clear immune complexes which normally travel between them to the hilus and out of the glomerulus via the abutting distal tubule. In diabetic animals deposition of glycosen and the development of vacuoles consistently occur in the distal tubule and the macula densa. Hence Mauer et al suggest that in diabetic nephropathy not only is there an increased flow of macromolecules into the subendothelial space but also some obstruction to their outflow from the base of the glomeruli in the region of the macula densa.

Complex changes also occur in the blood of diabetic patients. Firstly, they have abnormally high concentrations of the haemoglobin HbAIC, which differs from normal in having added glucose and mannose at the end of the β chain and in its greater avidity for oxygen. In well-controlled diabetics this is partly offset by higher red cell levels of 2,3 diphosphoglycerate (2, 3 DPG). Nevertheless, during the treatment of ketoacidosis a fall in the plasma phosphate concentration lowers the 2,3 DPG; Ditzel and Ditzel believes that this greatly augments tissue hypoxia.

Secondly, diabetics show an increased tendency for their red cells to aggregate, probably related to increased concentration of "acute-phase" proteins and decreased serum albumin. These changes may be caused by the action of other hormones on the liver in the absence of insulin. The increased red cell aggregation alters the flow characteristics of blood, particularly in small vessels. The rise in the apparent viscosity interferes with local autoregulatory mechanisms—so important in the retina.

All this is by no means the whole story. Local tissue trauma may also be important in determining the site and nature of the lesions, since the cellular response to injury is grossly abnormal in experimental diabetes. Diabetics' platelets show an increased sensitivity to aggregation from adenosine diphosphate and arachidonic acid (a precursor of prostaglandins). This sensitivity is probably related to increased levels of von Willebrand's factor, which in turn may be due to an excess of growth hormone—whose concentration is raised three- to four-fold in juvenile diabetics. Finally, diabetics have a decreased fibrinolytic activity of blood, possibly owing to a raised level of an α-2 macroglobin, a plasma protein that inhibits fibrinolysis.

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Rugby injuries to the cervical cord

June may seem an inappropriate month in which to consider rugby injuries. Yet a recent inquest has highlighted the danger of new techniques in the game, and the summer may be an appropriate time to consider whether any changes in the rules are needed.

The game of rugby has evolved slowly as a hard contact sport and some injuries are inevitable. Nevertheless, when these are severe enough to cause permanent disability or death we have a duty to examine both their incidence and causes. We know that injuries to the cervical cord in rugby footballers are rare, but exact figures of the incidence are hard to find. In Ireland between 1959 and 1963 there were estimated to be five serious injuries to the cervical spine, two of them fatal, with 10 000 players turning out per season. In Scotland between 1955 and 1965 only one fatal injury to the cervical spine was recorded in a playing population of 11 000. The Welsh Rugby Union recorded two fractures of the cervical spine, one resulting in complete permanent paralysis and the other with partial residual paralysis, occurring between 1945 and 1964 in a population of 18 000 to 20 000 players. A recent article from South Africa has described 20 patients who sustained cervical cord injuries while playing rugby. The patients came from an estimated total of 44 766 senior and schoolboy players and the injuries occurred over 12 years. Six players died, their ages ranging from 14 to 43. The injuries fell into two groups: those sustained while tackling (60%) and those while scrummaging (40%). The nature of the tackling injuries varied, including fracture-dislocation of the cervical spine, compression fractures of vertebral bodies, fracture of the neural arch of C2, fracture of a spinous process, and two in which there was no radiological evidence of injury. The injuries in the scrumming group were more uniform: seven out of eight sustained a fracture-dislocation of the cervical spine with bilateral locking of the facet joints, while the other had locking on one side only. This injury is caused by a combination of flexion and rotation of the cervical spine and is likely to lead to paralysis and death. Typically it occurs when the scrum collapses, with the front row being the main victims.

Tackling and scrumming are integral parts of rugby, and any dramatic change in the laws (such as three- or five-man scrums) would drastically alter the game. Sound tackling techniques should be taught and ingrained at school with specific attention to the position of the head. Rigorous refereeing is needed when there is dangerous tackling, particularly with the high, stiff arm—a very dangerous foul—

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