DISCUSSION
In the present series of work, findings which have been obtained with respect to retinal vessels in alloxanised (diabetic) rabbits with definite hyperglycaemia, glycosuria and acetoneuria as stated already showed that compared to normal and pre-diabetic rabbits, the alloxanised (diabetic) group shows vascular dilatation specially of the capillaries and the venules, the thickening of the basement membrane and microaneurysmal dilatations. The examination of the trypsin digest flat mount retinal specimen reveal dilatation of the capillaries with loss of pericytes in the alloxanised (diabetic) group. The microaneurysms which appear as spherical structures were chiefly in the inner nuclear and outer plexiform layers of the retina. This is in agreement with findings of Ashton (1949), Friedenwald (1950), Bloodworth (1962). Bloodworth in 1962, conclusively show that half of the aneurysms was situated in the superficial capillary plexus located in nerve fibre layer, ganglion cell layer and inner plexiform layer whereas the other half was situated in the deep capillary network located at the boundary between the inner nuclear and outer plexiform layers of retina wherefrom bulge into the outer plexiform layer. Bellantyne (1946). Ashton (1949), Friedenwald (1950), Bloodworth (1962) are unanimous in their observations that some microaneurysms are thinwalled but others are thickwalled. In the present series of cases of
alloxanised (diabetic) rabbits they appear to be thickest wall.
No haemorrhage nor any neuronal degeneration could be seen like that observed in human retina as studied by Bloodworth (1962).
Wolter (1961), Bloodworth (1962) observed extensive degeneration of nervous elements of the retina in case of diabetic retinopathy. In fact, Wolter (1961) considered these neuronal degeneration is responsible for the loss of vision in diabetic retinopathy. Bloodworth (1962) was so much dogmatic about the constancy of the degenerative changes in the retina that he considered it, the primary and fundamental event in the pathogenesis of the diabetic retinopathy. In alloxan diabetes of rabbits as studied, features do not corroborate their findings. It may possibly be due to the fact that the course of the metabolic events in diabetes due to pancreatic insufficiency and that produced by alloxan are not the same. In the cases of pancreatectomised rabbits no vascular change is shown. It may in all probability be due to the long continued diabetic state in human cases which precipitates the early vascular changes not only in the retina but also in the other capillary system of the kidney, heart, etc. In the case of the pancreatectomised rabbits they were sacrificed very early before vascular changes had any opportunity to occur. There are very few cases on record in which retinopathy developed which was reported by T.Y. Burton, T.P. Kearns and E.H. Ryneerson (1957, Proc. Mayo. Clin. 32, 735). The rarity of development of retinopathy
in pancreatectomised condition is further supported by the fact that patients with pancreatic diabetes have a far lower incidence of diabetic retinopathy than essential diabetes, as has been reported by D. Sevel, J. H. Bristow, S. Bank, I. Marks, P. Jackson (Arch. of Ophthal, 86:3, 245–250, Sept. 1971). The low incidence could be due to the fact that the majority of pancreatic diabetic die at a fairly early age and do not have diabetes for long enough. Recently it has been suggested that pancreatic diabetes are in fact being protected against retinopathy because of either a relatively deficient growth hormone level or a relative hypolipidemia which has been reported by Vinik AI, Joffe BI, Joubert SM. et al (J. Clin. Endocr., 31:86–88, 1970) and Joffe BI, Krut. L, Bank S, et al (Metabolism, 19:87–90, 1970). The situation and nature of the exudates as revealed in this study are consistent with the findings of earlier workers like Ballantyne (1946), Ashton (1949) and Bloodworth (1962). Dolger (1947) found an average duration of ten years of diabetes before retinopathy appear. He found after his follow up of diabetic cases for 6 to 22 years that none is free of retinal hemorrhage and he remarked that vascular changes is inevitable provided the diabetes lives long enough. He further remarked that control of the diabetic condition by present day treatment fails to avert the development of accelerated vascular damage which was regarded by him as an associated phenomenon of this
disease rather than as a complication. It was also observed by Waite and Beethan (1935) and Whittington and Lawrence (1958) that the only danger from insulin lies in withholding it. Gelis (1952) however remarked differently in as much as he opined that larger dose of insulin are contributing factors in the development of diabetic retinopathy. He went so far as to blame insulin for the rise in the incidence of retinopathy from 8.3% in 1921 to 30% in 1944. In the present series of alloxanised diabetic rabbits shunt vessels, focal acellular-rity were not observed although in diabetic patients these are the well recognised features as reported by K. Kojima, Y. Okochi and W. Ueda (Folia ophthal. Jap. 20: 178-188, Feb. 1969).

The formation of microaneurysms is also not a constant feature in these cases. The microaneurysms seem to be formed by biochemical changes in the basement membrane and loss of mural cells together with reactions of Muller's fibres and astrocytes. This is probably due to disturbed glycolysis through the pentose-phosphate shunt mechanism which is the usual course of carbohydrate metabolism in the retinal tissue. The yielding of the capillary wall producing the microaneurysms may also be due to high intracapillary pressure. Retinal microaneurysms were also studied by J. Francois, A. Neeens and S. Tarn (Ophthalmologica (Basel) 158, 273-283, No. 4, 1969) in the rabbits by light coagulation. They have opined that the formation of the capillary microaneurysms may be due to increased intracapillary...
pressure and/or traction from the surrounding tissue. Not only there is capillary dilatation but there is also associated venular dilatation. It is the present concept that venular dilatation is not a particularly early phenomenon in the development of diabetic retinopathy but rather an integrated part of diabetic retinopathy. As regards the calibre of the retinal arteries opinions are divided. According to M. Kojima (Rinsho Genke, 24, 383-467, April 1970) the calibre of the retinal arteries does not play in a significant role in the progression of diabetic retinopathy. According to M. Hiraiwa (Rinsho Genke, 24, 1139-1151, Sept. 1970) remarkable narrowing of the retinal artery was found in the diabetes mellitus cases. The question that arises are the venular dilatations and capillary changes reversible by dietetic management, insulin or an oral hypoglycaemic agent? Yes, it is reversible and this reversion provides further evidence in favour of the role of metabolic factors in the progression of diabetic angiopathy. The association of changes in the capillary wall in retina and renal glomeruli appear to be very striking.

Light microscopic appearances as described show increase in the size of the glomeruli together with thickening of the capillary basement membrane with accumulation of P.A.S. positive granules. The increase in the size of the glomeruli can be explained as due to deposition of mucopolysaccharide in the basement membrane which may be due to either the activity
of endothelial cell of the capillary wall or due to the activity of podocytic epithelial line in contact or may be due to both. The alloxan might in all probability decrease insulin concentration of the plasma either by disintegration of the beta cells of islets of Langerhans or by affecting the permeability of the walls of the beta cells resulting in deficient insulin release. The lack of insulin thus produced causes disturbances of carbohydrate metabolism locally and as a result the anaerobic pathway of glycolysis which is absolutely insulin dependent is deviated towards the more aerobic mechanism which is less insulin dependent. By this mechanism, glucose is converted into glucosamine which is incorporated into the biosynthesis of mucopolysaccharides. The capillary dilatation as seen in the retina is also encountered in the glomerular capillaries of these two conditions which one is earlier is not yet reported. The characteristic nodular lesion of diabetic nephropathy is not observed in these case groups. Just as the retinal capillary lesion can be seen as a early recognisable feature before oral glucose tolerance test is positive, similarly in the glomerular capillaries the changes precede detection of diabetes by chemical methods. The development of nodules in the glomeruli of alloxan diabetes might develop if the animals are maintained for a longer period of time with the progressive diabetic state. That no such changes are observed in the renal glomeruli of
pre-diabetic rabbits seem to indicate that the glomerular lesion is not in itself of genetic origin. The effect of insulin treatment on this type of glomerular lesion is not always associated with reversal of this condition. It would be reasonable to infer that replacement therapy with insulin should be of value in limiting a lesion which appears to be associated with insulin lack, in practice adequacy or inadequacy of such therapy seems to be have little direct effect on the progression of the lesion. It appears therefore that there must be some other factor which is still unknown and which is not being rectified by the apparent therapeutic control while renal biopsy and electron microscopy have improved the standard of assessment of the fundamental lesion of the capillary basement membrane the problem of its glycoprotein structure in relation to glucose metabolism and the influence of insulin is probably the most urgent challenge in this field at the present time.

The changes with respect to adrenal cortex as observed show that due to alloxanisation, a stress condition was produced and in order to counteract the same, the glomerular layer has undergone changes. The compensatory mitotic proliferation support the fact that an increase amount of mineralocorticoids were being produced to maintain a homeostatic condition as regards the electrolytes the metabolism of which has been disturbed by alloxanisation. The changes of the zona fasciculata
are suggestive of increased sterol metabolism for the production of both mineralocorticoids and glucocorticoids. The medullary cell proliferation is suggestive of increased output of catecholemides.

The pancreatic changes are suggestive of direct effect of alloxan on the insulin secreting Beta Cells of the islets of Langerhans resulting in insulin lack which is the predominant cause of the underlying phenomenon in the causation of both retinal and glomerular capillary lesions. The absence of any change in the islets of Langerhans in the pre-diabetic rabbits suggest that there may not be any insulin lack with normal glucose tolerance test but the inherited potential developed diabetes and accompanying renal and retinal capillary lesions remain latent and might be developing to abnormality in course of time. Infection, growth spurts, etc. might accelerate the progression and ultimately lead to chemical diabetes and associated renal and retinal capillary lesions.

The relatively specific focal degeneration of the murel cells in retinal capillaries has been shown to be limited to patients with established chemical or clinical diabetes unrelated to aging or hypertension. Thus there is a basis for distinguishing between retinal microaneurysm formation and nodular glomerular sclerosis versus the diffused basement membrane thickness of capillaries in renal, muscle, skin and conjunctival tissues as seen in diabetic microangiopathy described by Bloodworth in

The hepatic changes as observed show sinusoidal dilatation and karyolysis at places suggestive of parenchymal damage due to hypoxia. The compensatory proliferation of the hepatic cells is an attempt to restore the metabolic functions and detoxication of the alloxan.