Observation of retinopathy in metahypophyseal diabetic Chinese hamsters

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Arteriolar and capillary aneurysms were observed in 12 metahypophyseal diabetic gray hamsters. The animals had been in a diabetic state from 4 to 6 months following combined administration of growth hormone and cortisone.

Considering the extensive use of experimental animals in diabetic research, the paucity of reports on retinal lesions in diabetic animals is striking. In a 1961 review on diabetes in animals, Meier1 does not list retinopathy in his pathologic survey. More recently, however, Patz and Maumenee2 have reported retinopathy in a spontaneously diabetic dog, and Hausler, Sibay, and Campbell3 have described similar lesions in a metasomatotrophin diabetic dog with a history of 10 years of diabetes. In rodents, Becker4 has reported the occurrence of a vascular abnormality in alloxan-diabetic rabbits that were given cortisone, and Musacchio, Palermo, and Rodriguez5 found irregular dilatation with loss of muscle fibers in retinal arterioles in alloxanized force-fed rats. Hausler, Sibay, and Stachowska6 have recently observed capillary and arteriolar aneurysms in a metahypophyseal diabetic Chinese hamster.7

This observation is now supplemented by the postmortem study of 17 animals rendered permanently diabetic by the combined injection of cortisone and growth hormone.

Methods

All the animals were adult hamsters weighing from 32 to 40 grams and were fed Rockland mouse breeder cubes ad libitum throughout the experimental period. Permanent diabetes was induced by the combined injection of 12 mg. of cortisone* and 4 mg. of growth hormone† per animal per day for a period of 10 days. The animals were observed from 4 to 6 months in the diabetic state and the urine was tested bi-weekly with test tape (Lilly). Blood sugar determinations were carried out on two occasions with values ranging from 179 to 532 mg. per cent. No attempt was made to control the diabetes by administration of insulin. It was only administered as a life-saver when an animal became moribund. Out of 40 animals rendered diabetic by the injection of growth hormone and cortisone, 17 have died so far. On the death of the animals, both eyes were enucleated, the anterior segments of the globes were removed, and the retinas were studied with the dissecting microscope while still in situ and then removed and trypsin digested, as described by Kuwabara and Cogan.8 The retinal vascular tree was mounted on a glass slide as a flat preparation and stained with hematoxylin-eosin or by the periodic acid-Schiff method.

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*Cortone, 1 c.c. sterile suspension, equivalent to 25 mg. cortisone acetate, Merck Sharp & Dohme, Montreal, Canada.

†Growth hormone (bovine) prepared by the Endocrinology Study Section, National Institutes of Health, Bethesda, Md., U. S. A.
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Results

Gross abnormalities, such as hemorrhages, exudations or proliferative changes, were not observed. Retinal microangiopathy was found in 12 out of the 17 animals studied, and, of 32 eyes examined, 20 showed lesions. The pathologic condition most frequently seen in the affected eyes was aneurysmal dilatation of arterioles, such as typically shown in Figs. 1 and 2. In these arteriolar aneurysms, the surrounding smooth muscle cells usually showed degenerative changes such as pictured in Fig. 3. In the affected retinas, capillary aneurysms were less frequently encountered than arteriolar changes, the ratio being approximately 1 to 3. Fig. 4 shows typical aneurysm formation at the capillary level, and another capillary aneurysm in larger magnification is seen in Fig. 5. Intercapillary mesodermal strands such as described by Reimer-Wolter in the human retina were frequently encountered in our flat preparations. Such a

Fig. 1. Retinal flat preparation from a diabetic gray hamster, trypsin digested, hematoxylin-eosin stain. A retinal arteriole showing several aneurysmal dilatations is pictured.

Fig. 2. Trypsin digested retinal flat preparation of a diabetic gray hamster. A retinal arteriole showing several aneurysmal dilatations is seen.
typical strand interconnecting two capillaries is shown in Fig. 6, where it seems to connect a pericyte on one vessel with an area of dilatation on another capillary loop. Fig. 7 shows one of these strands ending at the apex of a capillary aneurysm and in contact with a pericyte.

In 42 retinal flat preparations of normal Chinese hamsters, microangiopathy was never encountered.

Discussion

The Chinese hamster has a retinal circulatory system which is similar to that of the human. A central arteriole and venule supply the entire vascular system of the retina, without anastomoses with the ciliary system. The capillary connection between arterioles and venules appears similar to that seen in man.

Metahypophyseal diabetes in the gray hamster may differ from spontaneous diabetes in this species, and further study of these animals will be necessary in this

Fig. 3. Retinal flat preparation of a diabetic gray hamster, trypsin digested. Both degenerative and proliferative changes are seen in smooth muscle cells surrounding two arteriolar aneurysms.

Fig. 4. Retinal flat preparation from a diabetic gray hamster, trypsin digested. A capillary aneurysm is seen close to an arteriole.
regard. In the inbred hamster colony available to us (822 animals obtained from a stock of 10 males and 20 females) the incidence of spontaneous diabetes is at present 7 per cent. Fifty-seven of the spontaneously diabetic animals are now under observa-

Fig. 5. Trypsin digested retinal flat preparation from a diabetic gray hamster showing a small capillary aneurysm.

Fig. 6. Retinal flat preparation from a diabetic gray hamster. A strand is seen connecting an aneurysmal dilatation of a capillary loop to a pericyte of a second capillary.
tion, and it is intended to keep these animals in a diabetic state as long as possible. It will, therefore, be some time before the condition of their retinal vessels can be properly evaluated.

It has proved difficult in our hands to induce diabetes experimentally in the gray hamster either by pancreatectomy or by administration of alloxan. In search for other methods to induce diabetes, it was found that in our normal adult gray hamsters, when given for a period of ten days:

Cortisone, 6 mg. per animal per day, induced temporary glycosuria in 50 per cent.
Cortisone, 12 mg. per animal per day, induced glycosuria in 85 per cent; however, recovery was usually complete after a period from one to three weeks.
Growth hormone in doses up to 5 mg. per animal per day did not induce glycosuria.
Cortisone, 12 mg., combined with growth hormone, 4 mg. per animal per day, induced permanent glycosuria in 90 per cent.

It would seem that Cricetulus griseus, besides yielding a fair supply of spontaneous diabetic animals, is readily susceptible to a metahypophyseal form of diabetes. If the incidence of retinal angiopathy found in the present study on these animals is confirmed, the gray hamster might become a valuable tool in experimental research on diabetic retinopathy.

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REFERENCES
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Discussion

Dr. Arnall Patz, Baltimore, Md. One of the obstacles in the study of diabetic retinopathy has been the difficulty in developing an adequate experimental model. Dr. Hausler and co-workers have provided a convenient method by which diabetes was induced in Chinese hamsters by injection of growth hormone and cortisone. Their yield of 80 per cent with permanent glycosuria and a significant percentage with retinal vascular changes is a most important observation.

The authors were careful in their description not to label hamster retinal lesions as the exact counterpart of human retinopathy. In humans, Cogan and Kuwabara reported a selective loss and degeneration of mural cells as characteristic of diabetic retinopathy. Degenerative changes in mural cells (or pericytes as designated by the authors) are not described in the hamster. The aneurysmal dilatation of the arteries that occurred three times more frequently than capillary lesions is extremely interesting, but has not been described in human retinopathy.

With Drs. Maumenee and Berkow, we have noted a closer resemblance to human retinopathy in dogs with spontaneous diabetes. The following two slides illustrate changes we have detected in several dogs. One notes the capillary microaneurysm and selective degeneration of mural cells.

It has been difficult thus far to develop a large enough colony of diabetic dogs to conduct any large-scale study. Dr. Hausler’s hormone-induced diabetes in hamsters, however, provides a method for making readily available a large number of diabetic animals in a uniform species. Although not as similar to human retinopathy as occurs in dogs, these hamsters may be an extremely useful tool in experimental studies. It is conceivable that, by continuing the hamsters in the diabetic state for a longer period by controlling their diabetes with insulin, lesions closer to human retinopathy may develop.

The authors are to be congratulated on this investigation. They have made an important contribution to the experimental study of diabetic retinopathy and we will be anxious to learn the results of their subsequent studies. I would like to ask if the kidneys of these animals showed any glomerular changes.

Dr. Hausler. No glomerular changes were noted.