Retinal degeneration in mature rats.  
Comparison of the disease in an Osborne-Mendel and a spontaneously hypertensive Wistar strain

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Mature Osborne-Mendel and spontaneously hypertensive Wistar rats demonstrate a high incidence of retinal degeneration. We have examined animals from the two strains and found no differences in the histopathologic development of the disease. All of the affected rats showed more or less advanced stages of a degenerative process initiated by disintegration and disappearance of outer segments and progressing to destruction of all photoreceptor cells. There was no indication that the hypertensive state influenced the retinal degeneration in the Wistar colony. The severity of degeneration at a given age varied widely in both Osborne-Mendel and hypertensive Wistar rats, suggesting that the onset or rate of progression of the disease differed from animal to animal within the strains.

In 1972, we reported a high incidence of retinal degeneration in inbred and noninbred colonies of Osborne-Mendel rats. Histopathologic examination of 28 rats at that time indicated that the degeneration appeared relatively late in life, at about the age of nine months, began with destruction of photoreceptors in the central retina, and progressed to total loss of receptor cells with disruptive involvement of the inner retinal layers. In the same year, Mizuno and co-workers described a possibly similar retinal degeneration in a colony of spontaneously hypertensive Wistar rats isolated in Japan. We have since examined an additional 67 Osborne-Mendel rats as well as 13 animals from a subline of the Japanese colony which has been established at the National Institutes of Health (NIH). Comparison of the retinal degeneration in the two strains of rats is the subject of the present report.

Methods
The animals came from the following four colonies maintained by the NIH Animal Production Unit: inbred Osborne-Mendel (OM/N), noninbred Osborne-Mendel (OM), spontaneously hypertensive Wistar (SHR/N), and nonhypertensive Wistar (WsKy/N). The spontaneously hypertensive animals have been bred at NIH since 1966, and originated directly from the line of hypertensive Wistar rats developed by Okamoto in Japan. The nonhypertensive Wistar rats descend from the original Wistar colony at Kyoto.
University from which the SHR were isolated. The numbers and ages of the examined animals in each group are listed in Table I.

Some rats were killed shortly after they were received from the Animal Production Unit. Others were held in the animal rooms of our laboratory from one to 12 months. The maximum illumination at working surfaces in these rooms during the day was 40 foot candles provided by overhead fluorescent lamps. The rats were housed in clear plastic containers with perforated steel covers. Maximum illumination within the covered cages was either 5 or 11 foot candles depending on the size and position of the racks used to hold the cages. All rats had free access to food (Purina rat chow) and water. Lights were turned off at night.

One or both eyes of each rat were fixed in Zenker's solution and embedded in paraffin. Four to six micron sections were stained with hematoxylin-eosin or periodic acid-Schiff (PAS). The second eye of 22 rats was used to prepare whole mounts of the retinal vasculature by the trypsin digestion technique.

Results

The incidence of retinal degeneration in the examined animals is presented in Table I. Among the Osborne-Mendel rats, the over-all ratio of affected to normal animals is approximately the same as that reported previously.\(^1\) The prevalence of degeneration in the SHR group was similar to that noted by Mizuno and co-workers;\(^2\) they found that two out of three animals exhibited the disease in the Japanese stock. Retinal degeneration had not been detected previously in WsKy rats. We found that it does occur in this strain, although the number of animals examined was too small to permit any estimation of frequency.

Because of disparities in sample size at different ages, it is difficult to relate the presence or severity of degeneration to age, even in the relatively large group of OM/N rats. Some of these animals showed signs of degeneration by six months of age, and normal rats persisted in the population at least to the age of 15 months. At any given age, however, the severity of the disease varied widely. Total loss of the photoreceptor layer occurred as early as nine months in some individuals, while other animals of the same age, or older, had only incipient retinal degeneration.

Marked differences in the severity of the disease among animals of the same age was seen in the SHR/N group as well, suggesting that in both strains the onset or course of the degenerative process varies from animal to animal. In this regard, it is noteworthy that one SHR/N rat, born in the laboratory of parents which both had retinal degeneration, showed beginning photoreceptor destruction as early as two months of age.

Clinical and histopathologic examination. All stages of the degenerative process were represented in the Osborne-Mendel rats and the histopathologic changes conformed to those described in the previous series.\(^1\)

Ophthalmoscopic examination of the fundus of the SHR rats suggested moderate narrowing of the retinal arteries, but an accurate evaluation of vessel caliber could not be made because of the difficulty in obtaining a consistently reliable view of the eyeground in the rat. Definite vascular lesions, such as irregularity of vessel caliber, aneurysms, preretinal hemorrhages, and retinal opacities were not present in our group of animals, although they have been noted in some SHR rats.\(^3\) Neurologic abnormalities related to cerebral hemorrhages, also observed in this strain,\(^4\) did not

Table I. Incidence of retinal degeneration

<table>
<thead>
<tr>
<th>Age (Months)</th>
<th>OM/N</th>
<th>OM</th>
<th>SHR/N</th>
<th>WsKy/N</th>
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<td>7/9</td>
<td>8/13</td>
<td>1/5</td>
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appear in our sample. No cataracts were seen on slit lamp examination.

Signs of retinal degeneration in the SHR rats resembled closely those seen in Osborne-Mendel rats (Fig. 1). The earliest detectable change consisted of small globules of debris lying between proximal and distal portions of the outer segments in the central retina. The sections often showed as an artifact a fine split in the retina midway along the length of the outer segments. In eyes with retinal degeneration the globular debris was located along this split predominantly. Small wandering cells commonly were present among the disintegrating receptor processes (Fig. 1). The cytoplasm of some of these cells was filled with PAS-positive material, and they were assumed to be phagocytes. Further disintegration of outer segments was accompanied by disappearance of the inner segments and a reduction in width of the outer nuclear layer. Receptor cell nuclei were generally of normal appearance. Pyknotic nuclei were identified only rarely, even in retinas with advanced degeneration. In the most severely affected animals, the receptor cell layer was reduced to only a single row of nuclei with inner and outer segments completely absent or replaced by small amounts of eosinophilic or PAS-positive debris. This condition existed throughout the whole retina in some rats, while in others, a band of peripheral retina remained apparently normal. In none of the SHR rats did the degeneration reach the most advanced stages seen in the OM rats, that is, total loss of photoreceptor cells.
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with subsequent distortion of the remaining retinal layers. The inner retina, the pigmented epithelium, and the choriocapillaris were normal in all the SHR eyes examined.

Although no papilledema was noted during ophthalmoscopic examination, the sections of eyes from all SHR rats showed notable elevation of the optic disc, a swelling which was not present in animals of the nonhypertensive strains (Fig. 2), and which may represent chronic optic nerve edema. Takahashi has examined some SHR rats with ophthalmoscopically visible papilledema and retinal opacities, and noted round, PAS-positive deposits in the nerve fiber layer which he considered to be cytoid bodies. In SHR, OM, and OM/N rat eyes, we frequently saw PAS-positive spherical bodies in the nerve fiber layer in the area of the optic disc. These deposits, present in both normal and degenerating retinas, did not have the characteristics of cytoid bodies; they were homogeneously stained and structureless. Their nature is unknown.

Trypsin-digested preparations of the retinal vasculature of the SHR rats had markedly narrow arteries (Fig. 3). The diameters of 45 arteries, measured approximately 0.4 mm. from the optic disc in 11 animals, averaged $26 \pm 0.5 \mu$ (S.E.). In comparison, the average diameter of 39 arteries of 8 OM/N rats was $36 \pm 0.7 \mu$. There were no significant differences in vessel caliber within the two strains related to age (six to 15 months), or to the presence or absence of retinal degeneration. Although the eyes of only three WsKy rats were available for measurement, the mean diameter of eight arteries was $40 \pm 1 \mu$. Arterial narrowing, therefore, was confined to the hypertensive rats as was swelling of the optic disc. It was not evident in the normotensive parent strain and was not related to retinal degeneration. No other indications of vascular abnormalities were seen in the retinas of the SHR rats, including changes in the capillary bed which follow upon total loss of the receptor cell layer, since in none of these animals had retinal degeneration reached such an advanced stage.
Fig. 2. A, swelling of the optic disc in a 12-month-old SHR/N rat. B, normal appearance of the disc in an eleven-month-old OM/N rat. Neither of these animals had retinal degeneration (PAS-hematoxylin, ×130).

Fig. 3. Comparison of retinal arteries in (A) nonhypertensive OM/N and (B) hypertensive (SHR/N) rats. The photographed areas were within 0.4 mm. of the optic disc which lies below in both pictures. (Trypsin-digest preparation, PAS-hematoxylin, ×250).
Discussion

The retinal degeneration observed in the colony of spontaneously hypertensive Wistar rats at NIH closely resembles in incidence and characteristics that described for the original colony established in Japan, and is remarkably similar to the retinal degeneration occurring in Osborne-Mendel rats. No differences in the histopathologic development of the degeneration among the colonies was seen with the light microscope. All of the affected animals showed more or less advanced stages of a degenerative process initiated by disintegration and disappearance of outer segments and progressing to destruction of all photoreceptor elements. There was no evidence of excessive accumulation or persistence of outer segment material during this process. We do not know whether the rate of progression of the disease is similar in the different colonies. The extent of degeneration at a given age varied widely in all groups, suggesting that the time course of the disease varied from animal to animal within strains.

There was no indication that the hypertensive state itself contributed to the retinal degeneration in SHR rats. Although blood pressures were not measured in the particular animals we examined, the strain is characterized by 100 per cent incidence of hypertension (180 to 200 mm. Hg systolic pressure) after the age of 10 weeks, and all of our animals showed narrowing of retinal arteries without other signs of hypertensive retinopathy. Not all SHR rats, however, had retinal degeneration, indicating that this condition is independent of the abnormal elevation of blood pressure.

In view of the emphasis in recent years on the damaging effects of light on the rat retina, and particularly of continuous exposure to relatively low levels of illumination, an influence of light on the development of retinal degeneration cannot be excluded. It is possible that even cyclic exposure to the usual levels of illumination in the laboratory environment induces gradual attrition of receptors with age in these animals. Our observations of variation in severity of degeneration and the presence of some normal rats in groups of the same age, maintained in the same environment, suggest that there is an inherent difference in susceptibility to degeneration whether or not light is a contributing factor.

REFERENCES