Braun-Falco and Rupec (*3*) noted in the dermis of systemic scleroderma isolated collagen fibrils of reduced thickness (ranging from 500 to 800 Å) intermingled with normal collagen fibrils. Hayes and Rodnan (*4*) also described in the dermis variation in collagen fibrils (200 to 700 Å) and the presence of double stranded beaded filaments of 640-Å periodicity. The above authors concluded that their findings suggested an increase in the rate of collagen synthesis in scleroderma dermis.

Our study suggests that the most specific abnormality in systemic scleroderma is the replacement of the subcutaneous tissue by abnormal connective tissue, both within the fibrils and the ground substance. It is unlikely that the newly synthesized connective tissue arises from the dermis, since in this layer there were very few fine collagen fibrils, no increase in ground substance, and normal or reduced numbers of fibroblasts. Three types of cells were noted in the subcutaneous area: fibroblasts, fat cells, and lymphocytes. It is likely that the fibroblasts are responsible for the synthesis of the newly synthesized connective tissue. The persistence of immature collagen fibrils in long-standing cases suggests an impairment or delay in the mechanism of fibril aggregation probably due to interference by the increased ground substance. We believe that chemical analysis of the abnormal connective tissue in scleroderma may not only improve our understanding of this disease but may also yield useful information on the basic mechanism of collagen fibrillogenesis and its relationship to the ground substance.

RAUL FLEISCHMAJER
VICTOR DAMIANO
ALEXANDER NEDWICH
Departments of Medicine and *Pathology, Division of Dermatology, Hahnemann Medical College,* and *Franklin Institute Research Laboratories, Philadelphia, Pennsylvania 19102*

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Extracellular Recordings from Human Retinal Ganglion Cells

Abstract. *Ganglion cells were studied in the isolated retina, with extracellular recordings. Activity was found similar to that seen in the retinas of other animal species.*

The isolated retinal preparation has been employed for the investigation of biochemical and physiological activity in a variety of species, including mammalia (*1–4*). In previous reports, we have described studies of adaptation in the rat retina (*5–8*). When suitable conditions exist, the human retina may be studied in a similar fashion.

On several occasions, we have been able to learn in advance of the need for enucleation of otherwise normal eyes from patients harboring malignant melanomas of the choroid. Cooperation from both patient and surgeon was obtained so that a black, opaque contact lens could be worn for several hours prior to and during the operation, thereby permitting the retina to remain relatively dark-adapted. Surgical technique was modified so as to avoid interfering with the retinal circulation until the moment of severance of the optic nerve. The globe was then rapidly opened in dim red light, and the retina, in an area remote from the tumor, was gently dissected from its pigment epithelium and from the vitreous.

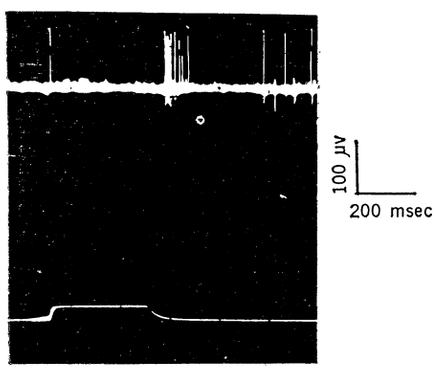

Fig. 1. Extracellular recording from a single human retinal ganglion cell. Upper trace shows maintained activity and burst of responses following cessation of stimulus, shown on lower trace. A few smaller action potentials from a second ganglion cell are also visible.

The procedure for mounting, incubating, and recording from the retina was identical to that used in our previous studies. The light source was a well-regulated, xenon-arc lamp (Bausch and Lomb). Narrow band interference filters (Baird-Atomic) were used for chromatic stimulation, together with a pair of rotating-wedge neutral density filters (Kodak Wratten) for stimulus attenuation. Most often, electroretinographic (ERG) responses, which closely resembled those from the living eye, could be obtained, although occasionally no ERG could be recorded. Ganglion cell action potentials of 100 to 300 μv were frequently encountered; although most units showed marked spontaneous activity, only a few were responsive to light stimuli (Fig. 1). Both ERG and ganglion cell responses usually remained stable for several hours.

When we used small (80 to 100 μm) spots, some units were found with center-surround receptive field organization. Both on and off center types were found.

Two units in one retina were studied with chromatic stimuli, although adapting backgrounds were not employed. The portion of the retina studied was from the temporal midperiphery. The sensitivity data obtained for these units are shown in Fig. 2. The data are plotted in relative log quanta per pulse incident on the retinal tissue versus wavelength in nanometers. Also illustrated is the π_5 curve of Stiles (*9*). Most points for both units lie on or close to this curve at about 540 nm, but above the curve at shorter wavelengths. These data also agree closely with Wald's sensitivity curve for the red receptors, obtained by microspectrophotometry

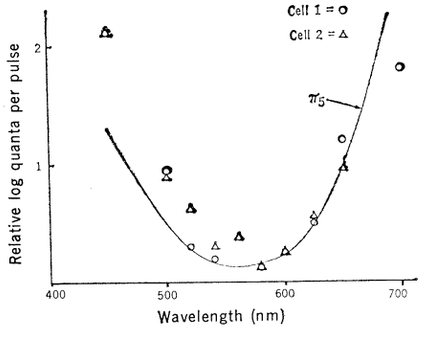

Fig. 2. Spectral sensitivity data for two human retinal ganglion cells. The continuous curve is the π_5 curve of Stiles.

(*10*). This might be explained by scatter into the surround, which would be more effective in producing inhibition at those wavelengths. These two units are in rough agreement with the findings of Gouras (*11*), who studied the intact monkey retina. However, Gouras used chromatic adaptation of the surround and thereby was able to eliminate the inhibitory effect.

Our findings suggest that, at the ganglion cell level, the visual system of man is not unlike that of other higher animals. This would lend support to the results of workers who attempt to correlate electrophysiological experiments with psychophysical data.

GEORGE W. WEINSTEIN*
ROBERT R. HOBSON, FRANK H. BAKER
Wilmer Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland

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* Present address: Division of Ophthalmology, University of Texas Medical School, San Antonio 78229.

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Decrease in Adrenal Tyrosine Hydroxylase and Increase in Norepinephrine Synthesis in Rats Given L-Dopa

Abstract. *When large doses of* L-*dopa* (*1000 milligrams per kilogram, given subcutaneously*) *were administered to rats, the rate of catecholamine synthesis was increased in both the heart and adrenal gland. It is likely that increases also occur in other sympathetically innervated tissues. When the same dose of* L-*dopa was given daily for 4 or 7 days, the levels of tyrosine hydroxylase in the adrenal were lowered in comparison to controls. These findings may be a further indication of the existence of a regulatory mechanism which modifies endogenous levels of tyrosine hydroxylase in response to changes in the biosynthetic demand for norepinephrine.*

L-Dihydroxyphenylalanine (L-dopa) is an intermediate in the biosynthetic pathway leading to the formation of the sympathetic neurotransmitter norepinephrine and the sympathetic hormone epinephrine. Studies on the effects of administered L-dopa on the enzymes involved in catecholamine biosynthesis were initiated because large doses of L-dopa are now used in the treatment of Parkinsonism (*1*). We now present data that administration of L-dopa to rats increases norepinephrine synthesis and brings about significant reduction of adrenal tyrosine hydroxylase activity.

Female Sprague-Dawley rats (Carworth Farms, New City, New York) weighing between 175 and 220 g were used. L-Dopa was administered subcutaneously as a fine suspension or in saline. Control animals received subcutaneous injections of 0.9 percent NaCl. The volume of all injections was 0.5 ml. The animals were killed 1 day after the final injection of either an L-dopa suspension or saline and were routinely fasted 16 hours before they were killed. Adrenal glands were removed and homogenized in 2.0 ml of 0.13*M* potassium phosphate buffer, *p*H 7.0. Portions (0.5 ml) of the homogenates were immediately added to 9.5 ml of 5 percent trichloroacetic acid, and the catecholamines were isolated by alumina adsorption (*2*, *3*). Norepinephrine and epinephrine were determined by the method of Crout (*3*) and dopa and dopamine were determined by a modification of the method of Drujan *et al.* (*4*). Portions of the adrenal homogenates and the supernatant fractions of brain homogenates were assayed for tyrosine hydroxylase activity by the method of Nagatsu *et al.* (*5*).

In the studies involving heart norepinephrine and adrenal catecholamine turnover, rats received either 10 μc of DL-[7-^{3}H]norepinephrine (10 c/mmole; New England Nuclear) or 200 μc of generally labeled L-3,4-[^{3}H]dihydroxyphenylalanine (9.9 c/mmole; New England Nuclear) intravenously, and the decline in the specific activity of heart norepinephrine or adrenal catecholamines was followed with time. The slope of the decline K was determined, and the half-life $T_{1/2}$ was calculated from the equation $T_{1/2} = 0.693/K$ (*6*). Tritiated L-dopa was used to label the adrenal catecholamine stores since this cannot be reliably accomplished with radioactive norepinephrine (*7*). The data were statistically analyzed by the Student *t*-test.

One day after the administration of L-dopa (1000 mg/kg) to rats for two consecutive days there was a small but significant and reproducible decrease in the level of adrenal tyrosine hydroxylase, from 23.6 ± 0.8 in controls to 18.4 ± 1.6 μmole per pair per 15 minutes (five to six animals in each group; $P < .025$). The questions of whether additional administration of L-dopa would result in a more pronounced decrease in adrenal tyrosine hydroxylase and whether similar changes occurred in other tissues were then studied. When L-dopa was administered for longer periods a progressive reduction of adrenal tyrosine hydroxylase occurred. After 1 week on L-dopa, the level of tyrosine hydroxylase in the adrenal gland was reduced to about 50 percent of that in the controls, while that in the brain remained unaltered (Table 1).

After L-dopa was administered for three consecutive days, the amounts of this amino acid in the tissues remained elevated for at least 1 day after the last dose. For example, in the heart 2, 5.5, and 18 hours after the last dose (subcutaneous), the amounts of L-dopa were 4.2, 1.6, and 0.7 μg/g, as compared to undetectable amounts in hearts from control animals. There was the possibility, therefore, that L-dopa or catecholamines or both might remain at a sufficient concentration in the adrenal to result in inhibition of adrenal tyrosine hydroxylase when measured in vitro (*8*). For this reason, catecholamines were assayed in the same adrenal homogenates used for the assay of tyrosine hydroxylase. One day after the administration of L-dopa (1000 mg/kg per day) for 4 or 7 days, small but significant elevations in adrenal dopa and dopamine were observed. However, total catechols were elevated only about 5 percent over control values (Table 2). This small increase could not account for the reduction in tyrosine hydroxylase activity as measured in the in vitro assay.