Physiology but have been used little in retinal applications, which have been confined largely to in vitro or eye cup preparations. The animal research has been confined primarily to the brief recording of retinal signals under general anesthesia. 0 A chronic preparation of multiply implanted retinal layer electrodes has been described by Dawson and Radtke 5 that extensions of this research will lead to an understanding of the current sensitivity of retinal elements in the absence of receptor control. Methods. Dawson and Radtke have described an implantation procedure in which nine and 14 electrodes were, respectively, placed upon the inner retinal layer of two cats. They demonstrated that these recorded unit and graded retinal potentials, without indications of toxicity, during a period greater than 8 months. 5

The electrical stimulation of the retina by indwelling electrodes. William W. Dawson and Norman D. Radtke.

Chronically implanted intracocular electrodes were used to stimulate visual cortical responses to current passage through the retina. Electrical current threshold for the light-adapted cat retina lies in the region of 30 to 100 × 10⁻⁶ amps. for the conditions used. Dark adaptation caused a large threshold increase. Retinal excitability also decreased when electrical stimuli were delivered more often than once per 5 seconds. Effective charge-density threshold was moderately greater than reported for frogs and humans.

The passage of electrical current through the human eye may produce visual experiences localized to regions of the visual field and of varying brightness. 1-4 Interesting interactions between the subjective brightness of spectral lights and electrical currents were reported by Motokawa and studied in an extensive series of studies by Riggs, Cornsweet, and Lewis. 5 who considered this area of great potential physiological importance. These extensive psychophysical studies have not been followed by quantitative physiological experiments in intact lower animals. The animal research has been confined primarily to in vitro or eye cup preparations. 5 Some in situ studies have been completed on the mammalian retina but these have been confined largely to the brief recording of retinal signals under general anesthesia. 5 A chronic preparation of multiply implanted retinal layer electrodes has been described by Dawson and Radtke 5 and provides for some repeated measures of the variables associated with electrical stimulation of the retina and pathway in the unanesthetized condition.

Electrical responses of neural tissue have been a classical vehicle for system analysis in neurophysiology but have been used little in retinal research, which has been dominated by the constraints imposed by receptor function. We hope that extensions of this research will lead to an understanding of the current sensitivity of retinal elements in the absence of receptor control.
Fig. 1. Cortical response relationship to retinal current pulses of constant duration (0.8 msec.). Response amplitude was measured from N1-P1 of the cortical response (see inset). Areas are integrations of the regions under reliable signal components N1-N3. Areas were converted to positive values before integration. Retina was stimulated (arrow) in light adaptation and after 30 minutes of darkness. The retina was relatively refractory in darkness.

Results. Electrical signals recorded by averaging the response at the visual cortical electrodes were replicable over several weeks of experimentation. Fig. 1 (inset) shows the cortical waveforms recorded following retinal stimulation. The cortical response was similar to that produced by a brief flash of light to which latency to the first negative component of the cortical response (N1) ranged from 20 to 30 msec. for an N1-P1 response amplitude of 20 to 50 μV. Fig. 1 (inset) shows similar latencies for electrical stimulation. Five cortical signal components were consistently evoked by electrical stimulation of the retina. These are identified as N1, P1, N2, P2, and N3. The large arrow (Fig. 1) indicates the electrical stimulus artifact. Several controls were used to avoid misinterpretation of the electrical artifact. These were: polarity reversal of the stimulus, injection of retrobulbar anesthesia, and dark adaptation. We found that the retinal excitability was greatly reduced by dark adaptation (Fig. 1, inset). Currents in excess of 3 mA. could evoke a small cortical response in the dark but such intense currents have been avoided since they have been demonstrated to produce tissue pathology.

There was a relationship between cortical response amplitude (N1 to P1) and stimulus current (Fig. 1). Since gross potentials require an unfortunate amount of interpretation, the area under the curve was converted to positive values from N1 to N3 and was integrated. The results are shown as the relative area in Fig. 1 and may be taken as an over-all indicator of cortical excitation. The initial response amplitude (N1-P1) and area increased rapidly from threshold, particularly after the stimulus current was increased from 0.8 mA. There was little increase in cortical response when stimulus currents were above 1.5 mA. Extrapolation of either function to the current baseline indicates that absolute threshold falls at about 30 μA (2.4 x 10^-8 coulombs—C).

In the light-adapted retina excitability was decreased when stimulus current pulses were delivered rapidly. Fig. 2 shows that there was a rapid decrease in both cortical response amplitude and area when the period between stimuli was less than 5 seconds and stimulus current was constant at 2.0 mA. For stronger currents the decline in responsiveness began at greater interstimulus periods.

Close analysis of the electrical stimulus artifact and the cortical signal is possible by recording
during the stimulation of three series electrodes in the far periphery (~60°). Signals were small and charge density was increased by extending the stimulation duration (0.8 to 4.0 msec.) with 1.0 ma. constant current. The artifact area increased with charge in the usual way but cortical activation reached a maximum at 24~7 C and declined (Fig. 3) as total charge increased (Fig. 3).

Discussion. Electrical stimulation of the cat retina, in situ without anesthesia, can be achieved in the 30 to 100 na current pulse region. Gebhard produced human threshold (phosphenes) visual experiences at 75 na with pulse stimuli delivered at a distance from the retina. Comparison of the charge density threshold (30.5 x 10^-6 C/cm.²) which we have calculated with other reports is more difficult. Although C is a more meaningful quantity its use assumes (1) that the consequences of vitreous body conductance are known, (2) equivalence of light adaptation effects across species, and (3) current-time reciprocity. With this caution noted, Knighton reported ERG threshold at 2 x 10^-7 C/cm. for frog retina and Bradley reported a 8.3 x 10^-9 C/cm.- threshold for human retina.

Although we were surprised that the retina is relatively refractory to electrical stimuli in darkness there have been similar findings in human psychophysical studies. Further confirmation may be found in the ganglion cell data of Crapper and Noell's eye cup preparations where electrical excitability was proportional to level of light adaptation. There is also a counterpart of reduced excitability from reduced interpulse period (Fig 2). A similar psychophysical phenomenon has been called "phosphene fatigue."

Controls for artifact contribution to "signal" are necessary where small electrical potentials are evoked by electrical stimuli. This is a particular problem in moving, unanesthetized animals where signal/noise ratio can be low but the physiological validity of results is high. In this preparation anesthesia improved signal/noise ratio only occasionally. Most frequently, signals were small and variable where doses of 20 mg./Kg. of sodium pentobarbital were used. Artifact amplitudes were not changed. Stimulus polarity reversal had small, inconsistent effects on the response. Retrobulbar anesthesia reduced by 50 to 70 per cent the responsiveness of the cortex to both light and electrical stimuli. We did not achieve a total block, probably because of the great care we use in manipulation of the eye in this year-old implant. Dark adaptation obliterated the electric stimulus sensitivity at safe current levels. The artifact was not changed by dark adaptation. Visible stimulus sensitivity was
increased in the dark. Fig. 3 shows that the major
cortical response elements (identified also in Fig.
1) seem to correlate poorly with increasing arti-
fact area and total stimulus charge. Smaller re-
sponses were produced by the higher charges and
associated artifacts.

The sites of electrical excitation of the retina
are not known. One would expect most retinal
cells to respond at some current level. Ogden
and Brown1 localized electrically stimulated re-

cordings have succeeded in evoking visual experiences in
persons with blinding diseases of the outer retinal
layers. If it was known that receptors were not
present in these patients, the expected excitability
of the inner retina would be verified. Future
work with the chronically implanted retina will
attack the contributions of the receptors.

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Calcification in retinoblastoma. JOHN D.
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Review of 40 cases of retinoblastoma revealed that
histologic evidence of calcification was noted in
38 of the 40 tumors, whereas only three of 16
roentgenograms were positive for calcium. Calci-
fication detected by roentgenograms and histo-
pathologic examination correlated poorly with
quantitative determination for tumor calcium. Com-
pared to control eyes, however, eyes with retino-
blastoma contain large amounts of calcium (1.2
vs. 218 µg/mg, ash). This calcification, though
frequently not observed in standard roentgeno-
grams, should be detected by the newer diagnostic
modalities such as hypocycloidal polytomography,
computed transaxial tomography, ultrasonogra-
phy, and radionuclide scintigraphy with tech-
netium diphosphonate, a bone-scanning agent.

Roentgenographic evidence of calcification is
considered one of the most useful signs in the
diagnosis of suspected retinoblastoma in patients
who present with leukokoria. The standard roent-
genographic examination, however, is not uni-
formly successful in establishing the correct diag-
nosis. The reported rates of calcification on roen-
tgenograms in patients with known retinoblastoma
have been as high as 80 percent in some series but
as low as 50 percent in others. These figures
are important because retinoblastoma is frequently
misdiagnosed. In patients with suspected unin-
lateral retinoblastoma, Howard1 found that 12
percent had no malignant disease, whereas Kogan
and Boniuk1 found 30 percent without malign-
ancy.

Recent technological advances have facilitated
the in vivo localization of calcium in tissue. These
include hypocycloidal polytomography, computer-
ized transaxial tomography, ultrasonography, and
radionuclide scintigraphy with technetium diphos-
phonate. The possibility of using these new
techniques to enhance the physician’s diagnostic
acumen prompted a study of calcification in retino-
blastoma.

Materials and methods. A study of 40 eyes
with retinoblastoma was undertaken to identify
and quantitate the degree of calcification present
within the tumors. Roentgenograms of the skull
and orbit, when available, were reviewed to

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