Summary. 1. In doses greatly exceeding the usual therapeutic range for man, para-aminobenzoic acid is a relatively non-toxic substance for the rat. 2. Aside from histologic alterations in the thyroid gland, no significant pathologic changes were detected in the treated animals or in their offspring. 3. The thyroid changes consisted of reduction in the amount and eosinophilia of intrafollicular colloid, associated with epithelial hypertrophy and hyperplasia. These findings were maximal after 2 months of treatment. 4. No hepatotoxic effect was detected.

Received September 29, 1950. P.S.E.B.M., 1950, v75.

Electrical Injury of the Cochlea of the Guinea Pig.*† (18229)

C. FERNÁNDEZ, B. E. GERNANDT, H. DAVIS AND D. R. MCAULIFFE.

From the Central Institute for the Deaf, St. Louis, Mo.

The original purpose of the present experiments was to polarize electrically the sense organ of the inner ear in the expectation that the thresholds of the aural microphonic and of the action potentials and perhaps also their maximum amplitudes would be modified. Any such modifications would be useful tools for analysis of the origin of the microphonic and of the excitation of the primary neurons by the sensory cells. The method seemed practical because of the success of Riesco and collaborators(1) in drilling small holes into the cochlea of the guinea pig and thereby placing electrodes in known positions relative to the basilar membrane. Our expectations were fulfilled and the results will be presented elsewhere. The present report describes injurious effects produced incidentally by electro-coagulation and electrolysis in our exploratory experiments.

Methods. Holes were drilled as described elsewhere(2) into at least 2 and sometimes 3 turns in the cochlea and another electrode was regularly placed on the round window. No. 38 enamel-insulated silver wire was substituted for the original copper wires. The usual positions of electrodes and their attachment by dental cement to the edge of the opening into the acoustic bulla is shown in Fig. 1. Frequently, however, the electrode in turn 1 was introduced into the scala tympani instead of scala vestibuli by placing it on the opposite side of the dark band that marks the position of the stria vascularis. The thresholds of the aural microphonic at frequencies 200, 1000, 2500 and 8000 cps and also of the action potential in response to a standard filtered click were measured(2). The par-

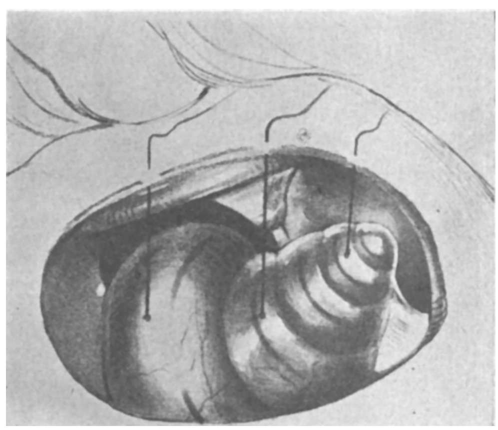

FIG. 1.
Three silver wires (black lines) are placed as electrodes in the first, second and fourth turns of the cochlea of a guinea pig. The wires are held in place by dental cement attaching them to the cut edge of the bulla. The dark band that marks the position of the stria vascularis is also shown.

* This work was carried out under Contract N6onr-272 between the Office of Naval Research and Central Institute for the Deaf.

† Presented in part at the meeting of the Missouri Section, March 22, 1950.

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2. Davis, H., Gernandt, B. E., Riesco-MacClure J. S., and Covell, W. P., *J. Acoustical Soc. Am.*, 1949, v21, 502.

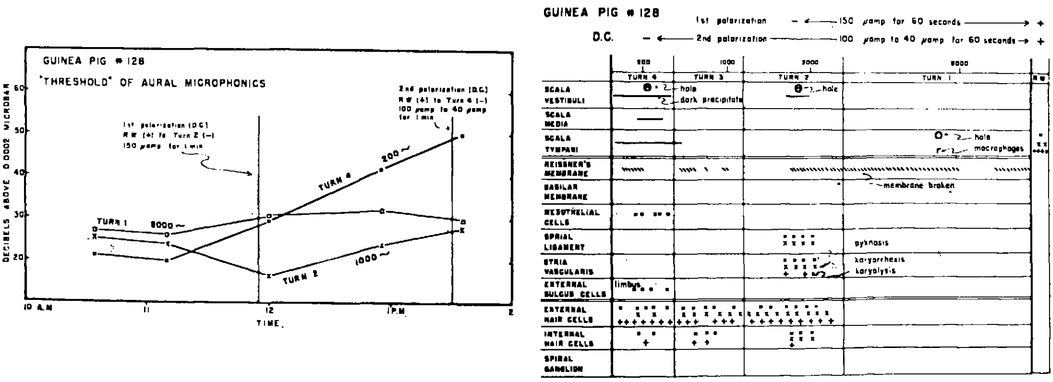

FIG. 2.
Effects of DC; 2 doses of 1 minute each between electrodes as indicated. Injury centering in Turns 4 and 2. Considerable rise in threshold for low tone. Little effect on 8000 cps or 1000 cps. (Turns 1 and 3 are less seriously injured).

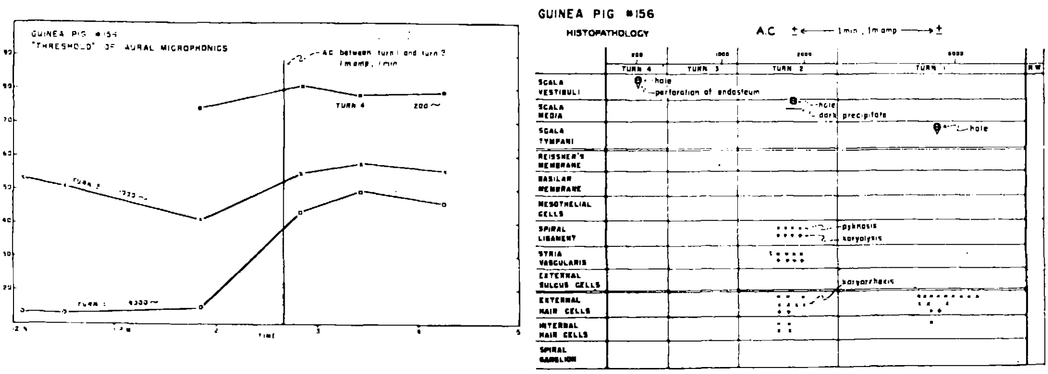

FIG. 3.
Effects of AC; 1 milliampere for 1 minute. Moderate injury in Turns 1 and 2. Great rise in threshold for 8000 cps, slight for 1000 cps (Turn 3) and 200 cps (Turn 4).

ticular test frequencies were chosen because the positions on the basilar membrane which they agitate most strongly correspond to the positions of the electrodes shown in Fig. 1.

A DC electric potential of known strength and polarity was applied between 2 electrodes. In a later series of experiments alternating current at 1000 cps or radio-frequency current at 4.0 megacycles was employed. Sometimes the two polarizing electrodes were located in the same scala but in different turns so that the potential drop was lengthwise of the basilar membrane. More often the basilar membrane lay between them. Sometimes only part, sometimes all, of the cochlea (round window to apex) was included. In many DC experiments acoustic stimulation was continued during the polarization and the responses were observed continuously on the oscilloscope. After the first few experiments the recording amplifier was provided with smaller inter-stage coupling condensers than usual to avoid artifacts from "blocking" by the polarizing current. In all cases the thresholds of the response were measured immediately, and again later, after treatment. The temporal bones were fixed and later studied histologically.‡ The histological changes observed in the serial sections were summarized in charts such as appear in Fig. 2, 3 and 4.

Results. When care was taken to avoid

‡ The histological preparations were made by Miss A. M. Denk under the direction of Dr. W. P. Covell. We are greatly indebted to Dr. Covell, both for his helpful advice and for the free use of his laboratory facilities in McMillan Hospital (Washington University).

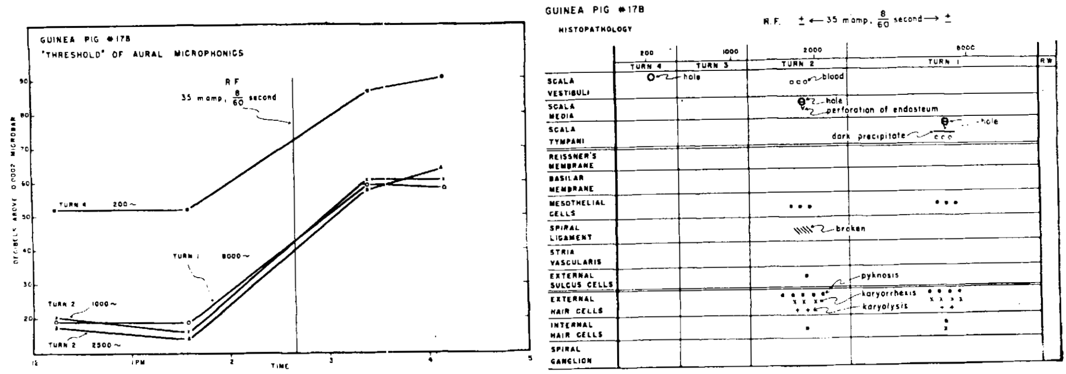

FIG. 4.
Effects of RF; 35 milliamperes for about 0.13 sec. Mild local injury at Turns 1 and 2, but great rise in thresholds for all frequencies tested. This is the typical effect of the formation of a bubble within the cochlea, either from electrolysis or heating.

polarization at the electrodes and to keep the current flow steady and below about 40 microamperes reversible modifications of the electrical responses of the cochlea were observed(3). With stronger DC currents (up to about 100 microamperes) the intra-aural muscles and sometimes other muscles of the head and neck were stimulated. When this occurred the cochlear responses were temporarily obscured by muscle action potentials. Changes in transmission occurred, particularly for low tones, and were reflected in corresponding changes in amplitude and shape of the patterns on the oscilloscope(5).

In addition, following DC current flow of 40 to 100 microamperes for 30 seconds or more, permanent elevations in the thresholds of response were produced (Fig. 2). Most of these changes were clearly correlated, according to the place principle(2), with signs of local necrosis found on microscopic examination. For example, necrosis at the apex caused profound and fairly selective depression of the cochlear microphonics and action potentials in response to a 200 cps tone. The necrosis was apparently caused chiefly by heating. It was confined to the immediate neighborhood of the tips of the wires and was very marked in cases in which the hole did *not* quite penetrate through the bone to the stria vascularis. The cells of the organ of Corti (and others) showed pyknosis, karyolysis and karyorrhexis and a loss of staining reactions and cellular structure generally. The holes in the bone often contained a black deposit (probably carbon) that tested negative for iron and for silver and was insoluble in concentrated sulphuric acid.

Sometimes, however, a large rise in the threshold of response for low tones (measured at the apex) occurred although DC current was applied only to the basal and/or second turns and although the organ of Corti was later found normal. Likewise four trials with very brief (less than 1 second) but strong (35 milliamperes) RF currents (4.0 megacycles) caused more widespread impairment of response than can be accounted for by the pathological changes. (See Fig. 4).

The explanation of many of the changes of threshold for low tones was found to be the formation of bubbles of gas inside the cochlea. (Fig. 5). DC currents of 100 microamperes passed between 2 of our silver wires immersed in boiled isotonic salt solution produce visible bubbles unless the cathode has previously been coated electrolytically with silver chloride. The bubbles are due to electrolysis and appear even when the solution has previously been boiled to drive off dissolved air. AC and RF currents also form bubbles in the cochlea, although much more current is required, probably chiefly from heating and thus driving out

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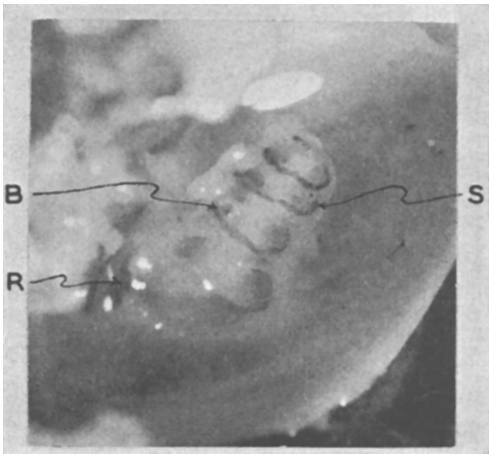

FIG. 5.
The bone of the cochlea has been dissected off under saline solution, leaving the membranous labyrinth nearly intact. The pigmented stria vascularis (S) is clearly visible in Turns 2, 3, and 4. A bubble (B) is still present in scala vestibuli of Turn 2. A larger bubble escaped during the dissection. The round window (R) is at the lower left. In the first turn the stria vascularis, spiral ligament and basilar membrane have been removed, exposing the spiral lamina. White spots are reflections from the surface of the saline solution. Treatment: DC; 100 microamperes for 1 minute.

dissolved gases.

We have noticed incidentally two anatomical features of the guinea pig's cochlea that may be of importance to electrophysiologists, as follows:

1. In the first turn the spiral ligament is separated from the scala tympani by a thin spiral shelf of bone. This shelf appears like a deposit of bone in the surface layers of the dense, non-vascular tissue that covers the tympanic half of the spiral ligament. A hole drilled into the spiral ligament behind this shelf is likely to bring an electrode into more direct contact with scala media than with scala tympani.

2. Within the modiolus a bony partition separates the channel that contains the spiral ganglion from the hollow central core that contains the cochlear nerve. Nerve fibers and blood vessels penetrate this partition freely but the holes are so small that it forms an effective barrier against any micro-electrode that may be thrust outward from the cranial cavity through the internal auditory meatus.

Summary. Direct, alternating and radiofrequency currents of 40 microamperes or more were passed between silver wire electrodes introduced in various positions within the guinea pig's cochlea. Irreversible depressions of electrical responses, both microphonic and action potentials were produced. Microscopic examination showed that two important mechanisms were a) necrosis due to heating and b) formation of bubbles by electrolysis or by heating. Reversible physiological effects can also be produced by weaker DC polarization.

Two details of the bony anatomy that may be of electrophysiological significance are described.

Received September 29, 1950. P.S.E.B.M., 1950, v75.

Effects of Progesterone upon Ovulation in the Rhesus Monkey.* (18230)

CARROLL A. PFEIFFER.

From the Department of Anatomy, Yale University School of Medicine.

The hormonal control of ovulation in the primate is not very well understood, and it is extremely difficult to obtain ovulation consistently in the monkey by experimental means. There are a few authentic cases reported where ovulation has been produced experimentally with gonadotrophins(1-5).

* This investigation was aided by grants from The Anna Fuller Fund, the National Cancer Institute (U.S.P.H.S.), and the James Hudson Brown Fund of Yale University School of Medicine.

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2. Hartman, C. G., *Anat. Rec.*, 1942, v82, 419.