of experiments over number of animals refers to multiple transplants.) Five experiments out of a total of 170 yielded evidence of metaplastic ossification. In each of these the bone was represented by a minute islet only.

Nine guinea pigs of both sexes and from 200 to 350 g in weight were next used for bladder transplants into the rectus muscle. At the end of a month, the animals were sacrificed. In other cases animals were initially sacrificed and their bladders cut up for homoplastic transplantation into 17 others. Takes were comparable in the two groups. Eighteen of the 26 cases manifested ossification at the transplant sites. Five were completely negative. In all 5, epithelium was absent. (It is, therefore, possible that the grafts did not take. This cannot be inferred, however, because bone was sometimes found when epithelium had disappeared.) The 3 remaining presented considerable areas of non-calcified ground substance.

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Action of Curare on the Brain of the Frog.

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It is generally accepted that curare action is peripheral. An effect of curare on the brain has been occasionally assumed (Koelliker,[1] Steiner,[2] Meyer[3]), but never demonstrated conclusively.

We have attempted to present a definite proof of a central action of curare by the investigation of electroencephalograms on frogs.

Procedure. Frogs *(Rana esculenta)* were divided into 2 groups. One group was poisoned by curare (injection in the ventral lymph sac). Following this the electrical activity of the brain was investigated. The frogs of the second group were first pithed. After the electrical activity of the intact brain was determined, these frogs were poisoned by curare, and a second determination of the cerebral electrical activity was made. In a separate series of control experiments (12 frogs) it was ascertained that the electroencephalographic

* Aided by a grant from the Dazian Foundation for Medical Research.

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1 Koelliker, A., *Virchow's Arch.*, 1856, **10**, 58.

2 Steiner, J., *Das Amerikanische Pfeilgift Curare*, Leipzig, 1877, p. 36 f.

3 Meyer, H. H., Gottlieb, R., and Pick, E. P., *Experimentelle Pharmakologie*, Vienna-Berlin, 1936, p. 36.

pattern of a pithed frog remains essentially unaltered for over 12 hours, if no drugs are administered (Fig. 1, first graph).

This method enabled us to trace the normal brain waves, and their alteration in the state of curare poisoning.‡

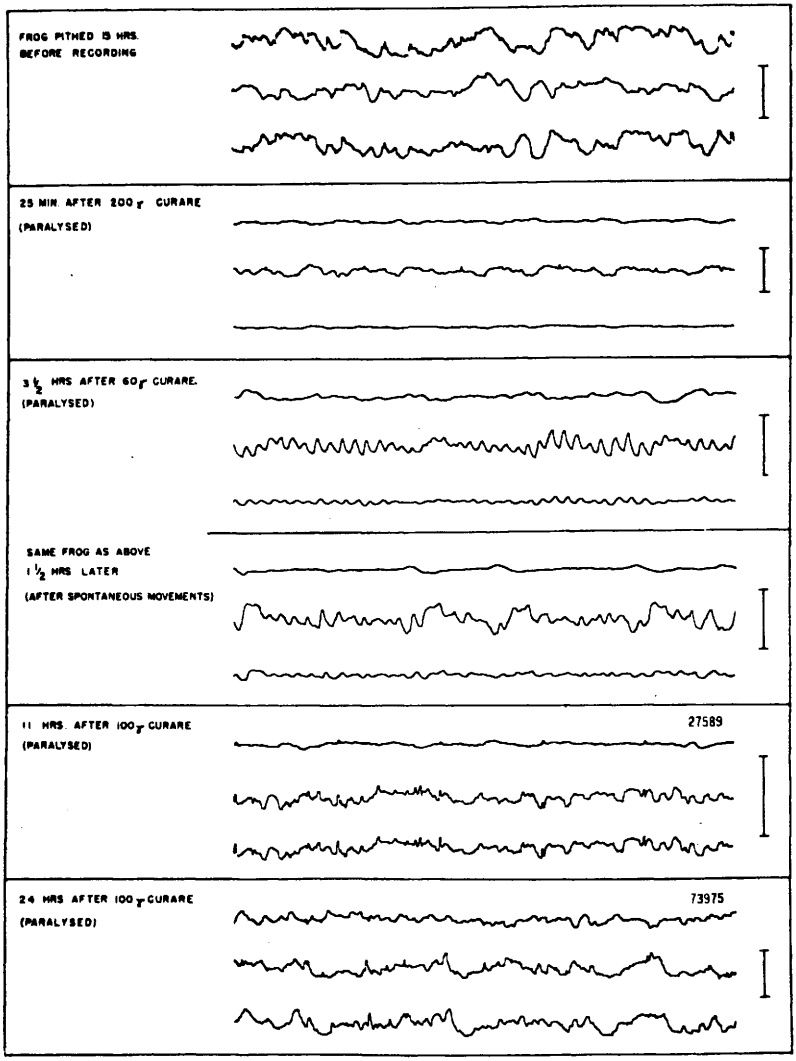

FIG. 1.

Electroencephalograms of frog. Length of each record—8 sec. Marks at right = 100 microvolt. All tracings from different frogs, except the third and fourth tracing.

‡ The highly effective curare (80 γ produces total paralysis of a frog of average weight of 40 g in about 15 to 20 min) was kindly supplied by Dr. Claus Unna from Merck & Co., Rahway, N. J.

We used 3 Hoagland electrodes.[4] The localization of the 3 electrodes in the brain of each animal was uniform. The first lead was taken from the midpoint of the left hemisphere, the second was taken from the anterior portion of the right hemisphere, and the third lead was taken from the right optic lobe. The leads were paired in 3 channels, the first from the electrodes 1 and 2, the second from electrodes 2 and 3, and the third channel from electrodes 1 and 3. Bleeding was carefully avoided.

Results. Curare dosage which produces even temporary paralysis of the legs causes a gradual disappearance of the electrical brain potentials. Thirty-eight frogs have been examined, and an alteration of the electroencephalographic pattern was observed in each experiment. First the small fast waves (beta waves) disappear, leaving only the slower alpha waves. These very soon decrease both in frequency and amplitude. After some time (the interval depending on the dose) an electroencephalogram similar to that seen in deep narcosis results. The heart rate remains apparently undisturbed in this state of curare poisoning. This can be recognized by the electrocardiogram which is superimposed on the electroencephalogram. This curare narcosis may continue for 12 to 24 hours after injection of small amounts of curare, and then gradually changes into a state of complete recovery and reappearance of normal electrical potentials (Fig. 1). This may occur before or after reappearance of muscular motility (Fig. 1, compare the last 3 graphs).

Conclusion. Curare produces in frogs a brain narcosis simultaneous with a peripheral motor paralysis. The former may be recognized in the gradual alteration and final disappearance of electrical brain waves, and after a period of several hours and even days in a complete restoration of the normal electrical pattern. The peripheral and central actions are independent of each other.

We are indebted to Dr. Israel S. Wechsler for the use of the electroencephalographic apparatus.

[4] Hoagland, H., *Science*, 1940, **92**, 537.