neutralize both MM and SK viruses but the reverse reactions do not occur.[13]

Theiler[1] reported the absence of serologic relationship between mouse encephalomyelitis and Lansing poliomyelitis but relative resistance of mice paralyzed by mouse encephalomyelitis to Lansing virus. He considered the resistance non-specific because it seemed to depend on the actual presence of paralysis. We have confirmed these results. Mice seem less suitable than hamsters for experiments of the kind.

The usefulness of MM virus as a laboratory tool deserves mention. The disease in intraperitoneally injected hamsters is remarkably like human poliomyelitis. Most of the animals survive and the majority of the survivors completely recover the use of their extremities. Antibodies develop rapidly. The virus is stable in glycerin for at least 17 months. Finally MM virus seems of especial interest by being intermediate between Lansing poliomyelitis and mouse encephalomyelitis and therefore especially adapted to taxonomic studies.

Conclusions. Neutralization and cross immunity tests indicate a relationship between MM and Lansing poliomyelitis but no relationship between MM and TO (Theiler original or low virulence strains) mouse encephalomyelitis. Complement-fixation tests relate MM virus and the GDVII strain of Theiler's virus. The results support the view that a group of poliomyelitis viruses exists which may be related by serologic tests.

[12] Francis, T., Jr., and Magill, T. P., *Brit. J. Exp. Path.*, 1938, **19**, 284.

[13] Jungeblut, C. W., *Am. J. Pub. Health*, 1944, **34**, 259.

15015

Further Investigations on the Recovery of Inhibited Conditioned Reactions.*

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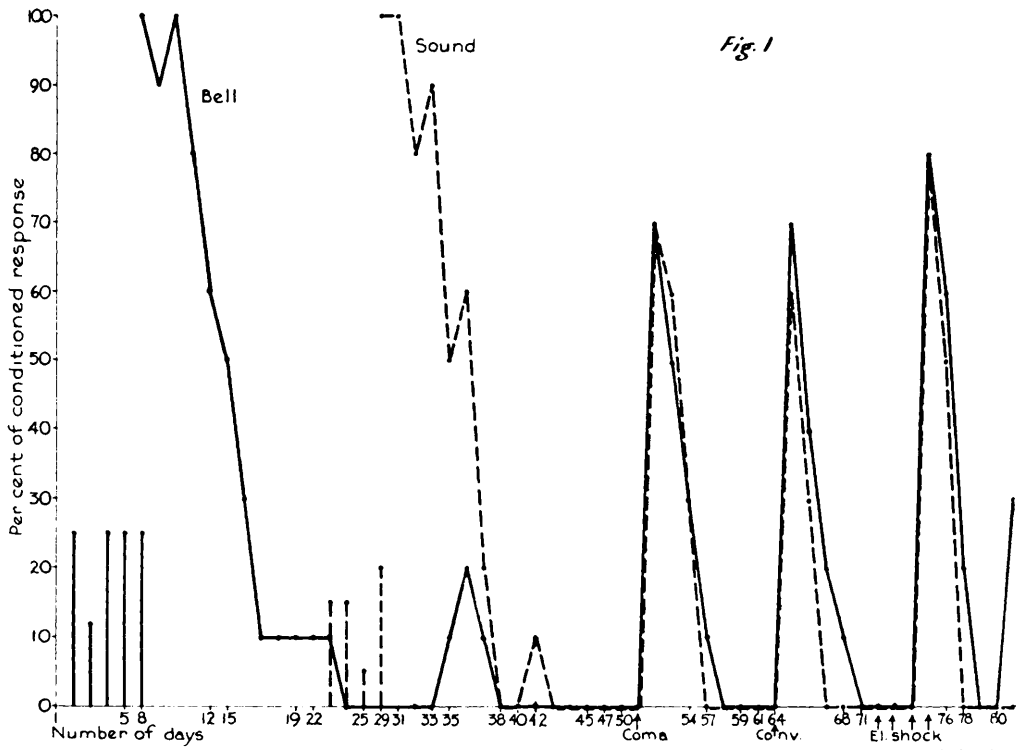
It has been shown in several preceding investigations[1] that conditioned reactions (c.r.) which had been inhibited in rats by lack of reinforcement can be re-established without further training process by subjecting the animals to either insulin coma or electrically induced convulsions. In order to gain insight into the neurophysiological processes underlying this effect it was thought desirable to extend the investigations to animals in which more than one c.r. had been established.

Method. Successful experiments were carried out on 10 rats. In some of these 2 to 3 c.r.'s were established in succession. However, no new c.r. was formed until the preceding c.r. had been inhibited by lack of reinforcement. A doorbell, a sound of 250 vibrations per second, and a light served as conditioned stimuli (c.s.). A shock applied to the grid on which the rat was standing was the unconditioned stimulus and the c.r. was an escape reaction as described in the previous papers.

In the second group of animals an attempt was made to maintain one conditioned reaction at about 100% and to inhibit another conditioned reaction without influencing the first. Such animals were used in order to decide the question as to whether the action of insulin coma and electrically induced convulsions is

* Aided by a grant from the Josiah Macy, Jr., Foundation.

[1] Gellhorn, E., Kessler, M., and Minatoya, H., PROC. SOC. EXP. BIOL. AND MED., 1942, **50**, 260; Gellhorn, E., and Minatoya, H., *J. Neurophysiol.*, 1943, **6**, 161; Kessler, M., and Gellhorn, E., *Am. J. Psychiat.*, 1943, **99**, 687; Gellhorn, E., *J. Lancet*, 1943, **63**, 307.

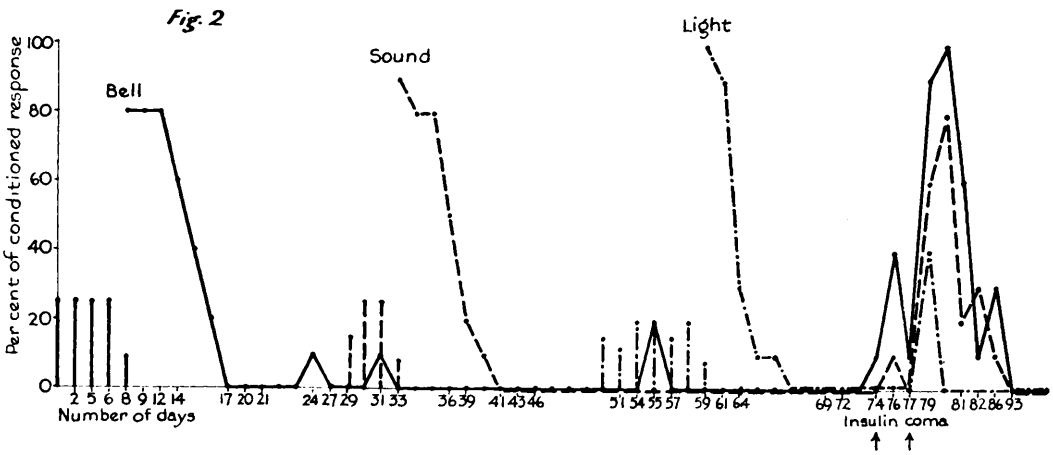


Effect of insulin coma, insulin convulsions and electroshock on the recovery of inhibited conditioned reactions of the rat.

———————— bell is conditioned stimulus.

— — — — — — "250" sound is conditioned stimulus.

The heavy and interrupted vertical lines indicate the number of reenforced conditioned stimuli which established conditioning in response to bell and "250" sound respectively.



The effect of insulin coma on the recovery of 3 inhibited conditioned reactions. Note that the conditioned reaction to the light recovers much less than that in response to the acoustic stimuli.

restricted to inhibited c.r.'s, or exerts a depressant effect on non-inhibited c.r.'s.

Results. I. *The Effect of Insulin Hypoglycemia and Electroshock on Several Inhibited Conditioned Reactions.* Fig. 1 to 4 are chosen as representative experiments in which

TABLE I.
Effect of Insulin Convulsions on the Restitution of Two Successively Inhibited Conditioned Reactions.

	Bell	Light
1. No. of reenforced conditioned stimuli	61	130
2. Degree of conditioning (%)	100	80
3. Duration of inhibition period (days)	49	9
4. Recovery of c. r. through insulin convulsions (%)	80	40

the effect of insulin hypoglycemia and electroshock was studied on the restitution of several inhibited c.r.'s. All figures confirm our earlier investigations in that electroshock and insulin hypoglycemia in the form of coma or convulsions restore previously inhibited c.r.'s but they demonstrate also that this effect may be shown simultaneously on several c.r.'s which had been established and inhibited in a definite sequence.

Fig. 1 shows the effect of insulin coma, hypoglycemic convulsions and electroshock on the restoration of previously inhibited c.r.'s in which the bell and the "250" sound were used as c.s. In this experiment one coma or one insulin convulsion was sufficient to induce a considerable recovery of the previously inhibited c.r. whereas several electroshocks given on successive days were necessary to produce a similar effect. The degree of restitution is similar for both types of c.r. studied in this experiment.

The experiment represented in Fig. 2 in which 3 c.r.'s were successively established and inhibited reveals after insulin coma some peculiar quantitative differences in the reestablishment of the previously inhibited c.r. After the coma the c.r. to light, to the "250" sound, and to the bell are temporarily reestablished but contrary to what one might expect, the reaction to the bell is restored most and that to the light least, in spite of the fact that the last reaction to be established and inhibited before the hypoglycemic coma was employed was that to the light. It is worthy of mention that the reaction to the bell could be re-established to 100% in spite of the fact that it had been completely inhibited for two months.

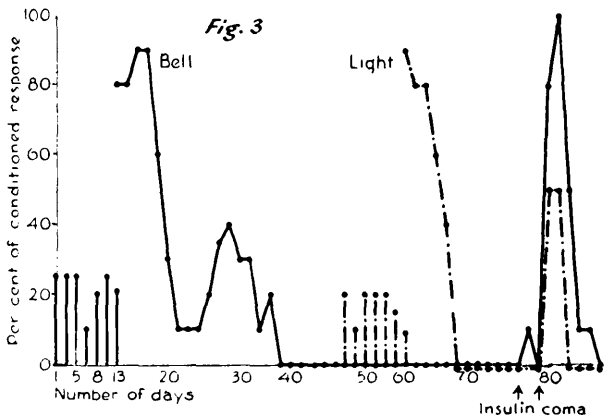
Table I and Fig. 3 and 4 give further examples of the recovery of 2 inhibited c.r,'s after insulin hypoglycemia and electroshock. In the experiments of Table I and Fig. 3 the c.r. to the bell was first established and inhibited and the same processes were induced with the light as c.s. In another experiment (Fig. 4) the same procedure was employed in the reverse sequence. The experiments show clearly that the results are independent of the temporal sequence. The restitution, after hypoglycemic coma, of the c.r. to the bell as c.s. is always greater than that seen in response to the light.

Fig. 4 shows also that during the training period 220 combinations of light and shock failed to establish a c.r. The conditioning test performed at the end of this period gave a positive response of only 10%. Hereafter, a conditioned reaction to the bell was established with 80 combinations of bell plus shock. Although the light was not employed as a c.s. during this period a positive reaction to the light was seen in 50% of the responses at the end of the training period involving the bell as c.s. Apparently processes of irradiation (Anrep[2]) are not entirely confined to stimuli belonging to the same modality.

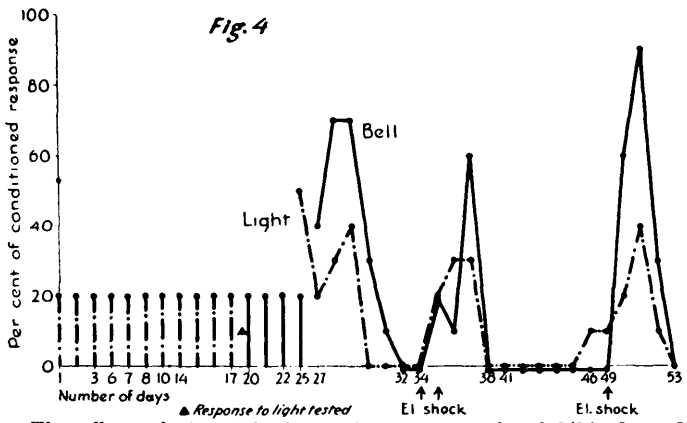
From these and other experiments not illustrated in this paper, we know that it is far more difficult to establish a c.r. to a light than to a sound in the rat. Moreover, the c.r. to the light is more easily inhibited by lack of reinforcement than the c.r. established in response to a sound. Taking these data into account, it seems to follow:

1. That the degree of temporary recovery of inhibited conditioned reactions is within fairly wide limits independent of the temporal sequence in which the reactions had been established. 2. That the degree of recovery is related to the stability of the conditioned reaction prior to its inhibition by lack of reenforcement.

[2] Anrep, G. V., *Proc. Roy. Soc. London, Ser. B*, 1923, **94**, 404.



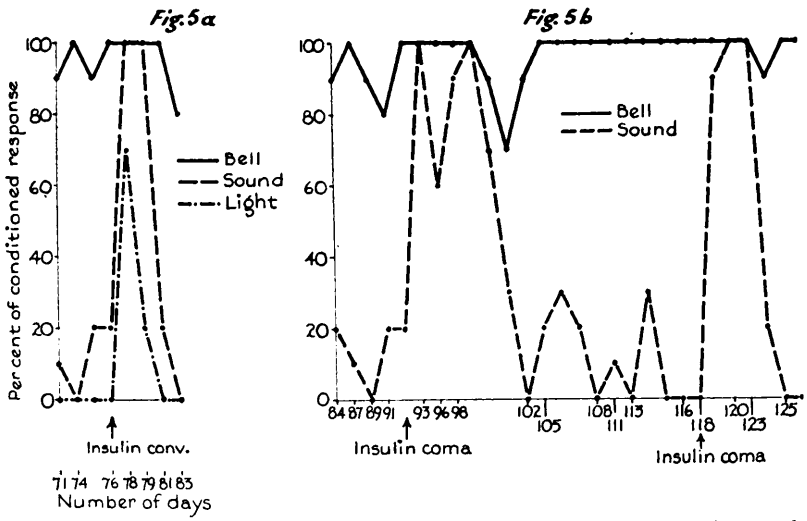
The effect of insulin coma on the recovery of 2 inhibited conditioned reactions.



The effect of electroshock on the recovery of 2 inhibited conditioned reactions.

II. *Experiments on Rats with Positive and Negative Conditioned Reactions.* In several instances experiments were performed in which we utilized the degree of stability of different c.r.'s in order to establish positive conditioned reactions and negative (inhibited) c.r.'s. In other experiments, one c.r. was more inhibited than another in order to maintain a positive c.r. of the latter but a negative c.r. of the former. The experiments of Fig. 5 may serve as an example.

In the experiment of Fig. 5A, a conditioned reaction to the bell was first established. This was followed by the establishment of a conditioned reaction to the "250" sound and finally to the light. Before the c.r. to the "250" sound was established, the c.r. to the bell had been extinguished by lack of reenforcement. When the reaction to the "250" sound was being established there was a decided state of irradiation (*cf.* Anrep) during which not only the reaction to the "250" sound but also to the bell became maximal. The animal was very alert and a 100% c.r. to the light was established in 4 days. Then the rat was tested for 3 weeks. This procedure usually leads to a complete loss of the c.r. in a few days. In this animal, however, the c.r. was retained almost completely. It was therefore decided to increase the rate of inhibition by subjecting the animal to an increased number of non-reenforced conditioned stimuli. This was done with the "250" sound only, with the result that the c.r.'s to this stimulus as well as to the light were quickly abolished, whereas the more stable reaction to the bell remained unchanged. Fig. 5A shows that at the beginning of the

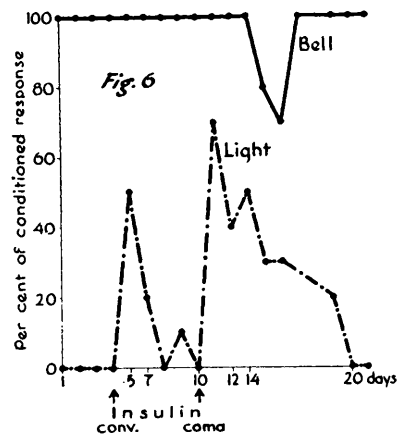


Represent sections of 2 experiments in which the conditioned reaction to the bell was maintained at 100% whereas the conditioned reaction to the light and to the "250" sound was inhibited. It is shown that under the influence of insulin coma and hypoglycemic convulsions the inhibited conditioned reactions are restored but the positive conditioned reaction to the bell remains uninfluenced.

record the reaction to the light was completely negative and that to the "250" sound varied between zero and 20%, whereas the reaction to the bell was strongly positive (90 to 100%). Insulin convulsions were induced and resulted in a temporary restitution of the c.r. for the "250" sound and for the light, while the c.r. to the bell remained uninfluenced and positive at 100%.

The story of the experiment, part of which is shown in Fig. 5B, is somewhat similar. Here again it was found that when the c.r. to the "250" sound was established, the reaction to the bell which had been inhibited, became positive again. The rat was tested for several weeks for its reaction to the bell and the "250" sound and again, contrary to the general rule, the c.r. remained positive for a long time. Eventually, however, the reaction to the "250" sound declined while that to the bell remained at a level varying between 80 and 100%. Thus the animal could be tested for the effect of insulin coma on the positive c.r. (bell) and the negative c.r. ("250" sound). As Fig. 5B shows, the hypoglycemic coma led to a temporary recovery of the inhibited reaction to the "250" sound without influencing the positive c.r. to the bell.

In Fig. 6 a similar experiment is presented with the modification that the positive and



The effect of insulin coma and convulsions on the positively conditioned reaction to the bell and the negatively (inhibited) conditioned reaction to the light.

negative c.s. belonged to different modalities (acoustic and optical respectively). Prior to the administration of insulin the reaction to the light was zero and that to the bell 100%. Insulin coma caused the reaction to the light to recover up to 50% during the first experiment and up to 70% in the second experiment. In both cases the reaction to the bell remained at 100%. Only 5 or 6 days after the administration of insulin did the reaction to the positive c.s. decline slightly. From the time rela-

tions it appears likely that this effect is not due to insulin hypoglycemia but rather due to some irradiation of inhibition associated with the decline in the c.r. to light. The experiments show clearly that insulin coma and convulsions act specifically on inhibited c.r.'s without influencing positively conditioned reactions.

Further experiments on animals with partially conditioned reactions support this interpretation. At first the c.r.'s to the bell and the "250" sound were fully established and then inhibited. Different degrees of inhibition were obtained with the procedures mentioned previously. In the first animal we succeeded in maintaining a c.r. to the bell varying between 50 and 60% whereas the reaction to the "250" sound was inhibited, the response varying between zero and 10%. This condition persisted for 10 days prior to the administration of insulin which caused a coma. During the following 2 days the reaction to the bell rose to 100% and that to the sound to 60%. In another experiment the c.r. to the bell varied between 30 and 40% whereas that to the "250" sound was completely negative. This condition was present for seven days before insulin was administered. Hypoglycemic coma induced the temporary restoration of the reaction to the bell to 100%, and to the "250" sound up to 60%. From these experiments it follows that the degree of restitution of inhibited conditioned reactions is somewhat related to the degree of inhibition. No inhibitory effect was found in any of these experiments on the positive conditioned reactions.

Discussion. The experiments show that the degree of restoration of an inhibited c.r. depends on the stability of the c.r., which, other conditions being equal, is determined by the nature of the c.s. Thus it was found that a c.r. in response to an acoustic stimulus was restored to a higher degree than a c.r. established in response to a light. This holds true even for those cases in which prior to the inhibition both c.r.'s had been perfected to a similar degree. The duration of the period of inhibition seemed to be of little importance.

Observations on positive and negative c.r.'s showed conclusively that insulin hypoglycemia and electroshock restored the inhibited c.r.'s without diminishing the positive c.r.'s. The latter result differs from that of Rosen and Gantt[3] who studied the effect of repeated metrazol convulsions on conditioned reflexes in 4 dogs and found in 3 of their dogs a diminished differentiation and in one dog which was characterized as a labile hyperexcitable animal an improved differentiation on the days when metrazol was injected. Rosen and Gantt interpreted the work of Gellhorn, Kessler and Minatoya as being in complete agreement with their own since in both instances inhibited reactions were converted into excitatory c.r.'s. However, the new experiments presented in this paper clearly show a fundamental difference between the study of Rosen and Gantt and our own work since restoration of previously inhibited c.r.'s is not accompanied by a loss or diminution of the positive (non-inhibited) c.r.'s. In other words, there is no indication whatever that a dedifferentiation characterized by a loss of conditioning of the positive c.r. and a gain of the negative (inhibited) c.r. is caused by insulin hypoglycemia and electroshock in our animals. The dedifferentiation observed by Rosen and Gantt may be due to the fact that dogs are more sensitive to convulsions than rats and that a relatively long series of metrazol injections was employed.

Summary. The recovery of inhibited conditioned reactions occurring under the influence of insulin hypoglycemia, and electroshock which was described earlier was subjected to further experimental analysis. It was found that:

1. Several conditioned reactions which had been established and inhibited in a definite temporal sequence may recover simultaneously under the influence of hypoglycemic coma or convulsions or as the result of electrically induced convulsions. The degree of recovery is related to the degree of stability of the conditioned reaction prior to its inhibition but is within wide limits independent of the time which has elapsed since the conditioned reaction had been established.

2. The restitution of inhibited conditioned reactions is not accompanied by a change in

[3] Rosen, V. H., and Gantt, W. H., *Arch. Neurol. Psychiat.*, 1943, **50**, 8.

the response of positively established conditioned reactions.

It is concluded that insulin coma and electroshock may act specifically on inhibited conditioned reactions without causing dedifferentiation.

I am much indebted to Miss Kathryn Seese for her help in this work.

15016

Postmortem Studies on Hypertensive Rats Chronically Intoxicated with Lead Acetate.

R. S. DIAZ-RIVERA* AND ROBERT C. HORN, JR. (Introduced by J. Q. Griffith.)

From the Robinette Foundation of the Hospital of the University of Pennsylvania.

Detailed descriptions of the clinical picture of chronic lead poisoning are found in almost all acceptable textbooks of general medicine. The accompanying hypertension in some cases of the disease has been the subject of many publications, but this problem is still unsolved. Exhaustive studies on the pathologic changes that may occur in chronic plumbism, especially among humans, have served to a certain extent to complicate the problem. Vigdortchik[1] states that "nephrosclerosis is not necessarily a companion of lead hypertonia; in most cases hypertonia is accompanied by no kidney modifications although work with lead undoubtedly predisposes to some kidney trouble and to nephrosclerosis in particular. Such kidney modifications in lead cases occur about 3 times as often as in non-lead cases." Belknap[2] denies the presence of hypertension among human beings chronically intoxicated with lead and in contact with the poison for a period of 5 to 20 years. Other investigators[3,4,5] claim that lead is perhaps the only vascular poison, and intoxication in man leads to hypertension not only during the acute episodes, but also in chronic plumbism. They agree that prolonged exposure to the poison results in an arteriosclerotic nephritis.

Fouts and Page[6] failed to produce hypertension in dogs chronically intoxicated with lead. They suggest further studies of this phenomenon on human beings since the evidence on which it is based is very slim. Dominguez failed to produce hypertension in rabbits with either lead acetate or lead carbonate.[7] Nevertheless, Griffith and Lindauer[8] were successful in producing a hypertonia in rats within 30 to 80 days after daily administration of 70 mg of lead by stomach tube.

The object of the experiment reported herein was to study the pathologic changes that occur in the tissues of rats which have developed hypertension following chronic lead poisoning.

Method. Thirty young and healthy albino rats were employed in this experiment. Lead acetate in doses of 90 mg (70 mg of lead) was administered daily for 50 days with omission of every 7th day. The poison was dissolved in 2 cc of water and was given by stomach tube.

Before the administration of the first dose of lead the systolic blood pressure of all rats was measured by the indirect method devised by Griffith.[9] These readings varied between 90 and 130 mm Hg. Subsequent blood pres-

* Formerly Fellow in Internal Medicine, University of Pennsylvania Medical School.

1 Vigdortchik, N. A., *J. Indust. Hyg.*, 1935, **17**, 1.

2 Belknap, E. L., *J. Indust. Hyg. and Toxicol.*, 1936, **18**, 380.

3 Fishberg, A. M., *Hypertension and Nephritis*, Ed. 4, 1939, Lea and Febiger Co., Philadelphia.

4 Zadek, E., *Z. f. Klin. Med.*, 1931, **116**, 241.

5 Teleky, cited by Zadek.[4]

6 Fouts, P. J., and Page, I. H., *Am. Heart J.*, 1942, **24**, 329.

7 Dominguez, R., *Arch. Path.*, 1928, **5**, 577.

8 Griffith, J. Q., Jr., and Lindauer, M. A., *Am. Heart J.*, 1944, **28**, 295.

9 Griffith, J. Q., Jr., PROC. SOC. EXP. BIOL. AND MED., 1934, **32**, 394.