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# Failure of Hypnotic and Convulsive Agents to Alter the Course of Experimental Poliomyelitis.

CLAUS W. JUNGEBLUT.

*From the Department of Bacteriology, College of Physicians and Surgeons, Columbia University, New York.*

Little is known concerning the metabolism of the central nervous system in its relation to the factors which support or inhibit the propagation of neurotropic viruses. Yet it would seem that better knowledge of the chemical reactions which underlie the interaction between virus and substrate should materially contribute to our understanding of the infectious process itself. With the present analytical methods it is doubtful that a direct biochemical approach would yield any more concise data than are already on hand regarding such changes as disturbance in the operation of the oxidation-reduction potential of virus-infected nerve tissue.[1, 2] However, an indirect attack of the problem may be feasible by studying the effect of comparatively crude alterations in the central nervous system—brought about by physiological or pharmacological methods—on the evolution of the characteristic virus lesion.

One recent attempt in this direction was made by Howe and Bodian.[3] By section of the axone, these authors evidently succeeded in inducing an irreversible change in the metabolism of the nerve cell which rendered the affected territory relatively refractory to subsequent invasion by poliomyelitis virus. Certain drugs also cause a profound derangement in the metabolic function of the central nervous system, particularly the narcotics and hypnotics, which are capable of inhibiting the oxidation of substances essential in carbohydrate metabolism.[4-7] The possible usefulness of drugs of this type in modifying the action of neurotropic agents of disease has not yet been explored, except for the observation that death from botulism can be delayed in guinea pigs when these animals are subjected to

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[2] Jungeblut, C. W., and Feiner, R. R., *J. Exp. Med.*, 1937, **66**, 479.

[3] Howe, H. A., and Bodian, D., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 346.

[4] Quastel, J. H., and Wheatley, A. H. M., *Biochem. J.*, 1931, **25**, 117; 1934, **28**, 1521.

[5] Emerson, G. A., PROC. SOC. EXP. BIOL. AND MED., 1935, **33**, 171.

[6] Dameshek, W., Myerson, A., and Loman, J., *Am. J. Psych.*, 1934, **91**, 113.

[7] Wortis, S. B., *Am. J. Psych.*, 1936, **93**, 87.

ether anesthesia or placed under the influence of sedatives.[8] More recently the property of excessive doses of insulin and metrazol to elicit shock or convulsions has been put to effective therapeutic use in the treatment of certain nervous disorders. The precise mechanism of this form of therapy is still obscure. Gross pathological changes in the brain, which occur as the result of shock, indicate severe structural damage to nerve cells;[9-15] there is also evidence of depressed cerebral metabolism since hypoglycemic shock diminishes the oxygen utilization of brain tissue through the absence of available dextrose,[16, 17, 18] whereas metrazol convulsions achieve the same effect by decreasing the oxygen necessary for the combustion of this sugar.[19, 20, 21] The resulting anoxemia may act by stimulating the sympathetic system,[22] but it may also affect the brain directly by increasing cellular permeability.[23] In view of what has been said above, it was decided to determine whether the protracted administration of a powerful hypnotic, *i. e.*, luminal, or the production of systemic shock, by means of insulin or metrazol, had any effect on the course of poliomyelitis in the monkey.

*Experiment I. Effect of luminal depression:* One Rhesus monkey, weighing about 2000 g, received daily doses of 100 to 150 mg sodium luminal (sodium salt of phenyl-ethyl-malonyl urea) by the subcutaneous route, beginning 3 days before intracerebral infection with poliomyelitis virus and continued for 7 days after infection. An-

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17 Gellhorn, E., *J. Am. Med. Assn.*, 1938, **110**, 1433.

18 Wortis, S. B., *N. Y. State J. Med.*, 1938, **38**, 1015.

19 Himwich, H. E., Bowman, N. M., Fazekas, J. F., and Orenstein, L. L., PROC. SOC. EXP. BIOL. AND MED., 1937, **37**, 359.

20 Low, A. A., Sonenthal, I. R., Blaurock, M. F., Kaplan, M., and Sherman, I., *Arch. Neurol. and Psych.*, 1938, **39**, 717.

21 Himwich, H. E., Bowman, N. M., Wortis, J., and Fazekas, J. F., *J. Am. Med. Assn.*, 1939, **112**, 1572.

22 Gellhorn, E., *Arch. Neurol. and Psych.*, 1938, **40**, 125.

23 Spiegel, E., and Spiegel-Adolf, M., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 834.

other monkey of approximately the same weight was subjected to similar treatment, except that the drug was administered first on the day of infection and maintained thereafter. The amount of luminal given to both animals sufficed to induce profound stupor which lasted for several hours. One control monkey, infected with the same dose of virus (0.01 cc of a 5% suspension of the RMV strain) but left without drug treatment, accompanied this experiment. The results are given in Table I. It will be seen that both experimental animals developed complete paralysis in approximately the same length of time as did the control animal. Moreover, the cord lesions were identical in all 3 monkeys.

*Experiment II. Effect of hypoglycemic shock:* A total of 13 animals were used in this experiment and arranged in 3 groups. The first group consisted of 3 monkeys which received daily doses of from 3 to 8 units of insulin by the intravenous route, beginning 3 days before intracerebral infection with poliomyelitis virus and discontinued after infection. The second group was made up of a total of 6 monkeys, all of which were injected daily with similar doses of insulin, beginning 3 days before infection and maintained thereafter for 6 days. The third group contained 4 monkeys in which insulin treatment of similar dosage was begun on the day of infection and continued daily for a period of 4 days. The above experiment included 3 control monkeys, infected with the same dose of virus (0.01 cc of a 5% suspension) but left without treatment. The amount of insulin used in these tests was sufficient to lower the blood sugar to the convulsive level of about 30 mg %. However the degree of systemic response varied widely among different monkeys, doses of insulin which, upon first administration, induced severe shock in some animals, failing to produce the same effect in others except as the result of cumulative injections. In some instances of extremely violent symptoms it became necessary to resort to glucose administration in order to prevent coma and death. Because of these irregularities the number of shocks and their intensity varied considerably throughout the whole series but the dosage was individualized to the extent that each monkey experienced at least 3 moderately severe

TABLE I.
Effect of Narcotic Doses of Luminal on Experimental Poliomyelitis.

| Monkey No. | Dose of Luminal Sc., mg | Type of treatment | Dose of virus (5% suspension) Ic. | Result |
|---|---|---|---|---|
| 1 | 100-150 | before and after infection | 0.01 cc | Complete paralysis, 9 days |
| 2 | 100-150 | after infection | " | " " 7 " |
| 3 | — | — | " | " " 8 " |

hypoglycemic shocks during the entire course of the experiment. The results are listed in Table II. It appears from this table that the progress of the disease in the insulin-treated monkeys deviated in no significant way from that observed in the control animals. Likewise, histological examination revealed no fundamental difference in the distribution or severity of the cord lesions between the treated and untreated group.

*Experiment III. Effect of metrazol shock:* One Rhesus monkey of 2000 g weight was injected intravenously with daily doses of 0.3 to 0.6 cc metrazol (1 cc = 100 mg of penta-methylene-tetrazol in 1% sodium phosphate solution) for a period of 4 days following intracerebral infection with poliomyelitis virus. Another monkey of similar weight received daily injections of the same dosage of the drug, beginning 5 days before poliomyelitic infection and discontinued thereafter. Two control monkeys, infected with corresponding doses of virus (1 cc or 0.1 cc of a 5% virus suspension) but left untreated, completed this experiment. The dose of metrazol was large enough to induce in both animals violent clonic-tonic convulsions which set in a few seconds after injection of the drug and lasted for from 5 to 10 minutes. The results are given in Table III. It will be noted that paralysis developed in the treated and untreated

TABLE II.
Effect of Insulin Shock on Experimental Poliomyelitis.

| Monkey* No. | Dose of insulin Iv. | Type of treatment | Complete paralysis in |
|---|---|---|---|
| 4 | 3-8 units | before infection | 8 days |
| 5 | " | " " | 8 " |
| 6 | " | " " | 12 " |
| 7 | " | " and after infection | 6 " |
| 8 | " | " " " " | 7 " |
| 9 | " | " " " " | 7 " |
| 10 | " | " " " " | 8 " |
| 11 | " | " " " " | 9 " |
| 12 | " | " " " " | 9 " |
| 13 | " | after infection | 6 " |
| 14 | " | " " | 6 " |
| 15 | " | " " | 6 " |
| 16 | " | " " | 9 " |
| 17 | — | — | 8 " |
| 18 | — | — | 7 " |
| 19 | — | — | 7 " |

*All monkeys were infected intracerebrally with 0.01 cc of a 5% suspension of virus.

TABLE III.
Effect of Metrazol Shock on Experimental Poliomyelitis. Complete paralysis in 5 days.

| Monkey No. | Dose of metrazol Iv. | Type of treatment | Dose of virus (5% suspension) Ic. |
|---|---|---|---|
| 20 | 0.3-0.6 cc | before infection | 0.1 cc |
| 21 | " | after infection | 1 " |
| 22 | — | — | 0.1 " |
| 23 | — | — | 1 " |

group with no perceptible difference. Upon autopsy all monkeys showed severe lesions in the cord.

*Conclusions.* Neither the administration of narcotic doses of luminal nor the production of systemic shock by means of insulin or metrazol were capable of influencing the course of experimental poliomyelitis. Moreover, the extent and severity of the lesions in the spinal cord showed no significant difference between treated monkeys and untreated control animals. Even though essentially negative, the above results are considered important in demonstrating that propagation of the virus of poliomyelitis in the central nervous system is not affected by profound cytological and metabolic changes in the nerve tissue, as were produced by the methods employed in this work.

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## On the Detoxication of Phenylacetic Acid by Glucuronic Acid in Humans.

HARRY WAGREICH, HENRY KAMIN AND BENJAMIN HARROW.
*From the Department of Chemistry, City College, College of the City of New York.*

Using reduction methods, Quick[1] working with dogs, concluded that phenylacetic acid is excreted in the form of its glucuronide to the extent of 34%; and a considerable portion of the remainder appeared in conjugation with glycine. Working with human subjects, and using similar methods of determination, Ambrose, Power, and Sherwin[2] claimed that by far the largest quantity eliminated is in combination with glutamine, whereas only 5% appears to be conjugated with glucuronic acid.

[1] Quick, A. J., *J. Biol. Chem.*, 1928, **77**, 581.

[2] Ambrose, A. A., Power, F. W., and Sherwin, C. P., *J. Biol. Chem.*, 1933, **101**, 669.