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Significance of Early Appearance of Neutralizing Substances in Poliomyelitis of Man.*

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Although it has long been known that the serum of patients convalescent from acute anterior poliomyelitis contains an antiviral substance, the fact that a similar substance is present in the blood of the majority of normal adults has been recognized only in recent years.[1, 2] By analogy to the known subclinical acquisition of immunity against diphtheria, the assumption has been made that a similar mechanism is operative in poliomyelitis. Such a belief postulates wide dissemination of the virus with a minor incidence of actual paralysis. Endocrine factors have been suggested in certain recent experiments.[3] However, another group of investigators[4] has been unable to reproduce the data of the first group. Further, the exact rôle that the poliocidal substances play in preventing infection under natural conditions and in recovery from the disease has not been elucidated, it having been assumed that these substances are the humoral expression of the immune state. One of us,[1] in collaboration with others, showed that occasional samples of convalescent human serum were devoid of neutralizing substances, while Howitt[5] found 80 of 141 samples taken weeks or months after an acute attack to be likewise without these substances. She attributed her findings to the fact that many of her patients received convalescent serum therapy.

In an effort to obtain further information upon the behavior of

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1 Shaughnessy, H. J., Harmon, P. H., and Gordon, F. B., PROC. SOC. EXP. BIOL. AND MED., 1930, **27**, 742; *J. Prev. Med.*, 1930, **4**, 463.

2 Aycock, W. L., and Kramer, S. D., *J. Prev. Med.*, 1930, **4**, 189, 201; Fairbrother, R. W., and Brown, W. G. S., *Lancet*, 1930, **2**, 895; Schultz, E. W., and Gebhardt, L. P., PROC. SOC. EXP. BIOL. AND MED., 1931, **28**, 409; Faber, H. K., *J. Am. Med. Assn.*, 1931, **96**, 935; Brodie, M., *J. Exp. Med.*, 1932, **56**, 507; Kolmer, J. A., *J. Am. Med. Assn.*, 1935, **105**, 1956.

3 Jungeblut, C. W., and Engle, E. T., *J. Immunol.*, 1933, **24**, 267; *J. Exp. Med.*, 1934, **59**, 43; *J. Am. Med. Assn.*, 1932, **99**, 2091.

4 Hudson, N. P., Lennette, E. H., and King, E. Q., *J. Exp. Med.*, 1934, **59**, 543.

5 Howitt, B. F., *J. Infect. Dis.*, 1932, **51**, 574; Personal communication.

the poliocidal substances following an acute attack of the disease, we have titrated the serums from patients obtained as soon as possible after the onset of the acute disease and again after several months. Each of these serums has been mixed *in vitro* in several dilutions with 10 paralyzing doses of the virus (PMV) contained in a one percent centrifuged emulsion of glycerolated spinal cord removed from monkeys *(Macaca mulatta)* at the height of paralysis. Injection of the serum-virus mixtures intracerebrally into unused rhesus monkeys was the indicator of unneutralized virus.

The results of the experiments show that a majority of serums (12 of 14) contain the neutralizing substance quite early. Indeed, one patient, an adult, had a greater than average quantity of these substances even before becoming paralyzed. This observation appears to be unique in that a person with poliocidal substances in the blood subsequently developed paralysis. Additional observations will have to be made to determine if this is a regular or an exceptional phenomenon. Collateral determinations by the same serological technique on the serums of monkeys at various intervals during convalescence from the experimental disease have shown that poliocidal substance is not demonstrable until the ninth to fourteenth day after the onset of paralysis and then only irregularly. In this light, the interpretation of the data assumes special significance. Although 8 of the 14 serums were taken 1 to 3 days after pooled convalescent human serum was given in treatment, it does not appear likely, in view of the known low titre of such serums[6] that this quantity of poliocidal substance has been solely produced by passive transfer. Since these were all instances of sporadic poliomyelitis in a non-epidemic year, it is possible that these substances had been produced during a long incubation period. Against this assumption is the observation, the first upon record, of poliocidal substance being present in a patient in the preparalytic stage.

Comparison of the titre of the neutralizing substances several months later showed one patient with none (under the conditions of these tests), many with a quantity identical with the first titration and only a few (4 of 11) in which an actual increase was seen. These observations taken in conjunction with the inability of Kramer and Aycock[7] to demonstrate an increase in the incidence of these substances in a child population from a community where abortive and clinical poliomyelitis was prevalent, casts doubt upon

[6] Hudson, N. P., and Lennette, E. H., *J. Prev. Med.*, 1932, **6**, 335.

[7] Kramer, S. D., and Aycock, W. L., PROC. SOC. EXP. BIOL. AND MED., 1931, **29**, 98.

the importance of a single attack of poliomyelitis for the production of antiviral substance.

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Oxygen Utilization, Cardiac Output, and Related Circulatory Functions in Graves' Disease.

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The increased metabolic and circulatory rates in Graves' disease have been subjected to repeated quantitative study. The relation of these two functions was indicated by Fick in 1870 and may be expressed as follows:

$$\text{Cardiac Output (liters of blood per min.)} = \frac{\text{oxygen consumption (cc. of oxygen per min.)}}{\text{arterio-venous oxygen difference (cc. of oxygen per liter of blood)}}$$

Although previous workers have uniformly reported an abnormal increase both in the cardiac output and the rate of oxygen consumption, there has been a definite disagreement regarding the arterio-venous oxygen difference, which represents the number of cc. of oxygen taken up by each liter of venous blood during its passage through the lungs, or the average number of cc. of oxygen given off by each liter of arterial blood during its passage through the several tissues. It is the arterio-venous oxygen or A-V difference which is measured by the various foreign gas methods subsequently mentioned, the cardiac output being calculated from the quotient indicated above. Thus Liljestrand and Stenström,[1] using the foreign gas method of Krogh and Lindhard, and Bansi,[2] using the indirect Fick methods of Haldane and Christenson and of Redfield, Bock, and Meakins found the A-V (arterio-venous oxygen) difference decreased below normal. Fullerton and Harrop[3] and Boothby and Rynearson,[4] using the foreign gas method of Marshall and Grollman found no significant change in the A-V difference in Graves' disease as compared to normal. It is important to attempt to settle this disagreement for 3 reasons. First, the cardiac output

[1] Liljestrand, G., and Stenström, N., *Acta Med. Scand.*, 1925, **63**, 99.
[2] Bansi, H. W., *Z. für klin. Med.*, 1929, **110**, 633.
[3] Fullerton, C. W., and Harrop, G. A., *Bull. Johns Hop. Hosp.*, 1930, **46**, 203.
[4] Boothby, W. M., and Rynearson, E. H., *Arch. Int. Med.*, 1935, **55**, 542.