

## Effect on Pernicious Anemia of Massive Doses of Parenteral Liver Extract.

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With the increased use of parenteral liver extract for both the treatment of the relapse of pernicious anemia and the maintenance of normal blood levels during remissions of the disease, the questions of dose and the intervals between doses have been shown to be of great importance. Castle<sup>1</sup> states: "The parenteral injection at appropriate intervals of material derived from an amount of animal liver equivalent to the weight of that organ in man will suffice to maintain a patient with pernicious anemia in health for at least a year." The accepted dose for most patients with pernicious anemia to maintain the normal blood level is the material derived from 100 gm. of liver given at intervals of one to 3 weeks.<sup>2</sup> There is, however, in the literature the record of one case<sup>3</sup> maintaining a normal blood level for 120 days after massive doses of potent material; and there are 2 other suggestions<sup>4, 5</sup> that for several months individuals might maintain normal levels if given massive injections of concentrated material.

We have tried to determine whether patients with pernicious anemia could store the potent substance if given in massive amounts over a short period of time, and use it as their needs required. If a patient with pernicious anemia requires the material from 400 gm. of liver (as parenteral extract) for remission from relapse, and then that from 100 gm. every 2 weeks for the maintenance of a normal blood level, that patient would require the material from 700 gm. of liver for maintenance through 14 weeks. It is conceivable, however, that if this were given in a short period of time, some of the antianemic substance might be broken down, and that part of it might be excreted whole.

We have given massive amounts of potent material in divided

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<sup>1</sup> Castle, W. B., *Science*, 1935, **82**, 159.

<sup>2</sup> Murphy, W. P., *J. Am. Med. Assn.*, 1932, **98**, 1051.

<sup>3</sup> Wood, I. J., and Gardner, H., *Med. J. Australia*, 1935, **1**, 543.

<sup>4</sup> Tochowier, L., *Folia Haematologica*, 1934, **53**, 16.

<sup>5</sup> Abstract of Lecture Delivered in Vienna by Professor Bence of Budapest, *Foreign Letters, J. Am. Med. Assn.*, 1935, **105**, 1447.

doses to 4 patients and have required that they refrain from taking liver or liver extract in any form during a period of observation following the last of the massive dose. These patients all were proven to have pernicious anemia; all had had one or more definite relapses; all previously had had definite reticulocyte responses to the antianemic substance; all had complete anacidity; 2 had definite neurological signs; and with each, previous clinical observations had shown that if the maintenance dose were not sufficient or the interval between doses were too long, the individual began to relapse. Only one of these patients was in relapse at the start of the experiment.

This patient had an erythrocyte count of 0.69 million and a hemoglobin of 28%.\* He received an equivalent of 100 gm. of liver by intravenous injection of extract. Then, over a period of 3 weeks, he received an equivalent of 1650 gm. of liver by intramuscular injection of extract. He left the hospital only partially in remission with blood values of 2.8 million erythrocytes and a hemoglobin of 48%; and 49 days later, his peak count of 5.0 million erythrocytes and 84% hemoglobin was obtained, and he was in complete remission. It was only after 91 days following his last intramuscular injection of extract that he showed signs of relapse as evidenced by a falling off in his erythrocyte count and hemoglobin concentration.

The second patient had a normal erythrocyte count and hemoglobin at the time the massive dose was administered. She was given the equivalent of 1650 gm. of liver by intramuscular injections of extract during a period of 10 days. Her erythrocyte count immediately following the last of the massive dose was 4.6 million and hemoglobin 89%. Fifty-six days later, she showed a peak erythrocyte count of 5.1 million and hemoglobin of 98%. Ninety-eight days following the massive dose, she showed no signs of relapse, and her erythrocyte count was 4.8 million and hemoglobin 95%.

The third patient also was in remission when she received an equivalent of 1500 gm. of liver by intramuscular injection of extract over a period of 10 days. Immediately following the last of the massive dose, her erythrocyte count was 4.6 million and hemoglobin 96%. Her peak count occurred 70 days later, at which time her blood values were 5.4 million erythrocytes and 105% hemoglobin. Eighty-four days after the last of the massive dose of

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\* Sahli hemoglobinometer, standardized, so that 100% equals 15.6 gm. hemoglobin per 100 cc. of blood.

potent material, she showed no signs of relapse and her erythrocyte count was 5.1 million and hemoglobin 103%.

The fourth patient was also in remission. Her erythrocyte count was 4.8 million and hemoglobin 100%. She was given only a relatively large dose or the equivalent of 265 gm. of liver in one intramuscular injection of extract. After 56 days, she had begun to show mild signs of relapse as evidenced by slight gastro-intestinal symptoms; but the erythrocyte count and hemoglobin level showed very little change.

From these 4 cases, we cannot conclude that all patients with pernicious anemia would be able to store the excess of massive doses of active principle given over a short period of time. Nor can we say that any one of these patients was able to store a calculated amount of the material, because so far the remission of none of them has been as long as if the massive dose were given as small doses over a period of 20 or 30 weeks. However, each of these patients shows evidence of storage of some of the active principle, which storage has enabled each one to maintain normal blood levels for a relatively long period of time.

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#### Partial Pressure of Oxygen in Arterial Blood of Patients: Description of an Aerotonometer Method.

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The partial pressure of oxygen in the arterial blood has been measured indirectly by interpolation of O<sub>2</sub> content on the oxy-hemoglobin dissociation curve, and by estimation of solubilities of CO and O<sub>2</sub> in the subject's blood (Haldane), and directly by aerotonometry. The latter method has been used by Krogh<sup>1</sup> and by Barcroft and Nagahashi.<sup>2</sup> In this method of the latter authors some difficulty is experienced in keeping the equilibration pressure constant and in securing repeated samples of the small gas bubble for analysis. The present method avoids these two difficulties.

It has been customary to study anoxic patients by determining the oxygen saturation of the arterial blood and to assume that the

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<sup>1</sup> Krogh, A., and Krogh, M., *Skand. Arch. Physiol.*, 1910, **23**, 179.

<sup>2</sup> Barcroft, J., and Nagahashi, M., *J. Physiol.*, 1921, **55**, 339.