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## A study of metabolic effects of experimental polycythemia in dogs.

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Although the clinical and morphological signs of *plethora vera* are known to a large extent, the metabolic effects produced by increasing the amount of blood in the body have been but sparingly investigated. The present research deals with the latter question. The augmentation of the supply of blood was effected by intravenous transfusion of defibrinated blood taken from the same species. In one experiment direct transfusion was performed after connecting a femoral artery of one dog with a small branch of a saphenous vein in another. After each transfusion, as will be shown later, there developed a condition of the blood that closely resembled polycythemia, as observed in man. These experiments also bear upon certain phases of the general question of parenteral nutrition.

Seven experiments were conducted on as many apparently healthy dogs that were kept under observation for some time before the experiments were started. The majority of the experiments lasted from 5 to 6 weeks. Some dogs were under observation for even a longer time. Each experiment was divided into preliminary periods of normal nutritional conditions, and subsequent periods during which the metabolic influences of blood transfusion were studied. Two animals were put through a period of fasting that lasted 16 days in one case and 25 days in the other, during each of which two blood transfusions were performed to ascertain their possible nutritive value and metabolic effects. In some cases

[1] This series of experiments is the sixth of a group of reseaches, inaugurated in 1902 by Dr. Gies and now in progress in this laboratory, on the biochemical effects of change of volume of the circulating blood. See Gies: *American Medicine*, 1904, viii, p. 155; Posner and Gies: *Proceedings of the American Physiological Society: American Journal of Physiology*, 1904, x, p. xxxi; Hawk and Gies: *ibid.*, 1904, xi, p. 171; Meyer and Gies: *Proceedings of the Society for Experimental Biology and Medicine*, 1904, i, p. 44; Weingarten and Crohn: *American Journal of Physiology*, 1908, xxii, p. 207.

the effect of the ether narcosis was determined as was also the influence on metabolism of the operation itself without the transfusion. The body weight, the amount, specific gravity, and reaction of the urine, and the weight of the dried feces were noted in the daily record. In all experiments the total amounts of nitrogen that were ingested and the corresponding totals that were excreted in the urine were determined; in some, the total sulfur and phosphorus intakes and outputs were ascertained in addition. The urine was examined for coagulable protein, urobilin, blood and casts. In a special experiment a microscopic examination of the blood was made to determine the variations in the number of erythrocytes. The specific gravity was also ascertained by means of Schmaltz's pyknometer and the presence or absence of hemoglobinemia determined.

In all cases autopsies were performed and in one animal, that showed the metabolic changes especially well during life, a microscopic examination of the liver and kidneys was made. In order to obtain emphatic results in the determination of the metabolic effect of blood transfusion, it was necessary to transfer rather large quantities. The amount of transported blood ranged between 3.5 per cent. and 7.5 per cent. of the body weight at each transfusion. It was also found expedient to perform a number of transfusions at comparatively short intervals (from 6 to 8 days) in order to develop cumulative effects, if possible. For the purpose of checking the metabolic influence of distention of the vascular system and its filling up with liquid material, infusions of 0.9 per cent. NaCl solution were performed in the same manner and under the same conditions as the blood transfusions. In order fully to understand the metabolic changes produced by blood transfusion, it is necessary to ascertain the effects of serum and corpuscles separately, a task which has been made the object of a series of experiments now in progress.

The results obtained so far may be summarized briefly as follows:

Transfused blood does not remain in its entirety in the vascular system, but, as indicated above, its several constituents are disposed of unequally. The first to be removed is the water, which fact accounts for the greatly increased volumes of urine

excreted during the first few days after transfusion. However, the diuresis following transfusion of blood is very much less than that produced by infusion of 0.9 per cent. NaCl solution. In the case of the latter, the total volume infused appears in the urine of the succeeding twenty four hours. Nevertheless, the diuretic effect of blood transfusion is quite marked.

The excretion of nitrogen in the urine was decidedly increased by the transfusion of blood, the rise becoming more and more pronounced with each successive transfusion. To cite one instance: The average daily urinary nitrogen rose from 6.28 grams in the preliminary period of nitrogen equilibrium to 10.23 grams after the 4th blood transfusion. To what extent the different constituents of the blood contribute to this result; whether the increase of nitrogen is derived from the blood (the serum or corpuscles), or from the body proteins destroyed by any toxic action of the transfused material, or whether the increase is caused by both (the most probable thing) will be investigated later.

"Blood counts" show that the number of erythrocytes per unit of volume rises with each transfusion, which fact is due to the elimination of water, the red cells being retained in the vascular system a much longer time, in this manner causing a distinct polycythemia. By a series of transfusions it was possible to increase the number of erythrocytes from 7,272,000 to 13,512,000 in one cmm. In this connection it is interesting to note that, after rising, the "blood count" showed a decline which set in after a few days. Then another transfusion was performed, and the number of red cells increased still further. In this manner a continued and more and more pronounced polycythemia was produced. The specific gravity of the blood rose also with each transfusion. It is noteworthy, also, that after a few transfusions the specific gravity was relatively higher as compared with the number of red cells, showing a greater concentration of the blood serum proper. The specific gravity rose after a few transfusions from 1.066 to 1.103.

No decided increase in the nitrogen output has been observed after saline infusion. The daily urinary output of nitrogen from the control dog increased from 5.29 grams in the preliminary period of nitrogenous equilibrium to 5.91 grams after the *ninth* saline infusion.

The excretion of total sulfur in the urine has been found to run approximately parallel with that of nitrogen. The fluctuations in the amounts of total phosphorus in the urine do not allow of any definite deductions at the present time.

The defibrinated blood, after being filtered by suction, was in all cases moderately hemolytic, a change produced by the act of defibrination. Nevertheless, in the great majority of cases the urine passed after transfusion did not contain any hemoglobin, the organism of the dog apparently disposing of the same, completely storing its derivatives in the different structures of the body, especially the liver, which on post mortem examination proved to be of a dark brown, almost black color and contained large amounts of hemosiderin in the ferric state, as shown by microchemical examination of sections. In some instances very concentrated bile was found in the gall bladder. Accordingly there was a decided increase in the coloring matter of the feces and especially in the urine, conditions which, after a series of blood transfusions, were very greatly emphasized, the urine containing a large amount of urobilin.

All experiments ended with the death of the animal, the 4th or 5th transfusion of blood invariably proving fatal. It was possible to predict close approach to the danger line from the appearance in the urine of coagulable protein. Coagulable protein never was found in the urine until after a third or fourth transfusion had been made; its appearance preceded a rapid decline of the animal, the urine examination showing the presence of granulated casts and epithelial cells. The succeeding transfusion usually sufficed to produce hemolysis accompanied by hemoglobinuria, from which condition the animal never recovered. On microscopic examination, a section from such a dog's kidney showed, besides enormous hemorrhagic areas, parenchymatous degeneration of the epithelial cells of the tubuli contorti. In these respects experimental polycythemia resembles the polycythemia occurring in human beings, the latter disease terminating fatally in almost all cases, the urine containing coagulable protein and granulated casts.

With reference to the nutritive value of blood transfusion hardly anything can be said in favor of it, the body weight which is naturally higher immediately after transfusion gradually sinking to or even below the initial level. Even in fasting animals the transfusion

of blood did not appreciably retard the daily average loss in body-weight, but actually quickened it as a rule.

The work is nearing completion and its results will shortly be published in detail.

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## On the metabolic influence of magnesium sulfate in dogs, with special reference to the partition of the nitrogenous constituents of the urine.

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In these experiments, in which relatively large doses of magnesium sulfate were given to dogs, abscesses and sloughing followed subcutaneous injections, but were not caused by intramuscular or intravenous injections nor by administrations *per os*. Very large doses of magnesium sulfate could repeatedly be injected intravenously without causing death, when care was taken to conduct the process slowly.

Daily fluctuations in the weight of the animals, as well as in the volume and specific gravity of their urines, resulted chiefly from diuretic or diarrheal influences and the consequent compensatory tendencies.

Administration *per os* caused diarrhea. Bone ash in the food appeared to exert only a mechanical diminution of such diarrheal tendencies. Injections under the skin or into a muscle or into the circulation failed to elicit any evidence of diarrhea, except in one doubtful case after subcutaneous application. On the contrary, such injections appeared to make the feces drier and harder than ordinarily, and the urine volumes greater.

If there was any effect on the quantitative elimination of solid matter in the feces, it was not more than a slight increase. The same may be said of the content of nitrogen in the feces, and also of the fecal discharge of magnesium (after intravenous injection of magnesium sulfate).

In a general way elimination of nitrogen in the urine was increased after the normal periods, but the increase was not suf-