5. The complement fixation is of the greatest value in diagnosis, or as an indicator to the results of the treatment.

6. In all doubtful cases at least two or three Wassermann tests should be made before a diagnosis is decided on.

HEMOLYSIS DUE TO INTRAVENOUS INJECTION OF DISTILLED WATER *

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In the performance of a clinical test in which, to wash in a certain salt, the prescribed technic called for the intravenous injection of indefinite amounts of distilled water, it was found by a physician, who was trying the test on his own person before applying it to patients, that sufficient hemolysis was caused to produce chills, fever, considerable malaise, albuminuria and hemoglobinuria, lasting about four hours. It was afterward estimated that, as the individual weighed 84 kg. and as between 300 and 400 c.c. of water were injected in about fifteen minutes in addition to the relatively isotonic drug solution used, the amount of water introduced was equivalent to about 0.4 per cent. of the body-weight. As a search of the literature concerning hemolysis failed to reveal exact information as to the amounts of distilled water that may be injected intravenously without causing noticeable hemolysis, it seemed advisable to work out such quantitative estimations experimentally.

Here and there isolated observations have been recorded which indicate that large amounts of distilled water injected intravenously with considerable rapidity will cause hemolysis. For instance, Ilkewitsch¹ has found that in rabbits amounts of distilled water equivalent to 3 per cent. of the body-weight will cause death; but he was unable to find ill effects from smaller amounts equivalent to from 0.8 to 1 per cent. of the body-weight, and even recommends the injection of such amounts in the treatment of puerperal fever. In experiments on the effect of pancreatic extracts on glycosuria, Murlin and Kramer² noted an increased elimination of nitrogen after the intravenous injection of 150 c.c. of distilled water into a medium-sized dog, and thought this "probably due to hemolysis." In the older literature, the action of hypotonic salt solutions on the red blood-cells and tissues was exhaustively studied,³ and it was known at least as early as the time of Johannes Mueller⁴ that intravenous injection of water might cause hemolysis, but failed to do so if a certain proportion of salt was added to it. Nevertheless, when the practice of blood transfusion was first attempted, we find distilled water recommended⁵ as a transfusion agent, in preference to physiologic saline solution or blood. Some of the leading physicians⁶ of this country even recommended fresh cow's milk as the best transfusion fluid in the treatment of cholera, etc., until it was shown by Culcerq⁷ that fat emboli might result. More recently there seems to be a tendency to disregard the dangers of the intravenous

use of distilled water, as is shown in Ilkewitsch's recommendations in connection with puerperal fever, its use with salvarsan and elsewhere.

The following experiments, in which marked hemoglobinuria could be produced at will, show that the danger is a real one.

METHOD

To determine the toleration limit, varying amounts of distilled water, proportionate to the body-weight, were injected intravenously into dogs at known rates of speed. The amount of fluid and the rate were controlled by allowing the freshly distilled sterile water to flow from a buret, connected with positive air-pressure, into a small branch of the femoral vein. The first appearance of hemoglobinuria was noted in a bladder catheter, and its duration by repeated observation of the urine.

The presence of hemoglobinemia was determined by withdrawing at frequent intervals small amounts of blood by skin puncture into capillary tubes, which

RESULTS OF INTRAVENOUS INJECTION OF DISTILLED WATER

Animal		Distilled Water Injected, c.c.	Body-Weight, Per Cent.	Results
Dog	1	100	1.6	Distinct hemoglobinemia.
Dog	1	100*	1.6	Distinct hemoglobinemia (i. e., no apparent decrease in resistance).
Dog	2	98	0.8	Slight hemoglobinemia ($\frac{1}{2}$ original amount).
Dog	3	224	3.2	Marked hemoglobinemia and hemoglobinuria (double amount).
Dog	3	224*	3.2	Marked hemoglobinemia and hemoglobinuria (no apparent increase in resistance).
Dog	4	160	2.1	Marked hemoglobinemia, albumin and bile in urine ($\frac{1}{4}$ original amount).
Dog	2	350	2.6	Marked hemoglobinemia, albumin in urine.
Dog	7	182	3.1	Marked hemoglobinemia and hemoglobinuria.
Dog	7	138	2.3	Marked hemoglobinemia and hemoglobinuria.
Dog	7	250	4.0	Marked hemoglobinemia and hemoglobinuria.
Rabbit	9	35	2.5	Marked hemoglobinemia and hemoglobinuria.
Dog	12	184	1.9	Marked hemoglobinemia and slight hemoglobinuria.
Dog	15	35	0.4	No hemoglobinemia.
Dog	13	88	0.6	Slight hemoglobinemia (persisting less than 1 hour).
Dog	14	225	1.8	Marked hemoglobinemia; slight hemoglobinuria.

* Five days later.

were promptly sealed at one end and centrifuged. This method uniformly gave a clear colorless serum before the experiment and permitted the accurate detection of small amounts of hemoglobin in the serum. From 300 to 500 c.c. of water were given by stomach-tube half an hour before the experiment, to ensure sufficient diuresis. In a few cases complete blood examinations were made before and after the experiment.

RESULTS

In the first experiment (Dog 1) 100 c.c. (1.6 per cent. of body-weight) was arbitrarily chosen as relatively much greater than the estimated amount that caused hemoglobinuria in the human subject. At the same time a second dog (Dog 2) was given relatively one-half this amount (98 c.c., or 0.8 per cent.). The rate of injection in the two dogs was more rapid than in the man and yet, as may be seen in the accompanying table, both failed to produce more than a moderate amount of hemoglobinemia and no hemoglobinuria.

* From the John Herr Musser Department of Research Medicine, University of Pennsylvania. Department of Medicine.

1. Ilkewitsch, W. J.: *Zentralbl. f. Gynäk.*, 1913, xxxvii, 1399.

2. Murlin, J. R., and Kramer, B.: *Jour. Biol. Chem.*, 1913, xv, 365.

3. Hamburger: *Osmotischer Druck und Ionenlehre*, 1, 360.

4. Mueller, Johannes: *Textbook of Physiology*, Ed. 2, translated by W. Baly, 1840, 1, 118.

5. Netter: *G.-z. d. hdp.*, 1879, No. 139, p. 1107.

6. W. Pepper, J. W. Howe, T. Gaillard Thomas (quoted in *Med. Rec.*, New York, 1883, xxiii, 434).

7. Culcerq: Quoted in *Med. Rec.*, New York, see Note 6.

Then, because in the human case the toxic symptoms had appeared only after a second injection, repeated after five days interval, the first experiment (100 c.c. dose) was repeated on the same dog after five days, but again without hemoglobinuria.

In the next dog a relatively double dose, 224 c.c. (3.2 per cent.), was given during fifteen minutes. Five minutes after the injection was stopped, the urine appearing in the catheter was still yellow and free from hemoglobin; eight minutes later it suddenly changed to a dark claret color, which persisted for more than four and less than sixteen hours. The same results were obtained by repeating the experiment five days later, tending to show that no relative increased or decreased resistance of the blood had thus far been developed. Subsequent experiments seemed to show that the toleration limit in dogs and rabbits was near 2.5 per cent. of body-weight, when the water was injected during a period of from five to fifteen minutes; but in two other experiments, designed to determine whether larger amounts might be given without hemoglobinuria if the injection extended over longer periods of time, bloody urine appeared when less than 2 per cent. of the body-weight had been introduced (once at the end of 13 minutes when 1.9 per cent. had been injected, and once after forty-five minutes when 1.8 per cent. had been injected). It appears, therefore, that considerable individual variation exists, for in contrast to these results we have two earlier experiments in which 2.1 per cent. and 2.6 per cent. failed to give hemoglobinuria.

It was found that much smaller amounts of distilled water would give a transient though distinct hemoglobinemia, without hemoglobinuria. In Dog 2, above mentioned, 0.8 per cent. of body-weight of distilled water sufficed to give a distinct hemoglobinemia by the method described, although before the experiment, as in every case, the serum was absolutely clear. Experiments on Dogs 13 and 15 showed that (disregarding individual idiosyncrasy) the limit at which noticeable hemoglobinemia appear was between 0.4 and 0.6 per cent. of body-weight.

In the few blood examinations made, no anemia was noted, the only change being a decrease in the resistance of the red cells (especially in minimal resistance; that is, some hemolysis occurred in relatively stronger hypotonic salt solution). For instance, with Dog 7, whereas before the injection, complete hemolysis occurred in 0.4 per cent. sodium chlorid; partial in from 0.425 to 0.5 per cent., and no hemolysis at 0.525 per cent., one hour after injection of distilled water, complete hemolysis occurred at 0.425 per cent.; partial at from 0.45 to 0.55, and none at 0.6 per cent. These changes were still present after twenty-four hours.

The same toleration limit for hemoglobinuria, roughly speaking, was found to exist for the rabbit. Another experiment showed that, contrary to Ilkewitsch's statement, as much as 8 per cent. of body-weight might not cause death.

A consideration of the results of these experiments shows that although amounts of distilled water necessary to produce hemoglobinuria in the dog are larger than are apt to be used clinically (2.5 per cent. of 80 kg. being 2 liters), nevertheless the smaller amounts produce an undesirable hemoglobinemia. Also other factors, as lowered resistance or individual idiosyncrasy, might with even smaller amounts produce bad results. Furthermore, although these experiments show

fairly definite levels for the appearance of hemoglobinuria in dogs, it may well be that in man, as in the case above mentioned, these levels are considerably lower.

On account of the constantly growing number of diagnostic and therapeutic measures in which intravenous infusion is used, it is therefore important that clinicians should bear in mind the possibility of causing hemoglobinemia or hemoglobinuria by the use of fluids which are not rendered isotonic by the addition of the particular salt used.

CONCLUSIONS

1. Rapid intravenous injection of distilled water, in amounts equal to from 2 to 3 per cent. of the body-weight or more, will cause in the dog transient hemoglobinuria and albuminuria.
2. Lengthening the duration of injection time from five to forty-five minutes is without noticeable effect, though a much slower injection might give different results.
3. Hemoglobin-stained urine usually appears in the bladder catheter in from twenty-five to thirty minutes after the beginning of the injection. The hemoglobinuria lasts approximately from four to sixteen hours, depending on the severity of hemolysis.
4. Much smaller amounts (as low as from 0.4 to 0.6 per cent.) are sufficient to cause a noticeable hemoglobinemia without hemoglobinuria.
5. Hemoglobinemia appears within from two to four minutes after the beginning of the injection and may last twenty-four hours.
6. In doses that just fail to cause hemoglobinuria, albumin and bile may appear in the urine the next day.
7. No noticeable anemia is caused, but there is a temporary decrease in the minimal resistance of the red blood-cells.

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BLOOD TRANSFUSION

REPORT OF ONE HUNDRED AND THIRTY-FIVE TRANSFUSIONS BY THE SYRINGE-CANNULA SYSTEM*

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The purpose of this paper is to report some of the results of blood transfusion by the syringe-cannula system, in the cases referred to me from time to time. Limitations of space will not permit of a thesis on the scientific aspects of the subject and the many correlated problems, a discussion of the numerous theoretical considerations involved, or full case-reports and blood and hemoglobin records. These are reserved for a later publication.

The cases transfused vary considerably and include the diseases enumerated in Table 1. The ages of the patients are given in Table 2.

In no case was there thrombosis, embolism or sepsis; in no case was a skin incision made; in no case was anesthesia given; in no case was death due to any untoward effects of transfusion.

Post-mortem examinations were made in two cases several weeks after transfusion. Veins punctured were examined by Dr. Charles Norris, director of laboratories of Bellevue and Allied Hospitals, who could find no

* Read before the Clinical Congress of Surgeons of North America, Nov. 11, 1913.