Changes in the blood volume of coli fever dogs were followed by means of hourly determinations of hemoglobin and blood solids. In uncomplicated experiments the blood solids showed constantly an increase running parallel with the increase of body temperature. This increase varied at the maximum point from 3.3 to 7.6 per cent. in five different animals. It is illustrated in the accompanying figure (A) as well as in Figures 2 and 3 of the following paper on dextrose plethora. Similar hemoglobin changes were quite definite in some cases.

The increase in the percentage of the blood solids is interpreted as a diminution in the volume owing to loss of water. We are not yet prepared to discuss the fate of this water, but have noted no significant increases in the amount of urine. The loss of water from the circulation is probably the chief factor in the decreased heat dissipation which accompanies the initial rise of temperature in infectious fevers.

80 (1540)

Dextrose plethora and its antipyretic effect in coli fever.[1]

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The antipyretic action of dextrose was pointed out by one of us in the PROCEEDINGS of this Society about one year ago in connection with observations upon rabbits with peptone fever, and febrile human individuals to whom the sugar had been administered by mouth.[2] In view of the experiments reported some

[1] The assistance of an appropriation from the Bache Fund of the National Academy of Sciences in support of the researches reported in this and in the preceding paper is gratefully acknowledged.

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[2] "The Antipyretic Action of Dextrose," PROC. SOC. EXP. BIOL. AND MED., 1919, XVI, 136.

In connection with the demonstration that antipyretic drugs increase the blood sugar this has been interpreted as a potent factor in their action. See Barbour and Herrmann, "On the Mechanism of Fever Reduction by Drugs," *Proc. Nat'l. Acad. of Sci.*, 1920, VI, 136.

years ago from Dr. Lusk's laboratory by Fisher and Wishart[1] it was believed that our observations could be correlated with the dextrose plethora described by the last mentioned investigators.

To this end dextrose was first given to dogs by mouth in doses varying from 1 to 10 gms. per kilo with quantities of water, usually sufficient to make about a 30 per cent. solution. Observations were made upon dogs which had just been fasted for two days subsequent to receiving an adequate daily ration of meat, bread, and lard. Two dogs showed a maximum increase of 15–20 per cent. in the hemoglobin and 6.6–8.6 per cent. in the total blood solids. In no case was there any indication that the blood volume was increased.

The maximum rises of temperature in these two experiments were 0.6° and 0.2° C. respectively, the minimum temperatures noted being 0.2° respectively above and below normal, (hourly observations after injection of dextrose). In two similar experiments with normal dogs, no variation greater than 0.2° C. was observed in the course of the day.

In two dogs which had been given a coli injection (325,000 million bacilli per c.c.) on the previous day, reductions in temperature of −0.2° and −0.5° C. respectively were noted (at the end of three hours). From the above it was concluded that it is difficult to give dextrose by mouth in such a dose as constantly to affect the temperature either of normal or of fever dogs.

The changes in the blood above described must be attributed to a tendency of the sugar to enter the circulation slowly or else to leave it rapidly, in either case abstracting water. To confirm the observations on this blood concentration may be cited three experiments in which dextrose was given per os simultaneously with a coli injection. In one of these was noted an exaggeration of the usual (3–7 per cent.) increase in blood solids produced by such coli injections. In the hemoglobin content, 23, 29 and 15 per cent. increases were noted.

Knowing that a plethora could be induced by dextrose if introduced into the circulation in the proper amounts and at the proper rate, intravenous injections[2] were next instituted. Two

[1] Fisher, G. and Wishart, *J. Biol. Chem.*, 1912, xiii, 49.

[2] Starling, E. H., *Jour. Physiol.*, 1899, 24, 317.

normal dogs and two dogs with coli injections were carefully studied, being kept in a comfortable recumbent position throughout the day without anesthesia. The following table illustrates the results:

TABLE I.

SINGLE INTRAVENOUS INJECTIONS OF DEXTROSE IN QUIET UNANESTHETIZED DOGS.

Date.	Dog.	Condition.	Dextrose, Dose Gms. per Kilo.	Water, C.c. per Kilo.	Normal.		With Fever.		With Plethora.		With Secondary Rise.	
					Temp. °C.	Bl. Solids, %.	Temp. °C.	Bl. Solids, %.	Temp. °C.	Bl. Solids, %.	Temp. °C.	Bl. Solids, %.
1/24	41	Normal...	3.4	6.8	38.7	20.9	—	—	38.7	20.0	39.1	20.7
1/31	49	Normal...	2.2	4.4	37.2	18.5	—	—	37.2	17.5	37.5	19.2
1/24	47	Coli fever.	3.6	7.2	39.0	18.1	40.6	19.3	40.2	16.7	41.1	20.7
1/31	41	Coli fever.	4.3	8.6	38.1	19.7	39.0	21.1	38.4	19.4	39.0	22.5

From the table it is obvious that dextrose given intravenously in fever dogs produces a plethora. The volume change is approximately two to three times as extensive as that produced by corresponding injections in normal dogs. The normal dogs (Fig. 1) showed no diminution in temperature, but after about half an hour the curve began to rise, maximum increases of 0.4° and 0.3° respectively, having been noted. The return to normal occurs after about three hours. In the fever dogs (Fig. 2), on the other hand, the temperature was depressed within fifteen minutes in the one case falling 0.4° and in the other case 0.6°. This was followed by a prompt return to and above the former level. In

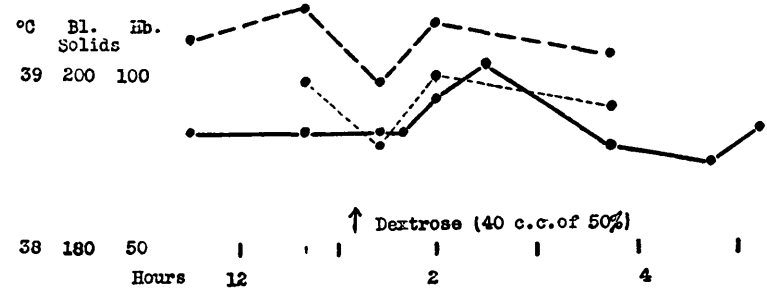

FIG. 1. Dog 41. January 24, 5.9 kilos.
— — — — blood solids.
- - - - - hemoglobin.
———— rect. temp.

both of these experiments the curves for hemoglobin and total solids ran qualitatively parallel to the temperature curve, both in changing from normal to fever, from fever to antipyretic effect, and from antipyretic effect back to the new high level.

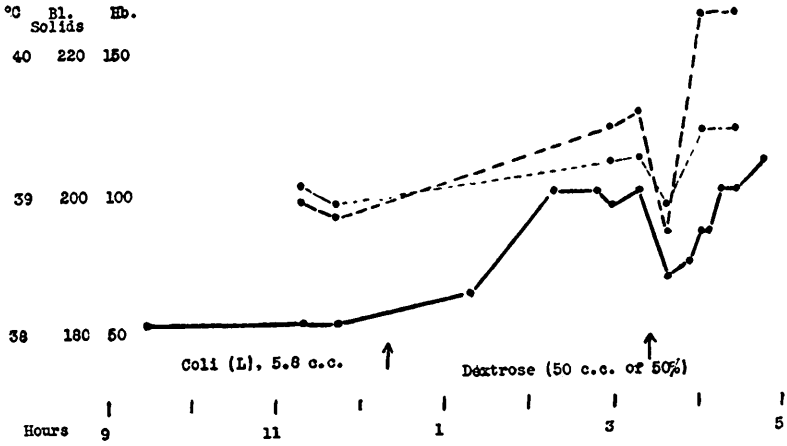

FIG. 2. Dog 42. January 31, 5.8 kilos.
— — — — blood solids.
- - - - - - hemoglobin.
———— rect. temp.

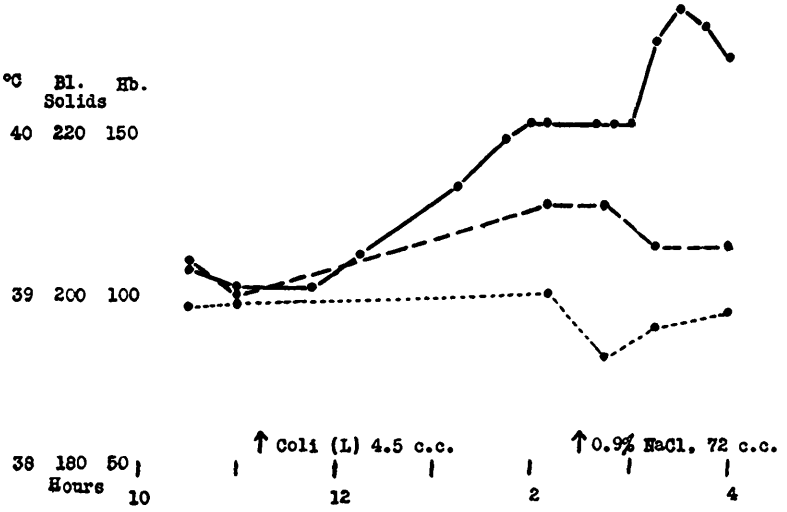

FIG. 3. Dog 53. April 2, 8.9 kilos.
— — — — blood solids.
- - - - - - hemoglobin.
———— rect. temp.

As a control to the above experiments, intravenous injections were made of 0.9 per cent. sodium chloride, of which was given 8 c.c. per kilo to each of two dogs exhibiting a typical coli fever. in the first fifteen minutes there was observed no change whatever in the temperature which subsequently ascended to points 0.7° C. and 0.4° C. respectively higher than the former febrile level. The blood solids on the other hand showed a slight diminution after half an hour, and the hemoglobin fell within the first quarter of an hour. (See fig. 3). The control experiments therefore showed that isotonic NaCI in amounts comparable to the dextrose injections is not able to reduce the temperature of coli fever dogs, nor is the increase in blood volume as marked as when the dextrose was given either to the normal or the fever dogs.

It is therefore concluded that the antipyretic effect (not noted in health) of intravenous dextrose injections is due to osmotic action by which in fever dogs an unusually profound increase in the fluids of the blood results for a short time. This increase in fluid is of value to the animal in promoting heat elimination. The tissues in coli fever appear to contain a higher percentage of "available water" than is normally present. Sensitivity to antipyretic drugs can thus be accounted for.

81 (1541)

Preparation and refining of diphtheria toxin-antitoxin.

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The mixture has been readjusted so that after standing eight months and longer, late paralysis will occur when the mixture is injected into guinea pigs. This is done by adding to each L+ dose one unit of a properly aged antitoxin. When five mils of this mixture is injected into guinea pigs acute death occurs within four or five days. The mixture is then stored in a refrigerator for a month to six weeks for stabilizing.

On reinjecting five mils, after storage, the guinea pigs die of late paralysis after twenty to twenty-five days. It is then properly