INFLUENCE OF DIET ON THE TOXICITY OF SUBSTANCES WHICH PRODUCE LESIONS OF THE LIVER OR THE KIDNEY *

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In a former communication¹ we have described the effect of diet on the toxicity of chloroform and showed that a diet consisting of fat increases the susceptibility of the liver to the necrosis caused by chloroform, whereas a diet consisting in large part of carbohydrates has a protective action. The influence of diet on the toxicity of phosphorus was next tested because it produces profound changes in the liver. Phosphorus causes fatty degeneration of the liver, but its action is not limited to the hepatic cells, for the kidney, heart muscle and other parenchymatous tissues show fatty degeneration. A 1 per cent. solution of phosphorus in oil (oleum phosphoratum) was employed; the amount of oil administered by subcutaneous injection to white rats was very small, since the lethal dose was found to be from 0.07 to 0.08 c.c. per hundred grams of body-weight. The animals, which are omnivorous, were fed during six days preceding injection of phosphorus on a diet consisting of (a) oats and sugar, (b) pig's heart, or (c) beef-fat (Table 1).

TABLE 1.—LENGTH OF LIFE IN DAYS OF ANIMALS
WHICH DIED

Oil of Phosphorus per 100 gm. of Body-Weight, c.c.	Oats and Sugar	Meat	Fat
0.05	*	11	*
0.06	*	4	*
0.07	2	4	*
0.08	4	4	4
0.09	4	2	2
Average dura- tion of life	3½+	5	3+

* Lived.

In the foregoing experiment pig's heart was given to the animals which received a diet of meat; in another series (Table 2) beefsteak was substituted. In both series the animals received the diet during six days, but in the present series after phosphorus had been administered, the animals receiving meat and fat were given oats in addition.

TABLE 2.—LENGTH OF LIFE IN DAYS OF ANIMALS
WHICH DIED

Oil of Phosphorus per 100 gm. of Body-Weight, c.c.	Oats and Sugar	Meat	Fat
0.05	*	4	*
0.06	2	3	*
0.07	*	3	3
0.08	2	3	1
0.09	3	1	2
Average dura- tion of life	2½+	2½	2+

* Lived.

The effects of diet on the toxicity of oil of phosphorus exhibit no resemblance to those observed with chloroform. A diet composed in great part of carbohydrates has no protective action, whereas fat does not increase susceptibility to the poison. Indeed, there is no noteworthy difference in the toxicity with carbohy-

drate and with fatty diet. Both series of experiments show that the toxicity of oil of phosphorus is increased by a diet of meat; the fatal dose with a meat diet is probably less than 0.05 c.c., whereas with diet of carbohydrate or of fat the fatal dose is 0.07 or 0.08 c.c. The experiments furnish no explanation of the difference in the effect of diet on the toxicity of chloroform and of oil of phosphorus. Nevertheless, well-known differences between the action of the two substances may be cited. Chloroform produces necrosis of the center of each hepatic lobule, whereas phosphorus causes wide-spread fatty degeneration. Both substances are soluble in fats, but phosphorus is absorbed much less slowly than the volatile chloroform and is less destructive in its action on the hepatic cells. Chloroform affects the centers of the hepatic lobules, and study of control animals which have received a fatty diet shows that fat accumulates in greatest abundance about the central vein. Phosphorus, on the contrary, seems to produce more profound changes in the periphery of the lobule, for in the foregoing experiments, even after four days, proliferation of connective tissue has been observed in this situation.

Since our experiments have shown that the toxicity of a substance, namely, chloroform, which causes necrosis of the liver is diminished by a diet consisting in great part of carbohydrates and notably increased by a fatty diet, experiments have been performed to determine if similar relations to diet are exhibited by substances which produce necrosis of the parenchymatous cells of the kidney. Potassium chromate and uranium nitrate have been chosen because they have a selective action on the kidney, causing necrosis of the cells of the convoluted tubules, and because they have been much used to produce acute nephritis in animals; albuminuria occurs and casts are numerous within the kidney.

The animals were given, during nineteen days, diets consisting of (a) oats and sugar, (b) pig's heart or beef, or (c) beef-fat. At the end of this time an aqueous solution (2.5 per cent.) of potassium chromate was injected subcutaneously (Table 3).

TABLE 3.—LENGTH OF LIFE IN DAYS OF ANIMALS
WHICH DIED

Sol. of Potassium Chromate per 100 gm.	Oats and Sugar	Meat	Fat
0.1	*	3	6
0.15	5	3	3
0.2	8	1	3
0.25	1	2	2
0.3	3	1	1
Average dura- tion of life	4¼+	2	3

* Lived.

Similar results were obtained in another series of experiments in which oats were added to the diets of meat and fat.

TABLE 4.—LENGTH OF LIFE IN DAYS OF ANIMALS
WHICH DIED

Solution of Potassium Chromate per 100 gm., c.c.	Oats and Sugar	Meat	Egg Yolk
0.05	*	2	*
0.1	*	2	*
0.15	*	4	*
0.2	*	5	6
0.25	5	3	3
Average dura- tion of life	5+	3½	4½+

* Lived.

The experiments indicate that meat increases susceptibility to nephritis caused by potassium chromate, whereas a carbohydrate diet protects the kidney from injury. These conclusions are confirmed by an experi-

* From the Pathological Laboratory of the Washington University Medical School.

1. Opie, Eugene L., and Alford, Leland B.: The Influence of Diet on Hepatic Necrosis and Toxicity of Chloroform, THE JOURNAL A. M. A., March 21, 1914, p. 895.

ment (Table 4) in which animals were given during six days diets consisting of (a) oats and sugar, (b) meat (beef) and (c) boiled egg-yolk, which contains 35 per cent. of fat, including cholesterol and lecithin. After injection, animals on diets of meat and of egg-yolk received oats in addition.

In the experiment recorded in Table 5, an aqueous solution (0.5 per cent.) of uranium nitrate was administered to animals which had been given during four days a diet consisting of (a) oats and sugar, (b) beef-steak or (c) beef-fat; the diets were continued six days after injection.

TABLE 5.—LENGTH OF LIFE IN DAYS OF ANIMALS WHICH DIED

Solution of Uranium Nitrate per 100 gm., c.c.	Oats and Sugar	Meat (Beef)	Beef-Fat
0.05	*	*	10
0.1	6	*	8
0.15	7	7	6
0.2	2	4	7
0.25	*	4	6
0.3	10	8	9
Average duration of life	8+	5½+	7½

* Lived.

In another series of experiments animals were on various diets only three days, and oats were given to those receiving meat and fat immediately after injection. Differences referable to diet were much diminished, but carbohydrate, meat and fatty diets exhibited the relations noted in the foregoing experiment.

In a third series of experiments uranium nitrate in small doses was given to animals which had received the diets already enumerated during five days; after injection, oats were added to the diet of all animals (Table 6). The use of small doses of uranium nitrate in this experiment has made the protective action of carbohydrates very conspicuous.

TABLE 6.—LENGTH OF LIFE IN DAYS OF ANIMALS WHICH DIED

Solution of Uranium Nitrate per 100 gm., c.c.	Oats and Sugar	Meat (Beef)	Fat
0.02	*	9	7
0.04	*	*	*
0.06	7	7	9
0.08	*	10	11
0.10	—	11	7
Average duration of life	7+	9¼+	8½+

* Lived.

A carbohydrate diet diminishes the toxicity both of potassium chromate and of uranium nitrate. The toxicity of potassium chromate has been greater after a diet of meat, but the toxicity of uranium nitrate has been somewhat greater after a diet of fat. The pathologic changes produced in the rat by potassium chromate and by uranium nitrate differ. Both substances produce necrosis of tubules in the cortex of the kidney, leaving the glomeruli apparently uninjured. Both substances produce albuminuria, and casts are numerous within the convoluted and straight tubules of the kidney. With potassium chromate the convoluted tubules undergo necrosis and with moderately large doses they may be almost uniformly destroyed. Uranium nitrate causes necrosis which is often limited to the cortical striae and to a narrow zone in the medulla just below the cortex; this distribution appears to be dependent on a selective affinity of the poison for the loops of Henle, which in the early stages of poisoning may exhibit almost uniform necrosis. After administration of relatively large doses of uranium nitrate there is abundant deposition of cal-

cium salts within the dead tubular epithelium. The second series of experiments mentioned above shows that the occurrence of calcification bears a relation to the severity of intoxication. In four kidneys, after a diet of oats and sugar, calcification occurred only with the largest dose; in four kidneys, after a diet of meat, calcification occurred with the two largest doses. In five kidneys, after a diet of fat, calcification occurred in four.

CONCLUSIONS

The toxicity of phosphorus, which causes fatty degeneration of the liver, is greater in animals which have received a diet of meat than in those which have received diets consisting in large part of carbohydrates or of fat.

Animals on a diet rich in carbohydrates are much less susceptible to nephritis produced by potassium chromate and uranium nitrate than animals on a diet consisting of meat or of fat.

A diet of meat increases the toxicity of potassium chromate, which produces necrosis of the convoluted tubules of the kidney.

A diet consisting of fat increases the toxicity of uranium nitrate, which alters the loops of Henle and produces nephritis.

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THE TECHNIC OF THE INTRADURAL INJECTIONS OF NEOSALVARSAN IN SYPHILIS OF THE NERVOUS SYSTEM

REPORT OF CASES

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In a preliminary report,¹ I described the technic employed in the treatment of syphilis of the nervous system by intradural injections, as first advocated by Ravaut. At the risk of repetition, I shall briefly outline the method of procedure before presenting the report of cases.

The solution used for injection consists of a 6 per cent. solution of neosalvarsan in distilled water. This solution is hypertonic and made of such a concentration that each minim must contain 3 mg. of the drug. The dosage injected is from 3 to 12 mg. — that is, from 1 to 4 drops of the solution, which is made up as follows:

An ampule containing 0.3 gm. of neosalvarsan is dissolved in 5 c.c. of freshly distilled water. If the ampule contains 0.6 gm., 10 c.c. of water are used. In both solutions, each drop will contain 3 mg. of the drug. The syringe employed for the injection is accurately graduated in drops. The patient is placed in a position for lumbar puncture, either sitting or lying, according to the choice of the operator. The puncture is then made with a needle, the end of which fits the graduated syringe. After a few drops of the spinal fluid have flowed out of the cannula, or a greater quantity if a diagnostic puncture is desired at this time, the syringe is fitted into the needle, and the fluid is allowed to run back into the syringe barrel.

1. Wile, U. J.: The Technic of the Intradural Injections of Neosalvarsan in Syphilis of the Nervous System, THE JOURNAL A. M. A., April 11, 1914, p. 1165.