experimental 4-hr. period, sometimes more plainly in the second, and always in the night period following feeding at 8 p. m.

The one dog which did not respond with a marked increase of D:N ratio, for the 24 hours, nevertheless showed a large increase of sugar excretion in the night period following injection at noon. This dog gave typical respiratory quotients for complete pancreatic diabetes on 2 different days and, as shown in Table II, exhibited a delayed depression of the R.Q., beginning 3 hours after administration of the fat fraction. The R.Q. was depressed as much or more than this in one other depancreatized dog and in a castrated but otherwise normal dog. Since depancreatized dogs exhibit very little ketosis, the depression of the R.Q. below the diabetic level is suggestive of gluconeogenesis from fatty acids.[2] We have not found any report in the literature of a similar effect from a similar lipid fraction.

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Dinitrophenol Hyperglycemia. I. Its Independence of Asphyxia.*

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The fact that 1-2-4 dinitrophenol, which greatly accelerates the oxidative metabolism of tissues, increases blood sugar concentration has been reported by Magne, Mayer and Plantefol[1] and confirmed by Hall, Field, Sahyun, Cutting and Tainter.[2] Since the large increase in oxygen usage of the tissues provoked by the drug might readily outstrip the ability of the respiratory and circulatory mechanisms to deliver oxygen and so lead to general bodily asphyxia, it seemed possible that the hyperglycemia might be of such asphyxial origin. The experiments described herein were designed to test this hypothesis.

Cats, anesthetized with pentobarbital, received doses of 15 or

[2] Hawley, Estelle E., Johnson, Carroll, and Murlin, J. R., *J. Nutrition*, 1933, **6**, 523.

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[1] Magne, H., Mayer, A., and Plantefol, L., *Ann. Physiol. Physicochim. biol.*, 1932, **8**, 1.

[2] Hall, V. E., Field, J., Sahyun, M., Cutting, W. C., and Tainter, M. L., *Am. J. Physiol.*, 1933, **106**, 432.

20 mg. per kilo of 1-2-4 dinitrophenol intramuscularly in the form of its sodium salt. Blood samples at half-hour intervals were analyzed for sugar by the method of Sahyun,[3] for oxygen and total carbon dioxide content by the manometric method of Van Slyke and Neill,[4] and for plasma pH by the colorimetric method of Hawkins.[5] Five experiments with 20 mg. per kilo, 2 with 15 mg. per kilo and 4 controls without any drug were performed. Within each group, the experiments agreed with each other satisfactorily. The results in animals with the higher dose and in the controls are presented in Table I. The animals receiving 15 mg. per kilo gave values intermediate between those of the other groups.

TABLE I.
Average Arterial Blood and Other Changes in Dinitrophenol Intoxication.

	Controls				"DNP," 20 mg./kg.			
	Initial	½ hr.	1 hr.	1½ hr.	Initial	½ hr.	1 hr.	1½ hr.
Glucose mg. %	98	110	125	146	102	164	211	220
Oxygen vol. %	17.2	17	17.2	18	18.8	18.8	19	19.2
Carbon dioxide vol. %	25.2	20.2	22	22	21.2	17.8	17.4	16.2
Plasma pH	7.3	7.32	7.37	7.39	7.4	7.46	7.48	7.49
Rectal temp. deg. C.	37.4	37.7	37.7	37.5	37.4	37.7	39	40.1
Resp. rate per min.	21	26	25	26	27	37	50	103
Arterial pr. mm. Hg.	136	127	111	100	137	121	117	115

From our results there is no indication of the development of asphyxia under the influence of dinitrophenol; the oxygen content of the blood is unchanged, the total carbon dioxide content falls, while the plasma pH rises. The findings thus support our[2] earlier conclusion that, at least before the terminal collapse sets in, the drug produces neither anoxemia, asphyxia nor acidosis. They are also in agreement with the determinations of plasma pH made by DeEds,[6] employing the glass electrode. The tendency to acapnia and alkalosis, which has appeared in these experiments, is no greater in the experiments with the drug than in the controls. The fact that the usual metabolic response was present and vigorous is attested by the marked increases in rectal temperature and respiratory rate.

In spite of the absence of asphyxia, there developed a marked

[3] Sahyun, M., *J. Biol. Chem.*, 1931, **93**, 227.

[4] Van Slyke, D. D., and Neill, J. M., *J. Biol. Chem.*, 1924, **41**, 523.

[5] Hawkins, J. A., *J. Biol. Chem.*, 1923, **57**, 493.

[6] DeEds, F., *Science*, 1933, in press.

hyperglycemia, the rise in blood sugar being approximately 3 times as great as that in the controls. The difference of the means of the final blood sugar values between the dinitrophenol animals and controls was 73.85 mg. per 100 cc. Since this difference exceeds its own probable error by 4.4 times, it is statistically significant.

A possible cause for the rise in blood sugar might be the development of a cerebral anemia. Since the general arterial pressure, on which the cerebral blood flow rate is primarily dependent,[7] declined to a smaller degree in the experiments with the drug than in the controls, the cerebral circulation is presumably at least as adequate in the former as in the latter. This conclusion assumes that no significant cerebral vasoconstriction has occurred. However, since dinitrophenol causes a great increase in cardiac output without much change in arterial pressure,[2] a marked general vasodilatation must occur. This is supported by the observation of Markee[8] that the drug causes a flushing of the uterine transplant in the anterior chamber of the eye. While the occurrence of general vasodilatation is no proof of a local cerebral vasodilatation, vasomotor adjustments tend to favor cerebral blood flow.[9] Accordingly we feel that the occurrence of cerebral vasoconstriction under the influence of the drug is improbable. The above considerations render it unlikely that cerebral anemia was the cause of the blood sugar rise.

We conclude that the hyperglycemia produced by dinitrophenol is not secondary to a general bodily asphyxia, as is the case with that produced by many other drugs. The possibility that a local cellular anoxemia or acidosis of the sympathetic glycogenolytic centers of the brain stem may be the mechanism of this hyperglycemia is now under investigation.

[7] Wiggers, C. J., Circulation in Health and Disease. 2nd Ed., P. 155. Philadelphia, 1923.

[8] Markee, J. E., personal communication.

[9] Bronk, D. W., and Gesell, R., PROC. SOC. EXP. BIOL. AND MED., 1926, **24**, 257.