

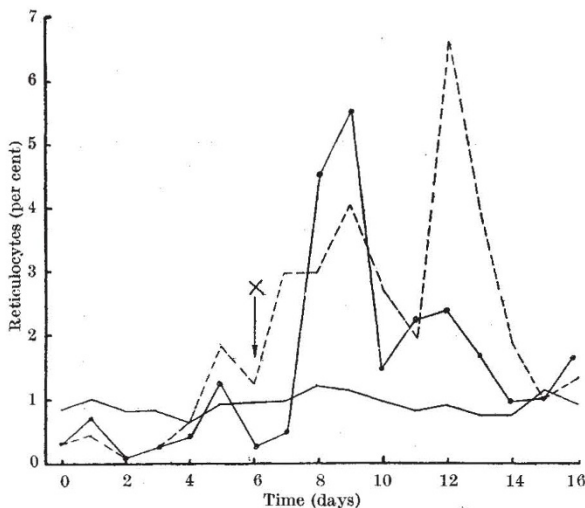
Reticulocytosis following the Administration of Thymine to Splenectomized Rabbits

Jacobson and Williams^{1,2} have reported that splenectomized rabbits show a reticulocytosis after intramuscular injections of liver extract, and have suggested that this observation could form the basis for a method of bio-assay of liver extracts.

Following Jacobson's report, we have carried out a number of experiments on a series of eighteen splenectomized rabbits and have confirmed, qualitatively, the response of these animals to an injection of liver extract. We are not in a position at this stage to comment on the quantitative nature of the response, except as noted below. The appearance of a series of papers by Spies and his collaborators^{3,4,5,6} on the value of thymine (5-methyl uracil) in the treatment of sprue and pernicious anaemia suggested the investigation of the action of thymine in splenectomized rabbits.

We have now shown that intramuscular and intravenous injections of thymine produce a marked reticulocytosis in these animals. With intramuscular injections, a latent period of 2-4 days is usually observed, but using the intravenous route, a more rapid response is obtained. This effect is marked in doses varying from 50 mgm. to 250 mgm., and was still apparent in one animal on a dose of 5 mgm.

The smaller doses of thymine were usually given in warm aqueous solution (1-3 mgm./ml.) and the larger doses in suspension in the same medium. The accompanying graph shows the result of administering 100 mgm. and 20 mgm. to splenectomized rabbits. It also shows the absence of effect due to the administration of distilled water alone.



-----, 100 mgm. thymine intramuscularly; —, 5 ml. distilled water intramuscularly; —○—, 20 mgm. thymine intravenously. Injections were made at X.

All the rabbits used in these experiments showed a normal reticulocyte level of 1.0-2.0 per cent, and a response was considered positive only if a level of 2.0-3.0 per cent or more was observed. Two or three weeks prior to being treated with thymine, each rabbit was given an intramuscular injection of 1.0 ml. of purified liver extract ('Examen'), and any animal not showing a positive response was rejected from further experimental work. Although the responses of different rabbits to an equal dose of thymine

showed considerable variation, it was observed that a dose of 100 mgm. or more of thymine usually resulted in a higher reticulocyte peak than that obtained with 1.0 ml. of 'Examen'.

The foregoing results supply further evidence that splenectomized rabbits respond to materials active in pernicious anaemia, and the fact that the height of the reticulocyte peak appears to run roughly parallel with the size of the dose of thymine suggests that the response may be more or less quantitative. The results also lend support to the view that thymine or some substance of similar structure may play an important part in haemopoiesis.

Further work is in progress with related compounds to determine whether they have an action similar to that of thymine.

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¹ Jacobson, W., and Williams, S. M., *J. Path. Bact.*, **67**, 101 (1945).

² Jacobson, W., and Williams, S. M., *J. Path. Bact.*, **67**, 423 (1945).

³ Spies, T. D., Vilter, C. F., and Cline, J. K., *South. M. J.*, **39**, 269 (1946).

⁴ Spies, T. D., Frommeyer, W. B., Vilter, C. F., and English, A. *Blood*, **1**, 185 (1946).

⁵ Spies, T. D., Frommeyer, W. B., Lopez, G. G., Toca, R. L., and Gwinner, G., *Lancet*, **i**, 883 (1946).

⁶ Frommeyer, W. B., Spies, T. D., Vilter, C. F., and English, A. *J. Lab. Clin. Med.*, **31**, 643 (1946).

Carbohydrate Metabolism in Alloxan-diabetic Rats

Mering and Minkowski¹ and also Hédon² have already found that the glycogen content of the liver and of the skeletal muscles, during experimental pancreas-diabetes, is being very much decreased. This was always confirmed by later authors and led to various hypotheses concerning the action of insulin on carbohydrate metabolism. By means of their mode of experimental procedure, Major and Mann³ were able to show that the formation of glycogen in pancreatectomized dogs is not suppressed in the case of permanent glucose infusion. Concerning the glycogen content of liver and skeletal muscles, Lackey, Bunde, Gill and Harris⁴ obtained the same results in alloxan-diabetic rats as Mering and Minkowski in pancreatectomized dogs. The investigations of Laszt⁵ and Laszt and Vogel⁶ on the carbohydrate metabolism in alloxan-diabetic rats make it probable that the formation of glycogen cannot be lowered. We were, therefore, induced to verify this point. The rats were made diabetic by the method suggested by Laszt⁵. There was no steatosis of the liver to be observed, neither macroscopically nor microscopically. This fact is of importance, as the formation of glycogen and its deposition is suppressed in fatty liver⁷.

As the accompanying table shows (average rates), the glycogen content of the liver after 24 hr. fasting is higher in alloxan-diabetic rats than in normal ones, whereas the glycogen content of the muscles is lower. One hour after glucose feeding (1 gm.) the liver glycogen, as well as the