appear of great importance in the period of reconstruction. Those who wish to join the society should complete an enrolment form and send it to the Hon. Secretary, Dr. J. R. Baker, University Museum, Oxford. Members are under no obligation except that of supporting the cause of freedom in science. It is assumed that all members will fight vigorously for this cause if an immediate threat develops.

My own connection with the society started about a year ago as a result of correspondence initiated by its secretary, Dr. John R. Baker, who had seen the part of my presidential address to the American Physical Society published in SCIENCE of February 12, 1943, in which I expressed concern over the growing tendency toward totalization of science. Dr. Baker has asked me to serve as the go-between during the initial stages of enrolment of members in this country; enrolment blanks may be obtained by application to me.

It is pertinent to mention that a book by Dr. Baker is shortly to be issued by Macmillan called "Science and the Planned State."

P. W. BRIDGMAN

RESEARCH LABORATORY OF PHYSICS,
HARVARD UNIVERSITY

SPECIAL ARTICLES

THE CORRELATION OF THE INSULIN CONTENT AND THE HISTOLOGICAL PICTURE OF THE PANCREAS AT INTERVALS AFTER THE ADMINISTRATION OF ALLOXAN[1]

IN 1937, Jacobs[2] showed that the intravenous injection of alloxan produced fatal hypoglycemia in rabbits. He did not report any histological studies. In 1943, Dunn, Sheehan and McLetchie[3] confirmed the hypoglycemic effect of alloxan in rabbits and found that it produced a selective necrosis of the islets of Langerhans. Bailey and Bailey[4] were the first to show that if animals were kept alive during the hypoglycemic phase by glucose administration, extreme hyperglycemia subsequently developed. Within a short time, this work has been confirmed and extended by a number of investigators (see E. P. Joslin, 1944).[5]

The way in which alloxan affects carbohydrate metabolism, particularly the means by which it induces a profound temporary hypoglycemia before it causes a severe and prolonged hyperglycemia, is a problem of considerable interest. Two hypotheses have been advanced to explain this action: (1) that alloxan overstimulates the islet cells, causing excessive liberation of insulin and subsequent death of islets perhaps from exhaustion, and (2) that alloxan primarily destroys islet cells and that there is a slow release of insulin from the dying or dead cells which is sufficient to account for the hypoglycemia (Hughes, Ware and Young).[6]

It was thought that experiments in which the insulin content of the pancreas was determined at different times after the administration of alloxan and correlated with the histological picture in the islets at these times might provide information to settle this point. An investigation of this kind has not previously been published, although Goldner and Gomori[7] have reported a low insulin content of the pancreas in two dogs after treatment with alloxan.

Experiments on Rats. Female Wistar rats (about 210 grams each) were used. These were divided into five groups and four of these were injected subcutaneously with an aqueous solution of 350 milligrams of alloxan per kilogram in 4 equal doses at 15 minute intervals. The insulin content of the pancreas was determined by the mouse method of assay, using from 200 to 240 mice for each solution (Table 1).

TABLE 1

Number of rats	Time after alloxan	Blood sugar	Insulin per group of 10 rats
	(hours)	(mgms. per cent.)	(units)
26	0	92	21.2
12	1.5	215	21.1
13	3.0	293	18.7
14	7.0	100	16.0
13	48.0	264	0.89

For each group of rats upon which insulin assays were made, 5 similarly treated rats were used for histological studies. In these the islets showed the following changes. At 1.5 hours after alloxan the islet cells bordering capillaries showed ragged disintegrating edges and the capillary spaces were widened; at 3 hours these changes were more pronounced and there were many pycnotic nuclei; at 7 hours there was a general disintegration of islet structure with most of the cells necrotic; and at 48 hours, although super-

[1] This research has been supported in part by a grant from the Banting Research Foundation.

[2] H. R. Jacobs, *Proc. Soc. Exp. Biol. and Med.*, 37: 407, 1937.

[3] J. S. Dunn, H. L. Sheehan and N. G. B. McLetchie, *Lancet*, 244: 484, 1943.

[4] C. C. Bailey and O. T. Bailey, *Jour. Am. Med. Asn.*, 122: 1165, 1943.

[5] E. P. Joslin, *New Eng. Jour. Med.*, 230: 425, 1944.

[6] H. H. Hughes, L. L. Ware and F. G. Young, *Lancet*, 246: 148, 1944.

[7] M. G. Goldner and G. Gomori, *Jour. Am. Med. Asn.*, 124: 802, 1944.

ficially the islet structure seemed greatly restored, many of the regenerated cells were fibroblasts.

Experiments on Dogs. The amount of insulin in the pancreas of dogs was estimated at different times after the administration of 150 milligrams alloxan per kilogram. D 27 was given the full amount in a single injection. The other four animals received 4 equal doses at 15-minute intervals. Sections were taken from different parts of each pancreas and the remainder used for the insulin assay. The values in Table 2 were calculated as units per gram of total pancreas.

TABLE 2*

Dog number	Time after alloxan	Blood sugar	Insulin per gram of total pancreas
	(hours)	(mgms. per cent.)	(units)
D 21	0	80	2.5
D 22	2	340	3.5
D 23	4	195	2.2
D 24	8	45	3.2
D 25	24	278	none detectable
D 27	36	40	0.16

* The blood sugars reported in Table 2 are the ones obtained immediately before the termination of the experiment. Blood sugars, however, were determined at frequent intervals throughout the experiment on each dog. With the exception of D 27 there was the initial hyperglycemia reported by other workers. In D 24 and D 25 hypoglycemic levels were reached in 8 hours. D 27 showed no increase in blood sugar throughout the whole experiment and in 10 hours the blood sugar had fallen to 40 milligrams. The animal had convulsions which continued in spite of intravenous glucose until it was sacrificed.

The histological findings in the islet cells of the above dogs were as follows: in D 2 the capillary spaces were widened; the islet cells were not as regularly arranged as normally; some of the nuclei were pycnotic and many cells appeared shrunken. In D 23 pycnotic nuclei were more frequent and the cell cords were greatly disorganized. In D 24 most of the islet cells were necrotic with their nuclei failing to stain blue with hematoxylin. Small hemorrhages were seen in the necrotic tissue. In D 25 the islets were shrunken and difficult to detect. Their internal structure was disorganized and dead cells were seen in them. The smaller veins throughout the pancreas showed many marginal neutrophiles and the epithelium of many of the smaller ducts was vacuolated. In D 27 the islets seemed to be fewer and smaller than normal and there was considerable variation in the histological picture they presented. Few normal cells were seen in them.

The experiments on both the rats and dogs support the view that alloxan quickly destroys islet cells and that the insulin content of the pancreas does not fall substantially until some time after most of the islet cells are dead. The subsequent release of insulin which presumably lowers the blood sugar can not then be in the nature of a secretory phenomenon because it occurs when the islet cells are dead; it must, therefore, be a process wherein the insulin content of the islets is leached from the dead cells into the blood stream.

Further evidence that the hypoglycemic effect of alloxan is due primarily to its action on the pancreas rather than upon the liver or other tissues is provided by the following experiment in which alloxan failed to exert a hypoglycemic effect in animals containing little or no islet tissue.

Alloxan was given as described above to 2 depancreatized dogs, to 2 dogs that had been made diabetic by previous treatment with alloxan and to a normal dog. The blood sugars of the diabetic dogs were controlled by an injection of protamine zinc insulin given 18 hours previous to alloxan. In both types of diabetic dogs receiving alloxan there was no reduction in blood sugar. This is in direct contrast to the result in this and many other normal dogs in which hypoglycemia occurred in 5 to 6 hours after alloxan.

Summary and Conclusions. Experiments are reported in which insulin assays and histological studies were made on the pancreases of rats and dogs at different times after the administration of alloxan. It was found that the insulin content of the pancreas did not fall appreciably until after most islet cells were found by histological examination, to be dead. A further experiment showed that alloxan did not exert a hypoglycemic effect in depancreatized dogs and dogs previously made diabetic with alloxan.

These experiments indicate that alloxan causes hypoglycemia because it kills islet cells and so allows their insulin content to be leached out into the blood stream. It appears most unlikely that it exerts its hypoglycemic effect by stimulating islet cell secretion because most of the islet cells are dead when the hypoglycemic phase occurs.

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J. H. RIDOUT
A. W. HAM
G. A. WRENSHALL

THE BANTING AND BEST DEPARTMENT OF MEDICAL RESEARCH AND THE DEPARTMENT OF ANATOMY,
UNIVERSITY OF TORONTO

THE CREATINE AND CREATININE EXCRETION OF NORMAL ADULT MALES[1,2]

IT is the purpose of this report to subjoin the data on the creatine and creatinine excretion of 30 normal human subjects which were collected from our investigations in human amino acid deficiencies to the existing and overwhelming factual evidence which indicates

[1] From the Department of Pediatrics, Johns Hopkins University, Baltimore, Md.

[2] Aided by grants from the Rockefeller Foundation, E. Merck and Company, Eli Lilly and Company, E. R. Squibb and Sons.