(or isopropanol) for benefits from ketogenic agents in epilepsy and for developing new or improving old antiepileptic agents is discussed.

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Hydropic Changes in Pancreatic Ductules and Islets in Alloxan Diabetes in the Rabbit.*

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(Introduced by J. B. Collip.)
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Several investigators have described hydropic degeneration of the pancreatic islets and ductules in dogs rendered diabetic by partial pancreatectomy[1,2] and by anterior pituitary extracts.[3-5] In dogs made diabetic by alloxan, hydropic degeneration of islet cells has not been observed even in the presence of extreme vacuolation of the epithelium of the intralobular pancreatic ducts.[6] Hydropic changes have been observed in the islets of cats that had become diabetic following partial pancreatectomy[2] or treatment with anterior pituitary extract[7] but the pancreatic ductules were not affected. While such alterations in occasional islet cells have been described in rabbits treated with alloxan[8,9] the duct epithelium is said to remain normal.[10] The only description of alterations in the epithelium of pancreatic ductules in diabetic rabbits is that of Ogilvie[11] who found slight vacuolation of the lining cells of "newly formed" intralobular ducts in 1 of 28 rabbits treated with anterior pituitary extract. It is interesting, therefore, to report a high incidence of moderate to extreme hydropic degeneration of both the ductules and islets of the rabbit's pancreas following diabetes of long duration induced by alloxan.

Materials and Methods. Each of 56 white domestic rabbits obtained from several different dealers received intravenously 200 mg of alloxan (Eastman) per kg of body weight in a 5% aqueous solution. They were treated with protamine zinc insulin and glucose for a period of not more than 14 days following alloxan injection. In all of these animals and in a control group of 26 untreated rabbits, repeated determinations were made of fasting blood sugar and urinary sugar and acetone. Surviving animals of the experimental group were killed with corresponding control animals at various intervals up to one year after injection of alloxan.

Observations. Of the 56 rabbits treated with alloxan, 53 became persistently diabetic

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† Medical Research Fellow of the National Research Council, Canada.

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TABLE I.
Summary of Experimental Data.

Duration of diabetes in mo.	No. of animals	Grade of Hydropic Degeneration: Islets 0	Islets 1	Islets 2	Islets 3	Islets 4	Ductules 0	Ductules 1	Ductules 2	Ductules 3	Ductules 4	Mean of avg blood sugar mg per 100 cc
0-1	19	19	—	—	—	—	19	—	—	—	—	428
1-2	8	1	2	4	1	—	1	3	2	—	2	388
2-3	4	1*	1	2	—	—	—	—	2	—	2	379
3-4	9	1†	2	4	—	2	1†	—	—	3	5	422
4-5	4	—	—	2	2	—	—	—	1	1	2	432
5-6	2	1‡	—	1	—	—	1‡	—	1	—	—	310
6-7	2	—	—	1	1	—	—	—	1	—	1	337
7-8	2	—		2	—	—	—	—	1	1	—	444
8-9	2	—	—	1	1	—	—	—	1	1	—	401
12	1	—	—	—	1	—	—	—	—	1	—	256
	—	—	—	—	—	—	—	—	—	—	—	
Totals	53	23	5	17	6	2	22	3	9	7	12	
Control	26	26	—	—		—	26	—	—	—	—	105
Alloxan resistant	3	3				—	3	—	—	—	—	123

* No islets identified.
† Blood sugar average 280 mg per 100 cc.
‡ " " " 177 " " " "

as indicated by persistent polyuria, glycosuria, polydypsia, polyphagia, loss of weight and hyperglycemia. Three animals proved to be resistant to the diabetogenic action of alloxan. The latter were killed and examined at intervals of 4, 6 and 11 months respectively after the administration of alloxan.

In Table I are shown the results of the experiments with particular reference to the incidence of hydropic degeneration of the islet and ductular epithelium and the duration of the experiments in which such changes occurred, the duration being calculated from the day of injection of alloxan. The degree and extent of hydropic change was graded histologically on a scale of 0 to 4.

In histological sections of the pancreas, the islets of Langerhans showed varying degrees of reduction in size from animal to animal with from very slight decrease in number to almost total absence of identifiable islets. The hydropic islet lesion consisted of varying degrees of vacuolation of the cytoplasm of the affected cells. The nucleus was centrally located and appeared normal but the cytoplasm in severely affected cells was almost totally replaced and the cell membrane distended by a single vacuole in which no content could be fixed or stained by routine histological methods (Fig. 1C). The other islet cells that were not affected were readily stained by routine methods and were shown to be almost exclusively alpha cells by the Gomori granule stain. These cells in many islets appeared to be considerably more numerous than could be accounted for by mere reduction in size of the islets from destruction of beta cells and consequent condensation of surviving alpha cells. Although this appearance suggested proliferation of alpha cells, mitotic figures were not found in any of the cells of the islets of Langerhans.

The affected intralobular ductules were only those that are normally lined by cuboidal epithelium. They were found to arise from normal ducts of larger size lined by columnar epithelium and in their finer ramifications to approach, and on occasion even to enter, hydropic islets (Fig. 1A). The earliest noticeable change was a swelling of the cuboidal epithelium that rendered the minute ductules more conspicuous than usual. This was followed by dissolution of the cytoplasm of varying degree up to complete disappearance of the cytoplasm, the place of which was taken by a large clear space bounded by the distended cell membrane (Fig. 1A and B). The centrally placed nucleus appeared slightly smaller and more deeply staining than

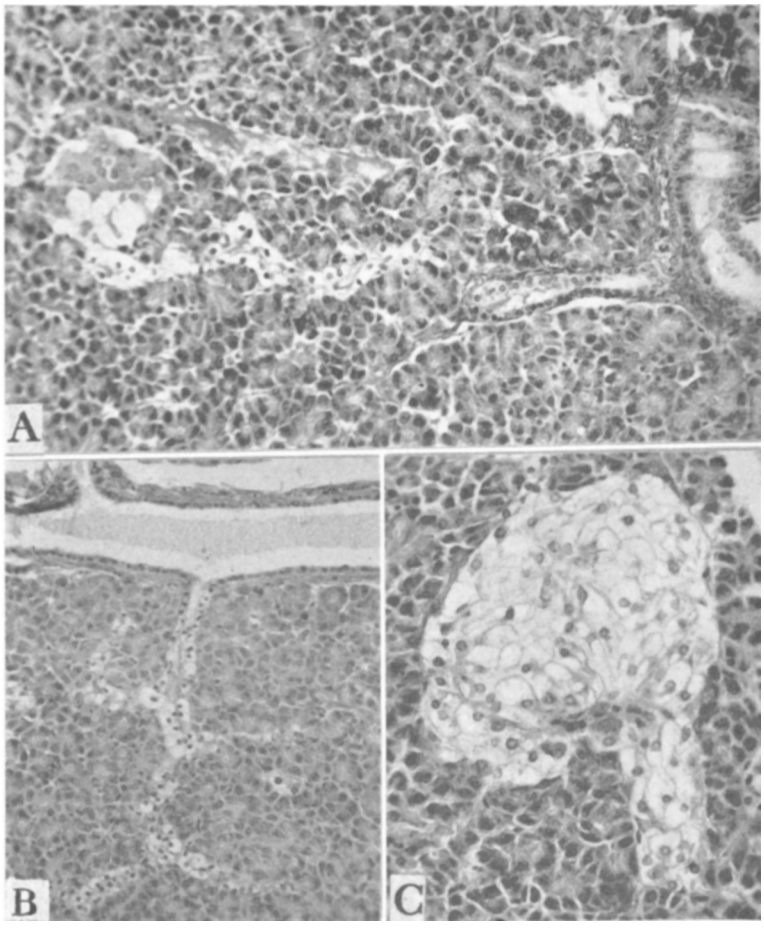

FIG. 1.
Photomicrographs of Sections of Pancreas Stained with Haematoxylin and Eosin.

A. At the right is a duct lined by columnar epithelium of normal appearance. A smaller duct arising from it is lined by cuboidal epithelium, the cells of which show a variable degree of hydropic change. From this latter duct an intralobular ductule exhibiting extreme hydropic degeneration comes into continuity with an islet composed of clear distended hydropic cells and a group of normally stained alpha cells. × 165.

B. A branching intralobular ductule presenting extreme hydropic degeneration of its lining epithelium is shown arising directly from a major duct, above, of which the columnar epithelium is normal in appearance. Note the compact hyperchromatic nuclei of the hydropic cells. × 135.

C. This unusually large islet of Langerhans illustrates the typical appearance of the hydropic changes observed in islet cells. The islet is exceptional in that it contains in the plane of section only two identifiable alpha cells which lie together toward its lower margin. × 200.

normal. The content of the vacuoles, as in the case of the hydropic islet cells, could not be fixed or stained and in both instances special staining to demonstrate glycogen, fat or mucin failed to reveal the presence of any of these substances. The lumina of many affected ductules were dilated by a small content of acidophilic, homogeneous material. It was found to be impossible in some cases to determine morphologically the islet or ductule origin of many groups of hydropic cells, especially where there was extreme hydropic degeneration in the absence of recognizable alpha cells. It is to

be noted, however, that, with one exception, islet and ductule lesions were found to occur concomitantly. This exception was accounted for by the absence of positively identifiable islets in the sections of pancreas from this one animal.

In addition, a similar hydropic change was observed in isolated single cells, and small groups of cells scattered throughout the acinar tissue. It was impossible to determine morphologically the origin of these cells. However, it was apparent that they were not hydropic acinar cells.

Discussion. Although our experiments were not designed to permit a detailed analysis of the etiological factors concerned in the production of hydropic degeneration of islet and ductule cells of the pancreas, nevertheless, it is apparent that both time and a diabetic state were essential. Table I shows that hydropic degeneration was not found in any of the animals that were diabetic for less than one month. The earliest occurrence of the lesion was found at 45 days, and it was invariably present after 90 days providing that the average fasting blood sugar level during this period had been 303 mg per 100 cc, or higher. One diabetic rabbit with an average blood sugar level of 256 mg showed moderate hydropic degeneration of islet and ductule cells after 12 months. A statistical comparison of the mean of the average blood sugar content of the animals showing hydropic changes of Grades 1 and 2 with that of animals showing Grades 3 and 4 indicated that there was no significant difference between the blood sugar levels of the 2 groups. The degree of hydropic degeneration, therefore, was found to be independent of the degree of hyperglycemia. The absence of hydropic pancreatic lesions in the 3 animals that were found to be resistant to the diabetogenic action of alloxan and in the 2 animals that exhibited relatively mild diabetes, indicated that alloxan *per se* was not the etiological factor concerned.

In the dog and cat, hydropic degeneration of the previously normal beta cells of the islets of Langerhans, whether produced by partial pancreatectomy[1,2] or by the administration of anterior pituitary extracts,[3-5,7] is followed by disintegration of the hydropic cells and a corresponding reduction in size of the islets. This stage of atrophy of islets is reached after 4 to 6 weeks of severe diabetes in the dog,[3-5] but only after 3 to 4 months in the cat.[7] In contrast to these relatively short periods, it is interesting to note that in alloxan diabetes in the rabbit the hydropic degeneration of the pancreatic islets persists without histological evidence of any disintegration of the affected cells in association with more or less severe diabetes lasting for periods up to one year. However, in this case it is not by any means certain that the hydropic cells are altered beta cells and, indeed, this would appear to be rather doubtful since most, if not all, of the beta cells of the islets were presumably destroyed by the initial administration of a rather large diabetogenic dose of alloxan. In the islets of Langerhans of various species studied histologically 5 days or more after the administration of alloxan several investigators have mentioned the presence of a few indifferent cells with clear, nongranular cytoplasm in addition to the surviving alpha cells.[6,8,12-14] If in our experiments the numerous vacuolated islet cells arose from the proliferation and subsequent hydropic degeneration of such indifferent cells or of undifferentiated ductular epithelium, these cells might be expected to be no more susceptible to ultimate destruction than the hydropic epithelium of the ductules themselves.

Nevertheless, preliminary experiments have demonstrated by repeated biopsy of the pancreas that the hydropic condition of both islet and ductular epithelium is reversible by adequate treatment of the diabetic state with insulin. Many of the reversed islet cells in the few histological sections of pancreas that we have thus far studied are indifferent cells with clear, nongranular cytoplasm, but others possess a finely granular cytoplasm in-

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distinguishable from that of the normal beta cells of the islets of normal rabbits. Still other cells present a patchy granularity of the same type and of varying extent, so that all stages of transition from the nongranular cells to cells with a full complement of granular cytoplasm are observed. It is possible that such a transition from nongranular to granular cells of beta type may actually occur under the influence of insulin therapy. This, together with the appearance of proliferation of both of these types of cells, suggests the possibility of improvement or even complete restoration of islet function in relation to carbohydrate metabolism by suitable manipulation of insulin therapy in alloxan diabetes in the rabbit.

Summary. Moderate to extreme hydropic degeneration of the pancreatic ductules and islets was observed in rabbits rendered diabetic by alloxan when the diabetic state had persisted for several months. Such changes have not hitherto been described in alloxan diabetes in the rabbit. The earliest appearance of these alterations was at the end of 45 days after the injection of alloxan and hydropic changes were never absent after 90 days providing that the average fasting blood sugar level during the experiment had been 303 mg per 100 cc, or higher. The hydropic state of the ductules and islets persisted without histological evidence of any further change in association with more or less severe diabetes lasting for periods up to one year. The alpha cells of the islets remained histologically normal but appeared to be increased in number. Preliminary observations demonstrated that the hydropic degeneration of both ductules and islets is reversible by adequate treatment of the diabetic state with insulin. The reversed islet cells appeared to be unduly numerous suggesting proliferation. They were made up in part of indifferent nongranular cells and in part of cells exhibiting varying degrees of granularity of the cytoplasm of beta type. Those with a full complement of granular cytoplasm were indistinguishable in appearance from the beta cells of the islets of Langerhans in the normal rabbit.

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Antibacterial Action of N-Alkyl *p*-Aminobenzoic Acid Derivatives.*

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Yeomans *et al.*,[1] have recently demonstrated the beneficial therapeutic effect of *p*-aminobenzoic acid in louse-borne typhus fever, and several investigators since then have shown its effectiveness in experimental rickettsial infections.[2-5] In a study on the mode of action of sulfonamides, Wyss, Rubin and Strandskov[6] synthesized several ring-substituted *p*-aminobenzoic acid derivatives and tested them for antibacterial action. They found that the 2-Cl, 3-Cl, 2-NH_2, 3-NH_2, and 3-F derivatives of *p*-aminobenzoic acid displayed varying degrees of bacteriostatic action which could be reversed by the addi-

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