It seems unlikely, therefore, that the ulcerogenic factor in non-insulin producing adenomas of the pancreatic islet cells is glucagon. Such ulceration may result from an endocrine dysfunction related to the co-existing multiple adenomatosis, or to some as yet undiscovered pancreatic hormone.

Summary. 1. Diminution in gastric motility, gastric secretory rate, and hydrochloric acid production has resulted from glucagon administration in 17 patients. 2. These antiulcerogenic properties suggest that some factor other than glucagon is responsible for the severe peptic ulcerations commonly associated with non-insulin producing tumors of the pancreatic islets.

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Development of Tolerance to Depressant Effects of Atropine on Isolated Rabbit Ileum.* (23526)

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The development of acquired resistance (tolerance) to the depressant action of atropine on gastrointestinal motility has been observed in man and in the dog(1,2). While suggestion of a related phenomenon in the isolated rabbit intestine can be found in the literature(3-5), a clear, controlled demonstration of the development of such tolerance *in vitro* has not been made. The work reported below is limited to studies of the depressant effects of atropine sulfate (atropine) and adiphenine hydrochloride† (adiphenine) on the amplitude of spontaneous contraction of the longitudinal muscle of isolated rabbit ileum. The results indicate that in this preparation tolerance to the effect of atropine is a reproducible and reversible phenomenon. Similar tolerance to adiphenine does not develop.

Methods. Sections of rabbit ileum were cut in lengths of 2 to 3 cm and mounted according to the classical method of Magnus in a bath containing 100 ml of oxygenated Tyrode's solution. Recordings of spontaneous contractions were effected electrically on a kymograph, the recording current being automatically shut off 10 sec of every minute. Contractions were recorded continuously for 5 min before and for 10 min after each addition of drug to the bath solution. At the end of these 10 min the bathing fluid was replaced with fresh Tyrode's solution. Second and third replacements followed at 2 min intervals. The ileum was then considered to be washed.

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† Adiphenine hydrochloride = diethylaminoethyl diphenylacetate hydrochloride (Trasentine hydrochloride: Ciba).

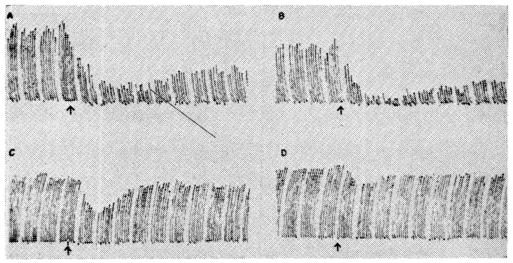

FIG. 1. Development of tolerance to atropine (40 μg%). Tracing A illustrates effect of first application of atropine; B, the second; C, the fifth; and D, the seventh. Time of application is indicated by the arrow.

This overall procedure was usually repeated every 30 min over a period of 3 to 5 hr. Concentrations of the drugs were expressed as mg or μg of the salt per 100 ml of bath solution (mg% or μg%).

Results. Atropine Tolerance. Repeated application of atropine (40 μg%) at 30 min intervals as described above invariably resulted in the development of tolerance, such that the sixth or seventh application produced little, if any, depression of the height of spontaneous contraction A typical experiment is shown in Fig. 1. Studies of 16 sections of ileum are summarized in Fig. 2. Curve B represents the average response to the first application of the above concentration of atropine, while curve C represents the average response to the sixth application. When once developed, tolerance persisted with continued periodic administration of atropine over the total course of 5 hr (10 applications of drug). The possibility that atropine tolerance was produced solely by the repeated washings of the ileum was investigated in the following experiment. Eleven sections of ileum were subjected to washings every 30 min for 2½ hr. Atropine (40 μg%) was then applied for the first time. Curve A in Fig. 2 shows the average depression of height of spontaneous contractions produced by this application.

Evidence for Accumulation of Atropine. The degree of spasm induced by 10 μg% acetylcholine chloride (Ach) was determined for each of 10 sections of ileum. After 10 min of exposure the sections of ileum were washed. Tolerance to atropine was then developed by the usual procedure *viz.*, 5 applications of atropine with each application followed 10 min later by the usual washing. After the final washing the degree of spasm induced by the same concentration of Ach was again determined. The development of tolerance reduced the average spasmodic response to Ach by approximately 75% of its control value. Inasmuch as this response to Ach does not change with semi-hourly applications and washings of the drug over 3 hr, the observed reduction is probably referable to incomplete removal of atropine by the washing process and a resultant accumulation of atropine. In 9 sections of ileum tolerance to atropine was developed by the usual procedure. The preparations were subsequently washed at 30 min intervals for 2½ hr, after which time atropine was again applied. The average results, shown in figure 3, support the probability of an association between the phenomenon of atropine tolerance and the accumulation of atropine within the tissues.

Adiphenine. Experiments were performed to investigate the possible occurrence of a similar type of tolerance in response to repeated applications of adiphenine. Sections of ileum were repeatedly treated with 1 mg% adiphenine in a manner similar to that described for atropine. Fig. 4 (upper tracing) illustrates the average reductions in height of spontaneous contractions in response to the first (solid line) and sixth (broken line) applications of adiphenine to 9 sections of ileum.

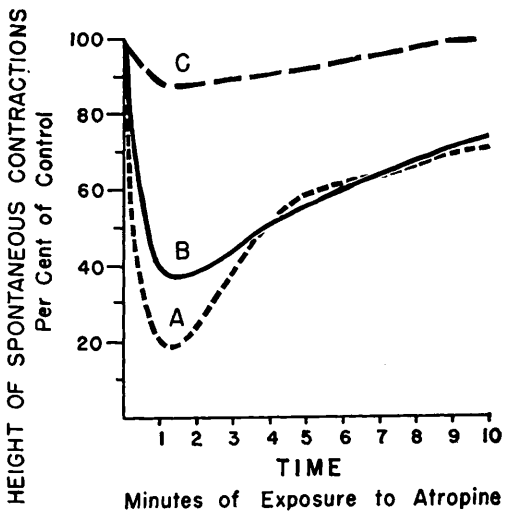

FIG. 2. Effect of washings on response of the rabbit ileum to atropine. See text.

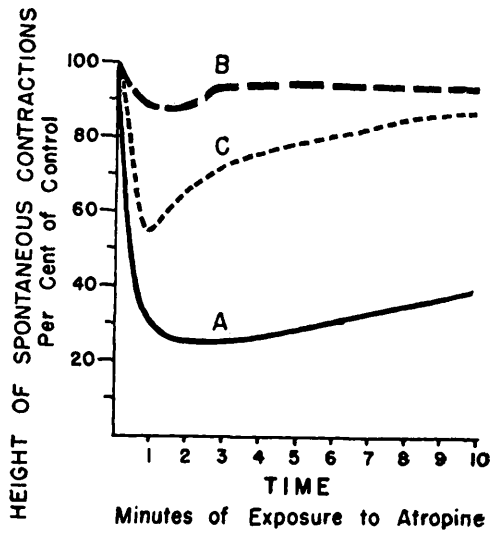

FIG. 3. Effect of washings on previously developed tolerance to atropine. Curve A represents average response to first application of atropine; B, the fifth; and C, the sixth. Between the fifth and sixth applications the ileum was washed at 30 min intervals for 2½ hr.

In no experiment was there any evidence of the beginning of the development of tolerance even over a time period of 5 hr. Moreover, when this concentration of adiphenine was applied to ileum which had been rendered completely tolerant to atropine, the depression was as great as it was in non-tolerant ileum. Fig. 4 (lower tracing) shows the average results of 4 experiments in which (a) 1 mg% adiphenine was applied to fresh ileum (solid line), (b) the ileum was made tolerant to atropine by the usual procedure, and (c) 1 mg% adiphenine was again applied (broken line).

Discussion. The results reported in this paper demonstrate the occurrence, under certain conditions, of a type of motility of smooth muscle, which is refractory to atropine. While the nature of the mechanisms responsible for this phenomenon are at present unknown, the phenomenon itself may be of great practical value. Hitherto, the degree of antispasmodic activity of an agent has been expressed in terms of its proportion to the degree of activity of atropine, papaverine and/or pyribenzamine. Adiphenine, for example, has been described as possessing low atropine-like activity as determined by its ability to reduce spasms induced by acetylcholine. On the other hand, because of its relatively high activity in depressing spasms induced by barium chloride, adiphenine is usually classified as a papaverine-like compound. Controversial data, concerned with the mode of action of barium chloride itself(6,7) further complicate this classification. The results presented in this paper reveal a clearly demonstrable difference between the actions of adiphenine and atropine on a physiological entity, *viz.*, amplitude of spontaneous contraction. Investigations of other antispasmodic agents on this preparation, with particular regard to their tendency to develop tolerance and to their action on atropine tolerant motility, would contribute significantly to the elucidation of true similarities and differences in antispasmodic activity.

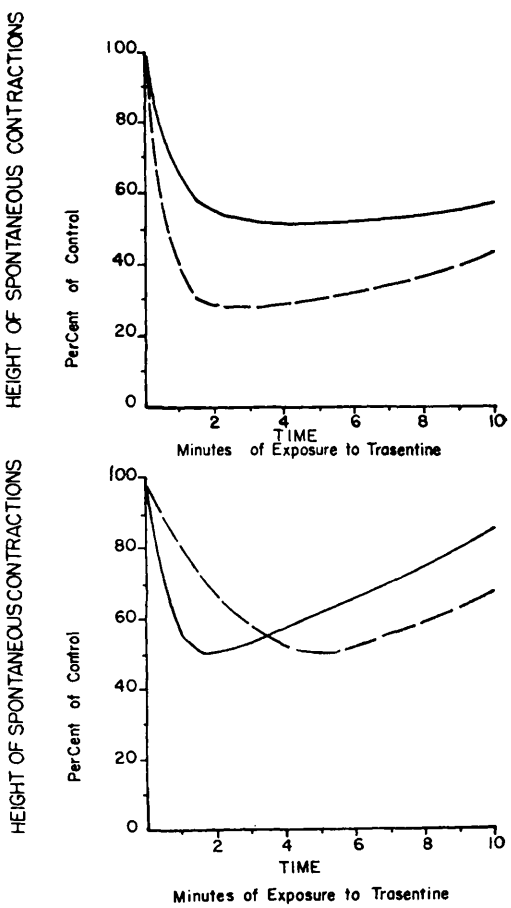

FIG. 4. Upper tracing: depressant effects of adiphenine (Trasentine) (1 mg%). Lower tracing: effect of adiphenine on atropine tolerant motility.

Summary. 1) Repeated exposure of isolated sections of rabbit ileum to atropine (40 μg%), with washings 10 min after each exposure, results in development of tolerance, such that by sixth or seventh exposure, the depressant effects of atropine on height of spontaneous contraction are minimal or even abolished. The phenomenon of tolerance appears to be associated with gradual accumulation of atropine within the tissue. 2) Repeated exposure of rabbit ileum to adiphenine (1 mg%) results in no observable tendency toward the development of tolerance. Moreover, when adiphenine is applied to ileum which previously has been made tolerant to atropine, adiphenine is fully effective in depressing the height of spontaneous contraction.

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A Kwashiorkor-Like Syndrome Observed in Monkeys Fed Maize.* (23527)

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To understand all aspects of the pathogenesis of a particular disease in man, one should be able to reproduce it in the experimental animal. This has been eminently true in the evolution of our knowledge of certain human nutritional disease syndromes, such as beriberi, scurvy, rickets and pellagra; for great advances were made in an elucidation of the biochemical and anatomical alterations in these disease states when they could be studied in the laboratory. In contrast, our woeful ignorance of the pathogenesis of such diseases as endemic goiter and, until recently, pernicious anemia stems from the fact that the physiologic and morphologic pattern has not yet been produced in experimental animals. Today, kwashiorkor has world-wide distribution and a high prevalence. Although clinical studies, particularly those dealing with therapy, have revealed something of its pathogenesis, a more basic understanding is likely to be obtained if the disease can be reproduced in the laboratory.

Kwashiorkor is one of a group of several syndromes which occur endemically and which are associated in many parts of the world with an intake of virtually a single foodstuff. In the case of kwashiorkor this foodstuff is maize. Many years ago corn was shown to be deficient in certain inorganic elements, amino acids and vitamins(1); hence, it is not surprising that a multiple disease syndrome might follow extended use of this grain. Because investigations dealing with deficiencies of *single* essential nutrients have now furnished a baseline of biochemical and anatomical changes which may occur in many animal species, the time appears favorable to renew the study of *multiple* deficiency states such as those which may be produced by feeding single natural foodstuffs. We have recently undertaken such a program in this laboratory in an attempt to reproduce in experimental animals certain nutritional diseases which occur naturally in man and whose pathogenesis is not clear. In the present com-

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