Pancreatic Function in Alloxan "Subdiabetic" Rats Long-term Treated with Tolbutamide

Jann W. Weber, M.D., Jean-Pierre Colombo, M.D., Richard I. Goldberg, B.A., Stanley Saperstein, B.A., Martin L. Shulkind, B.A., Doris Kanameishi, M.T., and Piero P. Foa, M.D., Chicago

It is generally believed that one of the reasons for the blood-sugar-lowering effect of the sulfonylureas is the release of insulin from the pancreas. This release has been documented convincingly in acute experiments.[1] However, one cannot say if this is due primarily to a discharge of preformed insulin, as the degranulation of the beta cells would suggest, or if secretion of newly synthesized insulin also occurs. The variety of animal species and strains, of ages and physiologic conditions, of drugs, dosage schedules and lengths of the experiments makes the effects of prolonged administration even harder to interpret. The problem is complicated further by the well-known difficulties which arise in assessing function from morphologic evidence, and in comparing morphologic data obtained at different times, with different technics in a different, or even in the same, laboratory.[2-5]

In an attempt to render their interpretation somewhat easier, pertinent data from the literature[5-31] have been tabulated and the period of 100 days, or about 10 per cent of the life span of a rat, has been selected as the arbitrary division between "short" and "long" experiments (table 1). From this table, one gains the impression that, in most "short" experiments in the normal animal,[6-9,14-18] the drugs either had little or no effect on pancreatic function and morphology, or resulted in beta-cell degranulation with some impairment of the animal's tolerance for glucose. On the other hand, in most "long" experiments,[10-14] stimulation of insular function, such as islet hypertrophy, beta-cell multiplication and increased glucose tolerance have been obtained. In the diabetic animal, the effect of sulfonylurea administration appears to have been determined more by the severity of the disease than by the duration of treatment. With the exception of one report,[24] when diabetes was mild or moderate, improvement, "remissions," and "cures" have been described, whereas in severe cases no significant effects have been obtained.[10-23,25-31] In addition to duration of treatment and severity of disease, some of the results may have been influenced by other factors. In some cases, the tendency of rodents to spontaneous recovery from alloxan diabetes[32] may have played a part; in other cases, changes in liver function[33] or glycogen content[1] may have influenced carbohydrate tolerance; in still other cases the response of the drug may have depended upon the pancreatic reserve of the animal. The extent of this reserve[34] may determine if continued stimulation of the beta cell will result in hypertrophy and increased insulin production or lead to exhaustion and functional insufficiency, a situation comparable to that observed after repeated doses of growth hormone, prolactin, cortisone, glucagon or glucose.[35-37] Beta cell exhaustion, leading to further impairment of the basic endocrinologic defect, is a serious matter and the possibility that it might happen in diabetic patients should be considered, even though countless diabetics have received oral therapy for several years and, in the relatively few cases of secondary failure, no significant increase in insulin requirement seems to have occurred.[38-40] For these reasons, the problem was reinvestigated in rats whose pancreatic reserve had been decreased by a subdiabetic dose of alloxan. It was hoped that, in these animals, any significant changes in pancreatic function could be detected either by an improvement in glucose tolerance or by the appearance of frank diabetes.

MATERIALS AND METHODS

About 200 Sprague-Dawley (Abrams) rats, weighing about 120 gm., were fasted overnight, and given a single intraperitoneal injection of alloxan monohydrate

Presented at the Twentieth Annual Meeting of the American Diabetes Association in Miami Beach on June 12, 1960.

From the Department of Physiology and Pharmacology of The Chicago Medical School, Chicago 12, Illinois.

(150 mg./kg. in a freshly prepared 5 per cent solution). Eight to ten days after the injection, the surviving rats were again fasted overnight and tested for urinary glucose. Rats with glycosuria were used for other purposes; those with negative urine were given an intraperitoneal glucose tolerance test (1 mg./kg. in a 10 per cent solution). Thirty-one aglycosuric rats, now weighing about 150 gm., having normal fasting blood sugar, but impaired glucose tolerance, remained. These were divided into two groups by a person who had no knowledge of each animal's tolerance curve. One group received a commercial diet and served as control; the second group received the same diet to which 2 per cent tolbutamide had been added. Occasional measurements of food consumption revealed that the daily drug intake was about 100 mg./rat, or 650 mg./kg. at the beginning of the experiment, and about 200 mg./kg./rat, or 500-600 mg./kg. at the end of the experiment, when the weight of the animals had increased to about 300-400 gm. Intraperitoneal glucose tolerance tests were repeated at various intervals, after an overnight fast and after discontinuing the drug for three days—one day for complete absorption of tolbutamide from the gastrointestinal tract, one day for its disappearance from plasma and tissues[41] and one day for the abatement of any acute pharmacologic effects of the last dose. Among these, insulin discharge, hypoglycemia and reactive secretion of blood sugar raising hormones[42] may cause changes in glucose tolerance. Duplicate blood samples were obtained from the cut surface of the tail and glucose was determined according to Nelson.[43] From the blood glucose values, two indices were calculated: an "index of comparison," calculated as follows:

$$I_{Co} = \frac{\text{1-hr. exper. blood glucose}}{\text{1-hr. control blood glucose}} \cdot \frac{\text{x-hr. exper. blood glucose}}{\text{x-hr. control blood glucose}}$$

and an "index of change," calculated as follows:

$$I_{Ch} = \frac{\text{1-hr. bld. gluc. at 12-15 mos.}}{\text{1-hr. blood glucose at start}} \cdot \frac{\text{x-hr. bld. gluc. at 12-15 mos.}}{\text{x-hr. blood glucose at start}}$$

where x = 2, 3 or 4. I_{Co} compares experimental to control animals at a given time; I_{Ch} compares those rats of a given group who survived at the end of the experiment to the same rats at the beginning of the experiment. An index of comparison of 1.0 is obtained when the values for the two groups are identical. An index of comparison greater or smaller than 1.0 indicates that the experimental animals are "more diabetic" or "less diabetic" than the controls, respectively. On the other hand, an index of change smaller than 1.0 indicates that the animals of a given group have improved and an index of change greater than 1.0 that they have deteriorated during the period of observation. The statistical significance of the results was calculated according to Fisher.[44] At the end of the experiment the animals were sacrificed with a blow on the head, the pancreas immediately removed, fixed in Bouin's solution and stained according to Gomori.[45] For better comparison and to minimize irregularities in staining and other procedures, all sections were stained simultaneously, photographed in color on the same day, using the same illumination and film batch, and all photographs were processed together.

RESULTS

Figure 1 shows the average glucose tolerance curve of control and experimental subdiabetic rats. The fasting blood glucose varied between 63 and 118 (average 85) mg. per 100 ml. in the experimental animals, and between 70 and 122 (average 95) mg. per 100 ml. in the controls. Statistical calculation demonstrated no significant differences between the initial blood sugar concentrations and between all other corresponding values in the glucose tolerance curves in the two groups. Figure 2 shows the deterioration of glucose tolerance in the control group, occurring after twelve to fifteen months of observation. This deterioration was noted in eight of the ten control rats surviving at the end of the experiment; two rats were unchanged. In figure 2 only the values at two, three and four hours in the

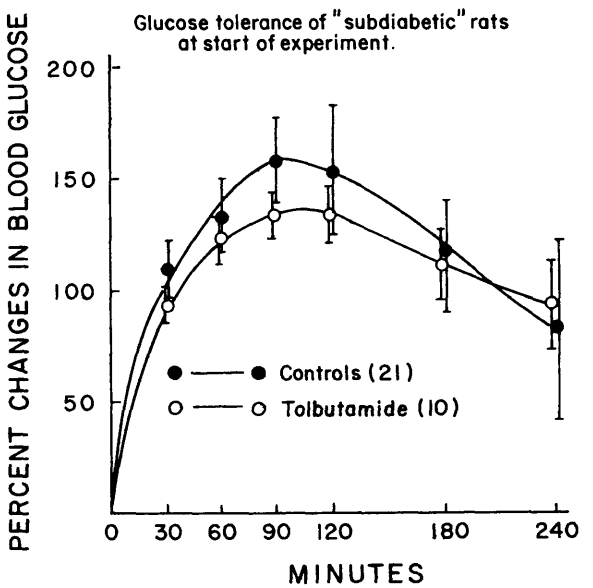

FIG. 1. Average glucose tolerance curves of alloxan "subdiabetic" rats at the beginning of the experiment. ± S.E.

TABLE 1

Effect of repeated doses of oral hypoglycemic drugs on pancreatic morphology and function. Data from the literature. h = hours; d = days; w = weeks; m = months; y = years; C = carbutamide; T = tolbutamide; Ch = chlorpropamide; 2254RP, or IPTD = p-aminobenzene-sulfamido-isopropyl-thiodiazol; 2259RP = p-amino-benzene-sulfamido-tertiobutyl-thiodiazol; S = "short" experiments; L = "long" experiments; g.t. = glucose tolerance; FBS = fasting blood sugar.

Animal	Weight or age	Drug	Dose	Duration of experiment		Effects	Ref.
			Normal animals				
Rat	50-55 gm.	C	1,000 mg./kg.	5 w	S	Increased islet tissue.	6
"	150-200 gm.	C	500 "	9-13 w	S	Gradual increase in FBS; B cell degranulation	7
"	130-160 gm.	C or T	750 "	4-45 d	S	No changes in islet mor-	
		IPTD	750-1,000 "	2-45 d	S	phology.	8
"	—	T	250-500 "	5-80 d	S	B cell degranulation; no change in g.t.	9
"	55-65 gm.	T	100 "	25-192 d	L	Possible inhibition of B cell multiplication.	10
"	130-250 gm.	C	25-500 "	12 h-7 m	L	Islet hypertrophy and hyperplasia; B cell degranulation and enlargement of nuclei.	11
"	175-450 gm.	C	250 "	4-100 d	L	Increased islet tissue; increase and degranulation of B cells.	12
"	200-250 gm.	C	500 "	6 m	L	Islet hypertrophy; B cell degranulation and vacuolization; normal g.t.	13
"	—	T	250-2,000 "	9 m	L	B cell degranulation; increased g.t.	14
Mouse	24-28 gm.	C	500 "	2 m	S	Slight islet hypertrophy and neoformation.	15
"	—	C	500 "	1-3 w	S	Potentiation of alloxan effect.	16
Rabbit	1.8-2.2 kg.	T	1,000 "	3-60 d	S	Decreased g.t.	17
"	—	T	500-1,000 "	4-8 w	S	B cell degranulation; no change in g.t.	9
Dog	—	T	100 "	9 m	L	Increased g.t.	14
"	—	T	100 "	4-6 w	S	Decreased g.t.	13
Calf	70 kg.	T	100 "	4 w	S	Slight decrease in pancreatic insulin content.	18

twelve- to fifteen-month curve and the value at four hours in the nine-month curve are significantly different from the corresponding values at the beginning of the experiment. The deterioration of the control rats is revealed also by the index of change which, after twelve to fifteen months of treatment, was 1.44 at two hours, 2.25 at three hours, and 2.34 at four hours. Figure 3 shows that the glucose tolerance of the experimental rats deteriorated during the first six months, but returned to the original, or possibly better, values after twelve to fifteen months of continuous treatment. At this time the index of change was 0.71 at two hours, 0.67 at three hours and 0.68 at four hours. Of the seven experimental rats remaining at the end of the experiments, four had improved and three were unchanged. In figure 3 only the values at two to three and five to six months are significantly different from the corresponding values at the beginning of the experiment. Figures 4 and 5 show that, during the first six months, tolbutamide feeding does not prevent and may tend to aggravate the diabetic state of the animals. Figure 6 shows that twelve to fifteen months after the beginning

TABLE 1 (CONTINUED)

Effect of repeated doses of oral hypoglycemic drugs on pancreatic morphology and function. Data from the literature. h = hours; d = days; w = weeks; m = months; y = years; C = carbutamide; T = tolbutamide; Ch = chlorpropamide; 2254RP, or IPTD = p-aminobenzene-sulfamido-isopropyl-thiodiazol; 2259RP = p-amino-benzene-sulfamido-tertiobutyl-thiodiazol; S = "short" experiments; L = "long" experiments; g.t. = glucose tolerance; FBS = fasting blood sugar.

Animal	Weight or age	Drug	Dose	Duration of experiment	Effects	Ref.
			Diabetic animals			
Alloxan rat	150-200 gm.	C	500 mg./kg.	9-13 w	B cell degranulation; no effect on diabetes.	7
"	—	2254RP	400 "	7 d	B cell degranulation; no effect on diabetes.	19
Alloxan rabbit	1.3-3.3 kg.	T; 2254RP	100 "	1-18 w	Remission or "cure" of diabetes.	20
"	1.8-2.5 kg.	T	1,000 "	5 d	Improvement of diabetes in mild or moderate cases.	21
"	—	2254RP	500-1,000 "	7 d	Improvement or "cure" of diabetes.	19-22
Alloxan dog	—	2259RP	2,000-2,500 "	36 h-21 d	Islet neoformation; "cure" of diabetes.	22-23
Alloxan subdiabetic rat	3-4 mg.	T	200-500 "	12 m	Decreased g.t.	24
Partially depancreatized rat	180-220 gm.	T	250 "	91 d	Reduced g.t.; "reactive" islet regeneration.	25
Metahypophyseal diabetic dog	10-17 kg.	T	50-100 "	4 w	Suppression of the diabetogenic effect of STH.	26
Obese-hyperglycemic mouse	55-64 gm.	C	300 "	2 m	No effect on diabetes.	15
Man	9 y	C	0.5 g/d	3-4 m	Increased g.t.	27
"	11-35 y	T	0.5 g.; bid	2-22 m	Normalization of g.t.	28
"	Adult	C	1 g/d	3 m	Increased g.t.	29
"	" (?)	C or T Ch.	1 g/d	38-96 h	Increased g.t.	5
"	"	C or T	—	1-21 m	Possible islet neoformation.	30
"	"	T	2 g/d	up to 6 m	No morphologic changes.	31

of the experiment this trend is reversed, resulting in a marked difference in glucose tolerance between control and tolbutamide-fed rats. At this time the initial blood glucose was 75 to 114 (average 84) mg. per 100 ml. in the controls and 80 to 114 (average 91) mg. per 100 ml. in the experimental animals. Statistical analysis shows that these two curves, after starting at similar levels, differ significantly at all succeeding points. (P smaller than 0.02 or better.) The index of comparison, which was 0.93 at two hours and 1.0 at three and at four hours when the experiment was started, had decreased to 0.34 at two hours, 0.22 at three hours and 0.17 at four hours after twelve to fifteen months of treatment, confirming the fact that, at the end of the experiment, the tolbutamide-fed rats were significantly "less diabetic" than the controls. Figure 7 shows a typical example of the degranulated islets of Langerhans observed in control rats. Figure 8 shows a typical pancreatic islet of a tolbutamide-fed rat with abundant beta granules. No differences in the number and appearance of the alpha cells, or in the number and size of the pancreatic islets were noted on careful examination of several sections from all rats of each group, although no serial sections were made.

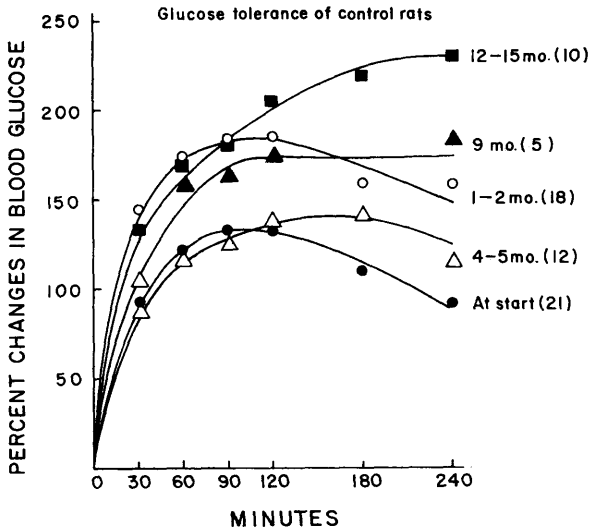

FIG. 2. Average glucose tolerance curves of alloxan "subdiabetic" rats after receiving a control diet for various periods of time.

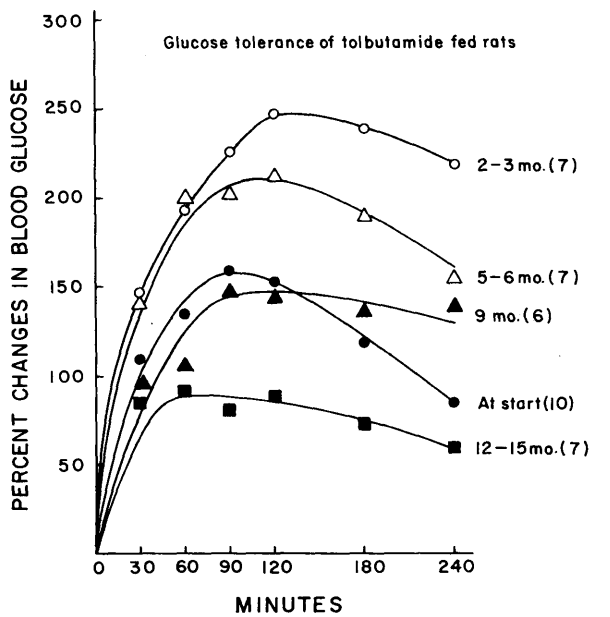

FIG. 3. Average glucose tolerance curves of alloxan "subdiabetic" rats after receiving a tolbutamide containing diet for various periods of time.

DISCUSSION

The deterioration of glucose tolerance in untreated animals confirms the tendency to spontaneous progression of alloxan diabetes observed by others,[24] and suggests that the marked degranulation of the beta cells observed in these rats at the end of the experiment was a lasting sign of the cellular damage caused by alloxan.

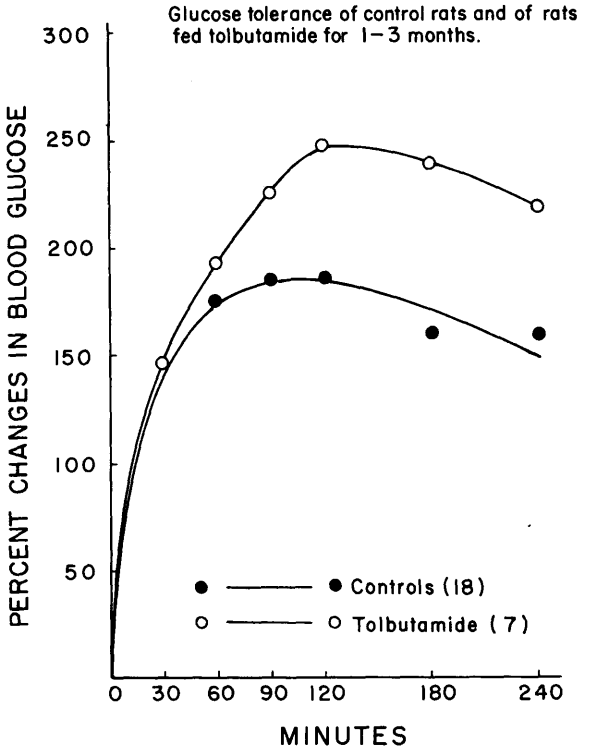

FIG. 4. Comparison of the glucose tolerance curves of control and tolbutamide-fed "subdiabetic" rats one to three months after the beginning of the experiment. Data from figures 2 and 3.

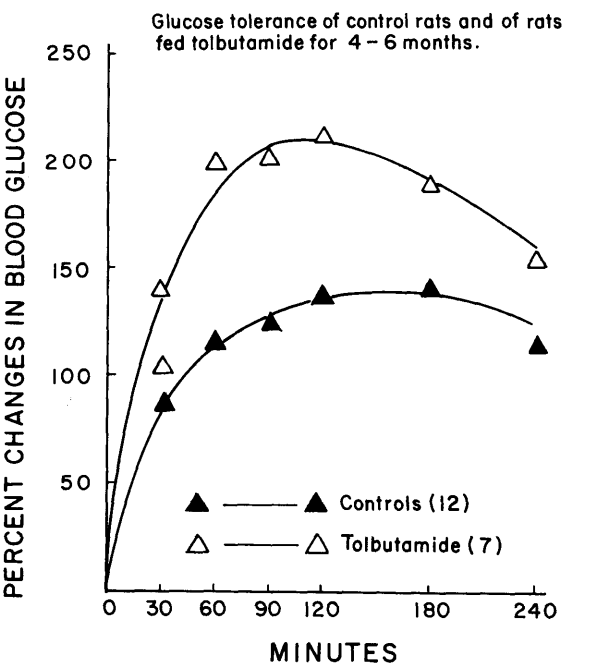

FIG. 5. Comparison of the glucose tolerance curves of control and tolbutamide-fed alloxan "subdiabetic" rats four to six months after the beginning of the experiment. Data from figures 2 and 3.

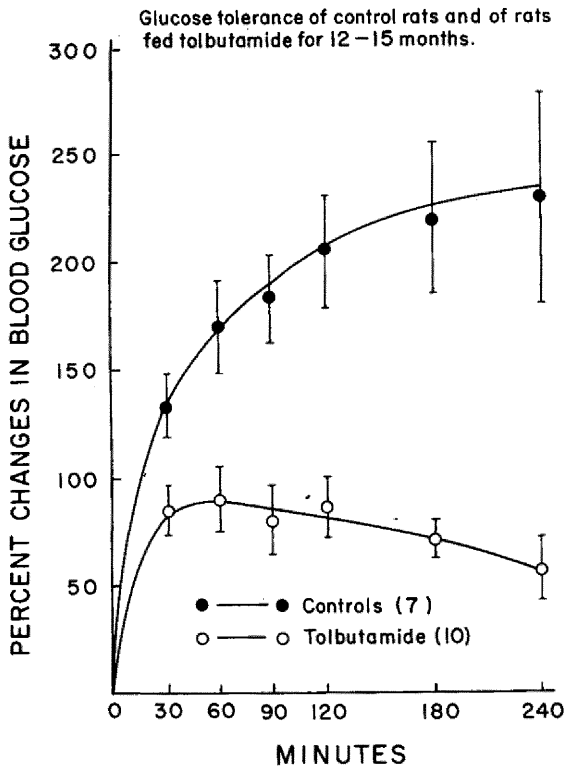

FIG. 6. Comparison of the glucose tolerance curves of control and tolbutamide-fed alloxan "subdiabetic" rats twelve to fifteen months after the beginning of the experiment. ± S.E.

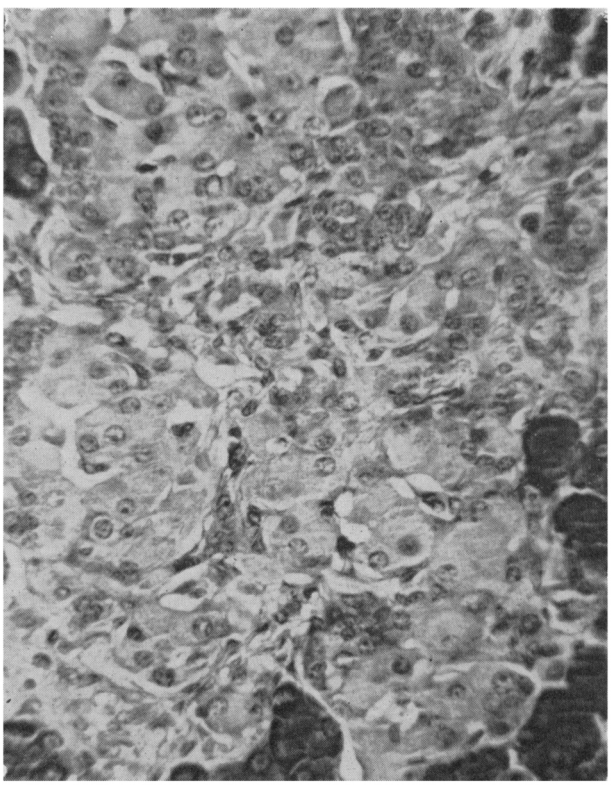

FIG. 7. Islet of Langerhans from a control alloxan "subdiabetic" rat showing characteristic degranulation of the beta cells. A few alpha cells can be seen in the upper left portion of the figure. Gomori stain X 400.

In no case did spontaneous amelioration occur. On the other hand, in the treated animals, after an initial deterioration lasting about six months, there was an increased tolerance for glucose, coincident with the appearance of abundant beta granules, suggesting restoration of islet function. These results are in partial agreement with those obtained by Lazarow and Treibergs[24] under similar, although not identical, circumstances. These investigators reported that tolbutamide feeding produced an impairment in the glucose tolerance during the first six months of treatment, but did not report any figures for the twelve- to fifteen-month period. It should be pointed out that the effects of chronic tolbutamide feeding were not very striking. Neither was the initial impairment of glucose tolerance sufficient to change subdiabetic rats into frankly diabetic ones, nor did the subsequent improvement result in a "cure."

In conclusion, the results described in this paper suggest that prolonged treatment of alloxan subdiabetic rats with tolbutamide does not cause further deterioration of insular function and may even result in some improvement.

SUMMARY

Alloxan-treated aglycosuric rats having normal fasting blood glucose, but abnormal glucose tolerance, were fed a control diet or a similar diet containing 2 per cent tolbutamide. After twelve to fifteen months of treatment, the glucose tolerance of the tolbutamide fed rats was significantly better than that of the controls. At this time, the islets of the control animals were markedly degranulated; those of the tolbutamide fed animals appeared normal. It is concluded that chronic tolbutamide feeding does not cause, and may prevent, further deterioration of pancreatic function in rats with decreased pancreatic reserve.

SUMMARIO IN INTERLINGUA

Le Function Pancreatic in Rattos "Subdiabetic" per Alloxano, Tractate a Longe Vista con Tolbutamida

Rattos, le quales—post tractamento con alloxano—esseva aglycosuric e habeva normal valores de glucosa sanguinee in stato jejun sed anormalitates in le tolerantia pro glucosa, esseva alimentate con un dieta de base supplementate—in le caso del animales experimental—

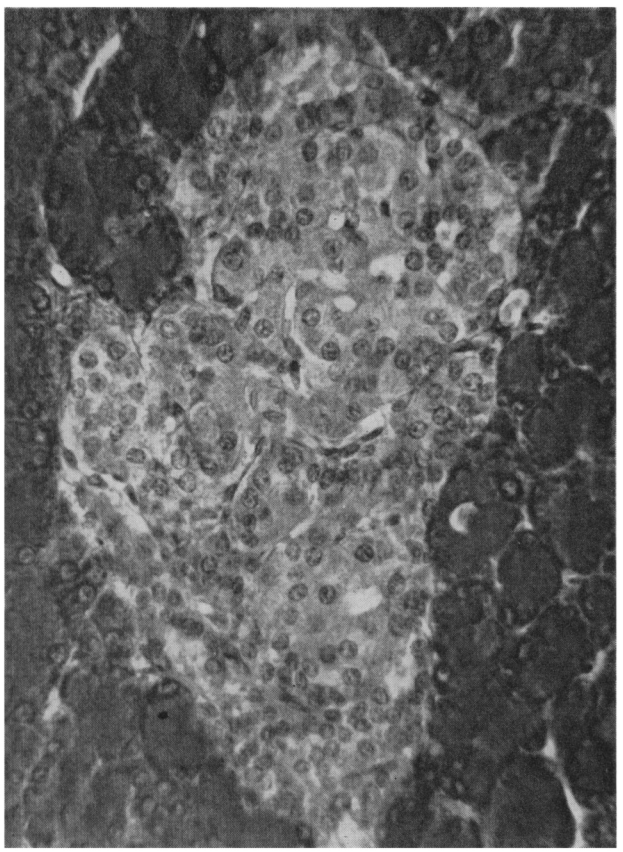

FIG. 8. Islet of Langerhans from a tolbutamide-treated alloxan "subdiabetic" rat showing characteristic beta cells rich in granulation. Alpha cells can be seen at the periphery and in the center of the islets. Gomori stain X 400.

de tolbutamida amontante a duo pro cento del total. Post inter dece-duo e dece-cinque menses de iste regime, le tolerantia pro glucosa esseva significativemente melior in le rattos tractate con tolbutamida que in le rattos recipiente le dieta de controlo. A iste tempore, le insulas del animales de controlo esseva marcatemente disgranulate, durante que illos del animales tractate con tolbutamida presentava un apparentia normal. Es formulate le conclusion que le perdurative administration de tolbutamida non age como causa sed possibilemente como factor preventive in le deterioration additional del function pancreatic de rattos in que le reserva pancreatic es reducite.

ACKNOWLEDGMENT

This study was supported, in part, by grants A-522 and 2A-5102 from the National Institute of Arthritis and Metabolic Diseases, United States Public Health Service. Tolbutamide was a gift of Dr. Enrico Adami, Istituto De Angeli, Milan, Italy.

REFERENCES

[1] Foà, P. P., and Galansino, G.: The orally active hypoglycemic agents. Chicago Medical School Quart. 20:80-87, 1959.

[2] Mosca, L.: Istofisiologia delle Isole Pancreatische. Milano, Ed. Premio Ganassini, 1958.

[3] Kracht, J.: Morphologische Kriterien zur Beurteilung der Inselaktivität. Endokrinologie 36:146-58, 1958.

[4] Creutzfeldt, W.: Morphologische Veränderungen der Pankreasinseln und ihre Beziehungen zum Kohlenhydratstoffwechsel; mit besonderer Berücksichtigung der peroralen Antidiabetika. Wiener Zeit. inn. Med. 37:217-30, 1956.

[5] Lundbaek, K., Nielsen, K., and Rafaelson, O. J.: Studies on the effect of oral antidiabetic compounds on glucose tolerance, on islet structure, and on the in vitro metabolism of isolated muscle. Ann. New York Acad. Sc. 74:419-26, 1959.

[6] Ashworth, M. A., and Haist, R. E.: Some effects of BZ-55 (carbutamide) on the growth of the islets of Langerhans. Canad. M.A.J. 74:975-76, 1956.

[7] Schöler, H. F. L., and Gaarenstroom, J. H.: The effect of BZ-55 on the pancreatic islets. Acta Endocrinol. 29:147-59, 1958.

[8] Lundbaek, K., and Nielsen, K.: A comparative study of the action of three hypoglycemic compounds on the blood sugar and the islets of the pancreas in the rat. Acta Endocrinol. 27: 325-38, 1958.

[9] Creutzfeldt, W., Detering, L., and Welte, O.: Das B-Zellensystem von normalen und hypophysektomierten Ratten sowie von Kaninchen unter D860 und diabetogenen Hormonen. Deutsche med. Wchnschr. 82:1564-68, 1957.

[10] Mosca, L.: Some effects of tolbutamide on the pancreatic islets of growing rats. Quart. J. Exp. Physiol. 43:265-69, 1958.

[11] Kracht, J., v. Holt, C., and v. Holt, L.: Morphologische Befunde zur Wirkungsweise oraler Antidiabetika. Endokrinologie 34:129-46, 1957.

[12] Gepts, W.: Contribution a l'étude morphologique des îlots de Langerhans au cours du diabète. Bruxelles, Acta Medica Belgica, 1957.

[13] v. Holt, C., Kracht, J., Kröner, B., and v. Holt, L.: Wirkung von N_1-sulfanilyl-N_2-n-butylcarbamid auf Kohlenhydratstoffwechsel und endokrines System. Schweiz. med. Wchnschr. 86:1123-29, 1956.

[14] Bänder, A.: Toxicological and histological studies with tolbutamide. Ann. New York Acad. Sc. 71:152-53, 1957.

[15] Gepts, W., Christophe, J., and Mayer, J.: Pancreatic islets in mice with the obese-hyperglycemic syndrome. Lack of effect of carbutamide. Diabetes 9:63-69, 1960.

[16] Mosinger, B., and Braun, T.: Potentiating the diabetogenic effect of alloxan by N-sulphonyl-N-butylurea (BZ-55). Experientia 15:317-18, 1959.

[17] Creutzfeldt, W., and Finter, H.: Blutzucker und histologische Veränderungen nach D860 bei normalen Kaninchen. Deutsche med. Wchnschr. 81:892-96, 1956.

[18] Pfeiffer, E. F., Steigerwald, H., Sandritter, W., Bänder, A., Mager, A., Becker, U., and Retiene, K.: Vergleichende Untersuchungen von Morphologie und Hormongehalt des Kälberpankreas nach Sulfonylharnstoffen (D860). Deutsche med. Wchnschr. 82:1568-74, 1957.

[19] Loubatières, A., Bouyard, P., De Laclos, C. F.: Action du para-aminobenzène-sulfamido-isopropylthiodiazol sur la glycémie, la structure des îlots de Langerhans et le métabolisme de

l'animal normal ou diabètique. C. r. Soc. Biol. *149*:1642-46, 1955.

[20] Segura, E. T.: Ensayos de curación de la diabetes metaaloxánica del conejo. Buenos Aires, Abstr. & Commun. XXI Intern. Congr. Physiol. Sci., 1959, p. 249.

[21] Creutzfeldt, W., and Böttcher, K.: Die Wirkung des D860 auf den Alloxandiabetes des Kaninchens. Deutsche med. Wchnschr. *81*:896-99, 1956.

[22] Loubatières, A.: The mechanism of action of the hypoglycemic sulfonamides: a concept based on investigations in animals and human beings. Ann. New York Acad. Sc. *71*:192-206, 1957.

[23] Loubatières, A.: The mechanism of action of the hypoglycemic sulfonamides. Diabetes 6:408-17, 1957.

[24] Lazarow, A., and Treibergs, B.: The effect of long-term administration of tolbutamide to (alloxan)-subdiabetic rats. New England J. Med. *261*:417-23, 1959.

[25] Creutzfeldt, W., and Geginat, G.: Glukosetoleranz und Inselregeneration bei teilpankreatektomierten Ratten unter ACTH- und langfristiger Behandlung mit N-(4-methyl-benzolsulfonyl)-N'-butylharnstoff. Arzneimittel Forsch. *8*:464-69, 1958.

[26] Mirsky, I. A., Gitelson, S., and Perisutti, G.: The effect of tolbutamide on the diabetogenic action of somatotropin. Endocrinology *64*:766-68, 1959.

[27] Kinsell, L. W., Michaels, G. D., Brown, F. R., Jr., and Friskey, R. W.: Observations with sulfonylureas in diabetes. Metabolism *5*:864-67, 1956.

[28] Fajans, S. S., and Conn, J. W.: Tolbutamide-induced improvement in carbohydrate tolerance of young people with mild diabetes mellitus. Diabetes *9*:83-88, 1960.

[29] Heineman, A., Cohn, C., Weinstein, M., and Levine, R.: Clinical experience with carbutamide and tolbutamide. Metabolism *5*:972-77, 1956.

[30] Gepts, W.: Die histopathologischen Veränderungen der Langerhansschen Inseln und ihre Bedeutung in der Frage der Pathogenese des menschlichen Diabetes. Endokrinologie *36*: 185-211, 1958.

[31] Creutzfeldt, W., and Sütterle, H.: Recherches expérimentales sur le mécanisme d'action des sulfamides hypoglycémiants. Ann. d'Endocrinol. *18*:184-95, 1957.

[32] Lawrence House, E.: A histological study of the pancreas, liver and kidney both during and after recovery from alloxan diabetes. Endocrinology *62*:189-200, 1958.

[33] Sirek, A., Sirek, O., Hanus, Y., Monkhouse, F. C., and Best, C. H.: Effect of prolonged administration of tolbutamide in depancreatized dogs. Diabetes *8*:284-88, 1959.

[34] Lazarus, S. S., and Volk, B. W.: Functional and morphologic studies on the effect of Orinase on the pancreas. Endocrinology *62*:292-307, 1958.

[35] Foà, P. P.: The control of the secretory activity of the islets of Langerhans. Ciba Foundation Coll. Endocrinol. 9:55-71, 1956.

[36] Lazarus, S. S., and Volk, B. W.: Pancreatic adaptation to diabetogenic hormones. Arch. Path. 67:456-67, 1959.

[37] Lazarus, S. S., and Volk, B. W.: The effect of protracted glucagon administration on blood glucose and on pancreatic morphology. Endocrinology *63*:359-71, 1958.

[38] Beaser, S. B.: Further experience with the use of sulfonylureas in diabetes. Ann. New York Acad. Sc. *71*:264-67, 1957.

[39] Dotevall, G.: Secondary resistance in oral treatment of diabetes. Acta med. Scandinav. *161*:251-56, 1958.

[40] Moss, J. M., De Lawter, DeW. E., and Canary, J. J.: Results of the treatment with tolbutamide of 200 diabetic patients: a discussion of secondary failure. Ann. Int. Med. 50: 1407-17, 1959.

[41] Knauff, R. E., Fajans, S. S., Ramirez, E., and Conn, J. W.: Metabolic studies of chlorpropamide in normal men and in diabetic subjects. Ann. New York Acad. Sc. *74*:603-17, 1959.

[42] Foà, P. P., and Galansino, G.: Glucagon. In Astwood, Clinical Endocrinology 1. New York, Grune & Stratton, 1960, p. 269.

[43] Nelson, N.: A photometric adaptation of the Somogyi method for the determination of glucose. J. Biol. Chem. *153*: 375-80, 1944.

[44] Fisher, R. A.: Statistical Methods for Research Workers. Edinburgh, Oliver and Boyd, 1950.

[45] Gomori, G.; in Ferner, H.: Das Inselsystem des Pankreas. Stuttgart, Thieme, 1952.

The distinct disadvantage of excess weight in persons with various types of impairments shown by the Build and Blood Pressure Study, 1959, is confirmed by clinical investigations and earlier insurance studies. For example, the prognosis for insured persons with a history of asthma or bronchitis was considerably less favorable among those who were overweight than among those of average weight. Overweights with elevated blood sugar just below the normal limit and those with glycosuria are more likely to become diabetic than average or underweight persons with these impairments. The mortality of overweights with elevated blood sugar is higher than that for lighter weight people primarily because of increased death rate from cardiovascular disease and diabetes.

The present study underscores the desirability of weight control in persons with various types of impairments, even if they are of relatively minor significance. Although overweight usually is not the cause of the impairment, weight reduction will often decrease the adverse effects of the impairment. It is particularly important for overweights to have periodic health examinations so that defects may be detected and, if possible, corrected early.

From *Statistical Bulletin*,
Vol. 41, pp. 5-6, May 1960.