Exhaustion of Insulogenic Reserve in Maturity-onset Diabetic Patients During Prolonged and Continuous Hyperglycemic Stress

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SUMMARY

Solutions of 15 per cent glucose were administered by continuous intravenous infusion for five to seven days to six normal subjects, seven tolbutamide-responsive adult diabetics, and six tolbutamide-nonresponsive adult diabetics. Blood glucose concentration, plasma insulin activity, and net assimilation of carbohydrate were determined daily. An "insulogenic index," relating level of circulating insulin activity to magnitude of glycemic stimulus, enabled comparison of the insulin-secreting capacity of respective groups.

In nondiabetic subjects, mean daily blood glucose levels remained normal, and carbohydrate loads averaging 717 gm. per day were wholly retained. In both diabetic groups, increasing blood glucose and glycosuria permitted net glucose uptakes of only 88 per cent in tolbutamide-responders and 56 per cent in tolbutamide-nonresponders.

Plasma insulin activity increased significantly in all groups. In both normal subjects and tolbutamide-responsive diabetics, enhanced levels appeared on the first day, were sustained at high titers each day thereafter, and exhibited mean maximal value on the last day of infusion. Conversely, in tolbutamide-nonresponsive diabetics, average maximal insulin activity was achieved on the second day, whereafter it declined progressively and sometimes disappeared completely.

Compared to an insulogenic index of 100 per cent to represent the greatest secretory response of normal subjects, the corresponding *maximal* index was 49 per cent for tolbutamide-responders and 17 per cent for tolbutamide-nonresponders. On the last day of infusion, capacity for *sustained* insulin release was reflected by insulogenic indexes of 55 per cent, 32 per cent and 0.1 per cent in the respective groups.

The data indicate that unremitting hyperglycemia tends to exhaust insulogenic reserve in adult-onset diabetics, and that betacytotropic collapse occurs most rapidly in patients with severest clinical intolerance to carbohydrate. This demonstration strengthens the view that maturity-onset diabetes and growth-onset diabetes represent different stages of the same disease. The findings suggest that the fundamental lesion in hereditary human diabetes is either primary beta cell deficiency or impaired responsiveness of peripheral tissues to the action of insulin—or, quite possibly, a combination of both.

Amidst the current vogue for postulating a circulating insulin antagonist,[1] or insulin resistance in peripheral tissues,[2] or even a defect in fat synthesis,[3] as the basic cause of hereditary diabetes mellitus, almost with trepidation does one cling to the view that the beta cell might be primarily involved. Nevertheless, previous work by the senior author[4] did support the thesis that both juvenile and adult-onset diabetes differ only in degree of deficient insulin secreting capacity. Whereas circulating "insulin activity"* in juvenile patients was always zero, in individual adult diabetics both fasting plasma insulin activity and its enhancement after an *acute* glucose load were inversely proportional to the severity of clinical disease. The present study indicates that in maturity-onset diabetics the exhaustibility of insulogenic reserve by *prolonged* hyperglycemic stress likewise depends upon the degree of antecedent carbohydrate intolerance.

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MATERIALS AND METHODS

All subjects and patients were males and were classified into three groups (table 1). Six metabolically normal subjects served as controls. Seven adult-onset diabetics were "tolbutamide-responders," who had either fasting normoglycemia but abnormal glucose tolerance

*Vallance-Owen emphasizes that his assay, which determines net glucose uptake from undiluted plasma by rat diaphragm, does not measure total insulin content, but estimates ". . . plasma-insulin activity, or the effective plasma-insulin concentration, i.e., the sum of insulin and its synergists, if any, on the one hand and its antagonists on the other."[5] His term has a more specific connotation than the more widely employed "insulin-like-activity (ILA)." The latter designation usually refers to values obtained by rat epididymal fat pad bioassay and/or from diluted plasma or serum.

tests, or moderately elevated fasting blood sugars which were subsequently controlled by diet alone or diet plus daily tolbutamide. Six other elderly diabetics were "tolbutamide-nonresponders," whose higher fasting blood sugars showed only minimal or transient depression on combined diet and tolbutamide therapy. The mean age of respective groups was forty-seven, fifty and fifty-seven years. Average duration of diabetes in tolbutamide-responsive patients was eighteen months, with a range of one month to eight years; in the tolbutamide-nonresponsive group, mean duration was five years with a range of one month to thirteen years. No patient received insulin within three days prior to onset of study.

After an overnight fast, 5 ml. of oxalated blood was drawn for blood glucose, and 50 ml. of heparinized blood for estimation of plasma insulin activity. A continuous intravenous infusion of glucose solution was then started and maintained as uninterruptedly as possible for five to seven days. Concentration of glucose was 15 per cent in all except two individuals who received 10 per cent glucose. Daily volume of infusion varied between 3,000 and 4,000 ml. Throughout the study patients consumed diets containing 220 to 300 gm. of carbohydrate per day. "Daily glucose uptake" denoted total daily intake of carbohydrate minus urinary loss. Each morning samples were obtained for blood glucose and plasma insulin activity. These samples were obtained one hour after breakfast in order to maximize the insulogenic stimulus.[4] In three normal subjects an additional specimen was drawn one hour after starting the continuous infusion of glucose. Blood and urinary glucose were determined by the Somogyi-Nelson method.[6]

Plasma insulin activity was assayed by determining the glucose uptake from 2 ml. of undiluted plasma by isolated rat hemidiaphragm, according to the technic described by Vallance-Owen.[4,7]

TABLE 1

Daily blood glucose and net glucose uptake during continuous infusion of 15 per cent glucose

		Day 0*	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Mean ± S.E.M.†
						Normal subjects (6)				
Blood glucose	Mean	77	100	73	90	97	98	82	96	91
(mg. per 100 ml.)	±S.E.M.	±3	±15	±7	±4	±9	±6	±2	±8	±4
Glucose intake	Mean		647	711	741	731	722	714	750	717
(gm. per day)	±S.E.M.		±39	±26	±21	±42	±13	±33	±25	±15
Glycosuria	Mean		1	0	1	1	1	0	0	1
(gm. per day)	±S.E.M.		±1		±1	±1	±1			±1
Glucose retained	Mean		646	711	740	730	722	714	750	716
(gm. per day)	±S.E.M.		±39	±26	±21	±42	±13	±33	±25	±15
Glucose retained	Mean		99.8	100	99.9	99.9	99.9	100	100	99.9
(per cent of intake)	±S.E.M.		±0.2		±0.2	±0.2	±0.2			±0.2
						Tolbutamide-responders (7)				
Blood glucose	Mean	149	281	286	299	259	264	305	325	288
	±S.E.M.	±22	±81	±73	±52	±49	±36	±83	±85	±9
Glucose intake	Mean		588	716	711	671	643	699	679	672
	±S.E.M.		±49	±39	±63	±36	±43	±52	±24	±16
Glycosuria	Mean		51	100	120	75	108	55	68	82
	±S.E.M.		±24	±49	±65	±27	±54	±15	±36	±10
Glucose retained	Mean		537	616	591	596	535	644	611	590
(gm.)	±S.E.M.		±43	±47	±81	±42	±65	±50	±43	±15
Glucose retained	Mean		91	86	83	89	83	92	90	88
(per cent)	±S.E.M.		±4	±6	±7	±4	±9	±2	±4	±1
						Tolbutamide-nonresponders (6)				
Blood glucose	Mean	265	440	509	536	564	557	605	499	530
	±S.E.M.	±28	±100	±78	±71	±103	±88	±107	±75	±24
Glucose intake	Mean		644	704	743	708	720	700	721	706
	±S.E.M.		±28	±34	±12	±25	±27	±24	±39	±14
Glycosuria	Mean		224	230	262	379	373	346	347	309
	±S.E.M.		±34	±58	±61	±97	±87	±89	±94	±22
Glucose retained	Mean		420	474	481	329	347	354	374	397
(gm.)	±S.E.M.		±57	±44	±65	±73	±63	±65	±55	±22
Glucose retained	Mean		65	67	65	46	48	51	52	56
(per cent)	±S.E.M.		±6	±7	±8	±12	±11	±12	±11	±3

*Day 0 = fasting value; days 1 to 7 = one hour after breakfast.
†Mean of days 1 to 7.

RESULTS

Initial response in normal subjects. In three control subjects, as expected, both blood glucose and plasma insulin activity had increased significantly above fasting values one hour after starting the continuous infusion of glucose. Mean blood glucose rose from 81 mg. per 100 ml. to 140 mg. per 100 ml. ($p < 0.001$), and mean plasma insulin activity from 19 micro-units per milliliter to 277 micro-units per milliliter ($p < 0.02$).

Daily blood glucose and daily glucose uptake (table 1 and figure 1). In successive groups, representing progressive loss of carbohydrate tolerance, blood glucose values were higher, glycosuria increased, and daily glucose uptake was correspondingly less. In normal subjects, fasting blood sugar was 77 ± 3 (mean ± S.E.M.) mg. per 100 ml., and maximal blood sugar level was only 100 ± 15 mg. per 100 ml. It is noteworthy that, although all daily samples were obtained one hour after breakfast, only seven of thirty-nine values exceeded the upper normal fasting limit of 100 mg. per 100 ml. Since there was no glycosuria, enormous glucose loads averaging from 646 to 750 gm. per day were wholly retained. In tolbutamide-responsive adult diabetics, fasting blood glucose of 149 ± 22 mg. per 100 ml. increased to maximal postprandial value of 325 ± 85 mg. per 100 ml. on Day 7. Mean uptake of glucose was 590 ± 15 gm. per day, or 88 ± 1 per cent of daily carbohydrate intake. In tolbutamide-nonresponsive adult diabetics, fasting glucose of 265 ± 28 mg. per 100 ml. rose to a peak of 605 ± 107 mg. per 100 ml. on Day 6. Since heavy glycosuria permitted daily retention of only 56 ± 3 per cent of administered carbohydrate, average uptake was only 397 ± 22 gm. per day.

Daily plasma insulin activity (table 2 and figure 2). In normal subjects prompt and persistent elevation of plasma insulin activity was evident from Day 1 through Day 7, at average levels four to ten times higher than the fasting value. Mean concentration rose from fasting of 45 ± 13 micro-units per milliliter of plasma to a maximal value of 460 ± 164 micro-units per milliliter ($p < 0.05$) on Day 7. Tolbutamide-responsive diabetics exhibited the same pattern of secretory response, with plasma insulin activity rising from fasting value of 31 ± 8 micro-units per milliliter to 458 ± 122 micro-units per milliliter on Day 2 ($p < 0.01$). Thereafter, comparably high levels were sustained through the infusion and, as in the normal subjects, maximal titer of 545 ± 164 micro-units per milliliter ($p < 0.01$) oc-

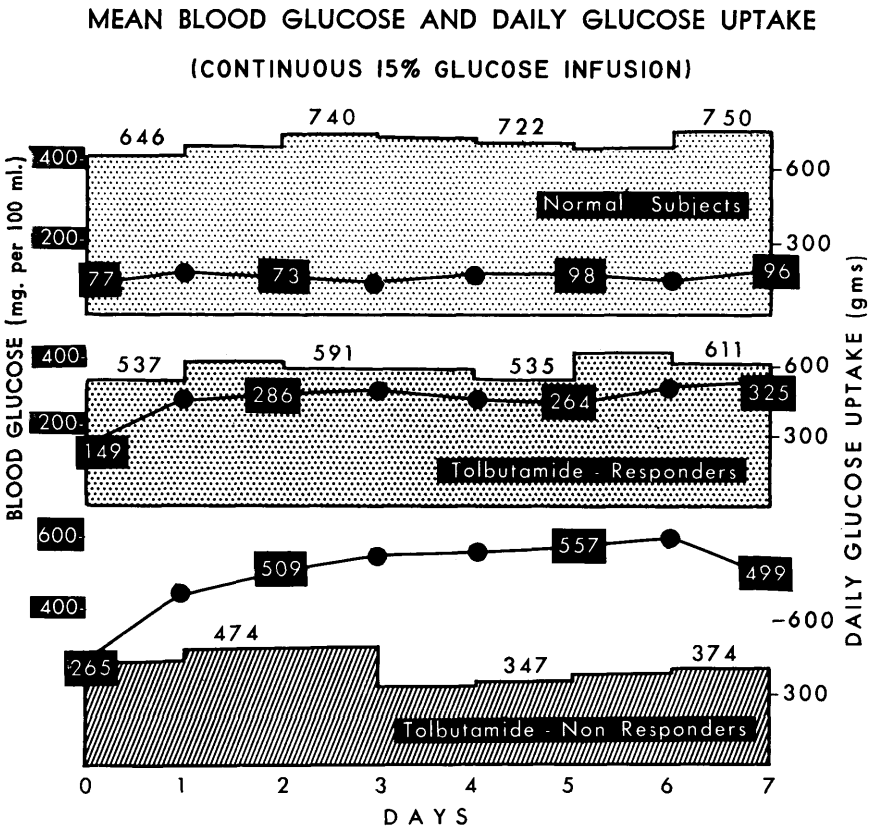


FIG. 1. Joined rectangles and circles show mean daily blood glucose concentrations; values on Day 0 are fasting, all others are one hour after breakfast. Shaded areas, with corresponding numbers above, represent average net glucose uptakes (total carbohydrate intake minus urinary loss) per day.

TABLE 2

Daily plasma insulin-activity (micro-units per milliliter) during continuous infusion of 15 per cent glucose

Patient	Day 0*	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
				Normal subjects				
VOI	87	365	107	222	83	145	129	155
DAN	48	700	394	230	102	780	107	810
ADA	75	30	110	163	95	248	129	151
SMI	35	—	—	325	600	755	1,000	725
HOU	13	19	184	394	590	66	135	—
GON	10	50	131	102	240	350	—	—
Mean	45	233	185	239	285	391	300	460
±S.E.M.	±13	±133	±54	±43	±86	±119	±179	±164
p		<0.2	<0.05	<0.005	<0.02	<0.02	<0.2	<0.05
				Tolbutamide-responders				
HOL	8	89	211	298	372	1,000	372	1,000
DAU	41	1,000	1,000	280	218	65	104	586
BRO	18	211	1,000	1,000	—	465	118	375
LEE	26	165	417	12	40	298	430	1,000
BAT	18	397	272	—	324	171	165	298
FRA	62	131	165	89	142	165	95	13
GAR	41	—	142	502	375	1,000	—	—
Mean	31	332	458	364	245	452	214	545
±S.E.M.	±8	±152	±122	±165	±54	±134	±56	±164
p		<0.1	<0.01	<0.1	<0.005	<0.01	<0.01	<0.01
				Tolbutamide-nonresponders				
JON	56	918	1,000	744	137	153	1	12
WIL	97	344	882	430	57	21	6	0
GAR	13	325	52	191	107	9	13	3
TUR	13	95	394	290	79	3	0	0
MAR	2	0	4	15	0	3	1	0
RIC	32	7	184	0	0	0	—	—
Mean	36	282	419	278	63	32	4	3
±S.E.M.	±16	±153	±166	±124	±23	±25	±3	±2
p		<0.2	<0.05	<0.1	<0.4			

*Day 0 = fasting value; days 1 to 7 = one hour after breakfast.

curred on Day 7. In the tolbutamide-nonresponsive patients, however, fasting plasma insulin activity was 36 ± 16 micro-units per milliliter and peak increase during glucose infusion occurred on Day 2 (419 ± 166 micro-units per milliliter $p < 0.05$), whereafter it decreased daily and was actually undetectable the last day in four of the six patients.

"Index of insulogenic reserve" (figure 3). The "insulogenic index," obtained by dividing the value for plasma insulin activity by the corresponding blood glucose concentration, related the amount of plasma insulin activity before and during glucose infusion to the magnitude of the insulogenic stimulus itself. The mean insulogenic index for each individual's day of *maximal* response was 7.10 ± 1.72 (100 per cent) in normal subjects, 3.45 ± 0.95 (49 per cent) in tolbutamide-responsive diabetics, and 1.18 ± 0.48 (17 per cent) in tolbutamide-nonresponsive patients. As a measure of *sustained* insulin secreting capacity, the index on the last day of infusion was still 3.91 ± 1.35 in control subjects (55 per cent of the normal maximum) and 2.25 ± 0.69 in tolbutamide-responders (32 per cent of normal maximum), but had fallen to 0.01 (0.1 per cent) in the tolbutamide-nonresponsive group.

DISCUSSION

The inability to produce sustained hyperglycemia in normal subjects was a distinct surprise. After the first day of continuous infusion of glucose not only was the prebreakfast blood sugar always normal, but the value one hour after breakfast was also below 100 mg. per 100 ml. in thirty-two of thirty-nine determinations. The situation was thus opposite that seen in the diabetic patients, namely, hyperinsulinemia in the *absence* of hyperglycemia. Continuous glycemic stimulation appeared to super-sensitize normal beta cells into discharging excessive insulin relative to the actual concentration of glucose in the islets; and, in turn, the surfeit of circulating hormone must have greatly enhanced assimilation of carbohydrate both by liver and peripheral tissues.

The net daily uptake of glucose depended upon the ability of circulating insulin to narrow the gap between

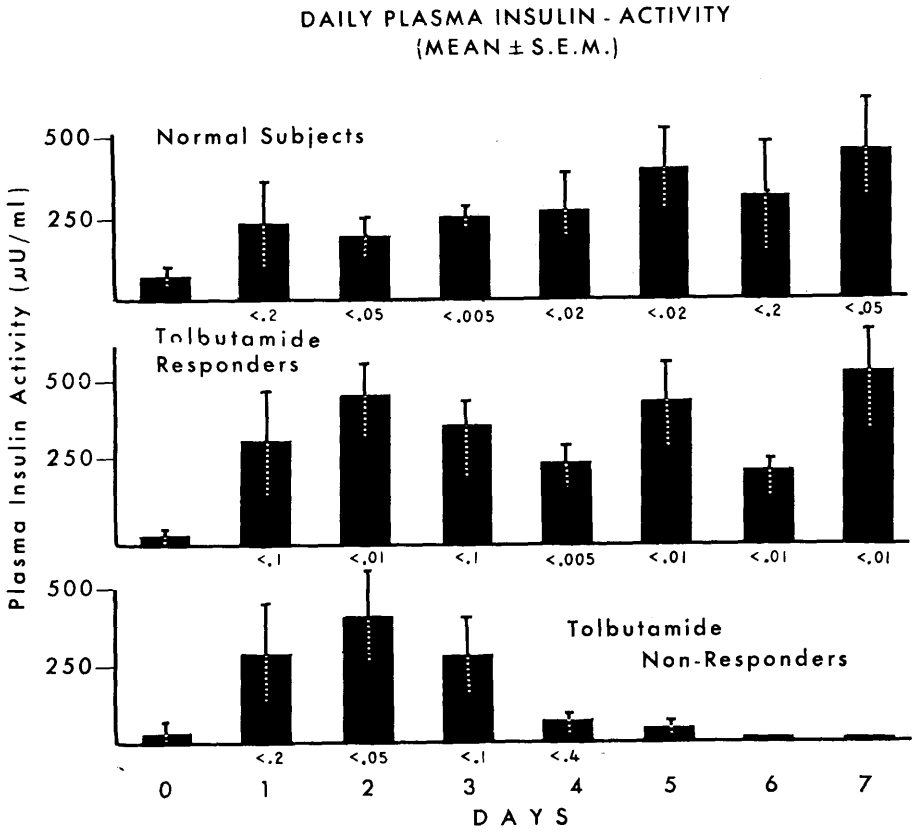
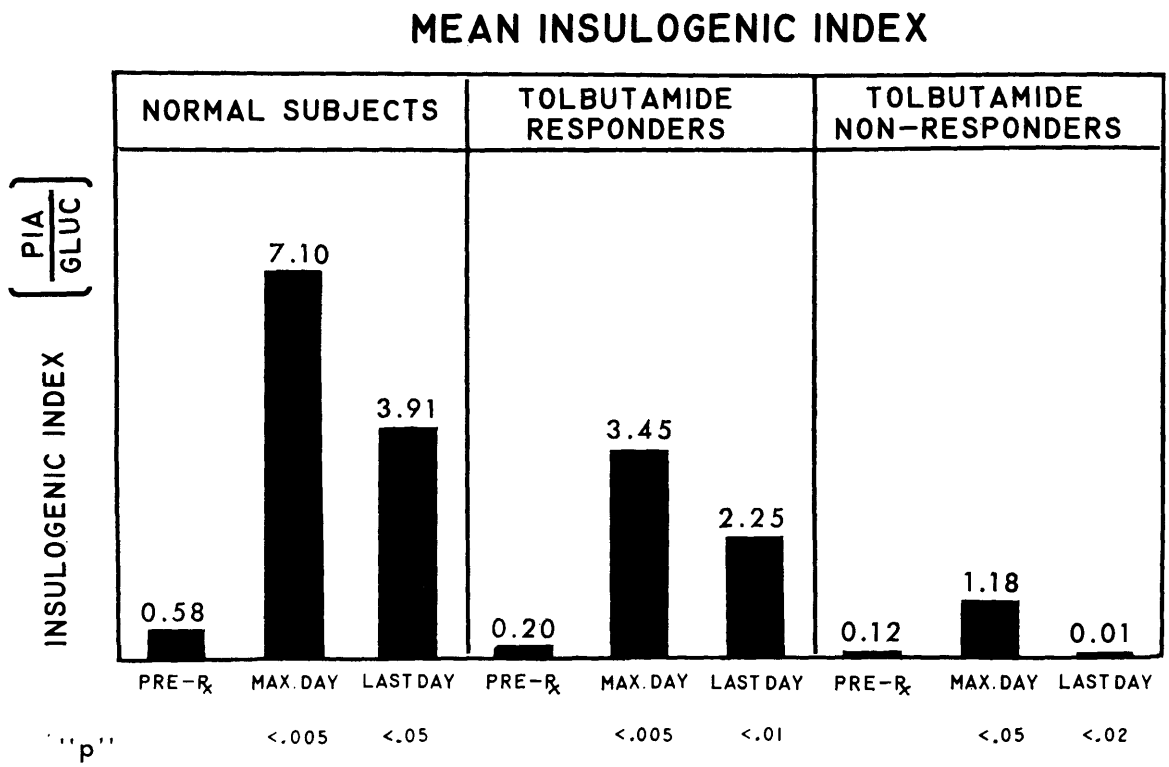


FIG. 2. Plasma insulin activity on Day 0 was determined after overnight fast. All other values were measured one hour after breakfast and during continuous infusion of 15 per cent glucose solution.

FIG. 3. (Below) Insulogenic index was obtained by dividing value for plasma insulin activity by corresponding blood glucose level. "Pretreatment" refers to fasting value on Day 0. "Maximal day" represents average of greatest insulogenic index for each patient within a group. "Last day" denotes mean index on final day of infusion for each individual. Values for "p" show comparison with pretreatment index.



blood glucose concentration and renal threshold for glucose. In nondiabetic subjects, since even normal postprandial hyperglycemia disappeared, both infused and ingested carbohydrate were wholly retained. In tolbutamide-responsive diabetic patients, sustained insulin secretion held daily blood glucose levels fairly constantly around a mean of 288 ± 9 mg. per 100 ml. (table 1), which permitted average daily uptake of 88 ± 1 per cent of administered carbohydrate. In tolbutamide-nonresponsive patients, however, diminishing insulin secretion was reflected by progressively mounting blood glucose and glycosuria, such that only 56 ± 3 per cent of total carbohydrate intake could be retained during five to seven days of glucose infusion.

A previous report from this laboratory[4] indicated that the superficially all-or-none distinction between the insulin secreting capacity of young and old diabetics is more apparent than real. Not only did mild, tolbutamide-responsive, elderly diabetics have higher fasting levels of plasma insulin activity than did more severe, tolbutamide-nonresponsive diabetics, but they also showed much greater increases after 100 gm. of glucose by mouth. The present study was designed to telescope into a week the effects of years of unremitting hyperglycemic stress upon the insulogenic reserve of untreated elderly diabetics. Not unexpectedly, the islets of tolbutamide-responsive diabetics retained the capacity to secrete significant insulin throughout the period of continuous hyperglycemia, whereas in tolbutamide-nonresponders insulogenic capacity quickly collapsed and actually became immeasurable in some patients. Thus, these data almost close the apparent gap between adult-onset diabetics who secrete endogenous insulin and are ketosis-resistant, and juvenile diabetics who secrete no insulin and therefore rapidly develop ketoacidosis when untreated. The key point is that the adult-diabetic population is heterogeneous and displays a spectrum of residual insulogenic reserve ranging from almost-normal to almost-exhausted.

If ketonuria or ketonemia had developed in patients whose plasma insulin activity fell to zero, the gap between adult-onset and juvenile diabetes would have been completely bridged. However, immeasurable insulin activity in peripheral plasma is not equatable with zero insulin secretion; and it is likely that only a tiny amount of insulin output, to which the liver has primary access,[8] maintains sufficient intra-hepatic carbohydrate turnover to prevent development of ketosis.

With respect to the etiology of the carbohydrate defect in diabetes mellitus, i.e., the reason for the initial appearance of hyperglycemia, the present findings together with previous evidence suggest that the primary lesion is either intrinsic beta cell failure, diminished responsiveness of peripheral tissues to the action of insulin, or a combination of both.

That normal islets respond rapidly and quantitatively to a rising blood sugar was demonstrated by Metz,[9] and confirmed by the senior author.[10] Rapid release of adequate insulin is clearly an important function of intact islets, and reasonably explains the low peak on the normal glucose tolerance curve. Conversely, Seltzer, Fajans and Conn[11] invoked the concept that the first step in functional deterioration of the beta cell is *delayed rate of secretory response* to a rising blood sugar, at a time when its *capacity* to respond is still almost normal, as the mechanism underlying the symptomatic hypoglycemia sometimes seen in early diabetes mellitus. The glucose tolerance curve in such patients is characterized by a normal fasting blood sugar, a prolonged hyperglycemic plateau and a late drop to hypoglycemic levels. The latter phenomenon was thought to result from sluggish initial release of insulin by islets which ultimately responded to the hyperglycemia with massive insulogenesis. Yalow and Berson[2] subsequently documented this interpretation by finding subnormal concentrations of plasma insulin at one-half hour but greatly elevated levels at two hours, during oral glucose tolerance testing of similar mild diabetics. In early diabetes, therefore, initial blunting of the normal swift response to an increasing blood glucose may set off a worsening cycle of (a) postprandial hyperglycemia, which (b) causes excessive stimulation of beta cells, which (c) progressively depletes insulin-secreting reserve until, finally, (d) *fasting* hyperglycemia supervenes and establishes round-the-clock overload of an already failing insulogenic mechanism. Within this context, the sustained high levels of plasma insulin activity in tolbutamide-responsive diabetics during continuous glucose infusion would signify that their islets were still able to respond essentially normally to seven days of maximal stimulation, which capacity had been lost by the islets of tolbutamide-nonresponders.

The foregoing sequence fits equally well the postulate that the inherited defect in diabetes is impaired sensitivity of peripheral tissues to the action of insulin. Hennes[3] suggested that such a block may occur in the incorporation of glucose into triglyceride.[3] By whatever mechanism, the first manifestation of deficient glucose utilization would be abnormal postprandial hyperglycemia, which would in turn activate the cycle of chronic overstimulation of beta cells. One facet of the present study particularly supporting the peripheral block thesis

was the difference in rate of disposal of glucose between normal subjects and tolbutamide-responsive patients. In the nondiabetic group, high insulin output accelerated glucose uptake so greatly that even normal postprandial hyperglycemia disappeared, whereas in mild diabetics even higher levels of plasma insulin activity were accompanied by a two-fold rise above the fasting blood sugar level. These findings certainly suggest that the cells of even mild diabetics are much less able than normal tissues to extract glucose.

Another explanation for the apparent paradox that high levels of circulating insulin failed to dispose adequately of excessive blood glucose in tolbutamide-responsive patients may be that the hormone was unavailable to the tissues. In this regard, Antoniades and associates[12] have proposed that insulin is present in blood in both a metabolically active "free" state, and an inactive "complexed" or "bound" form. However, the values reported in this study presumably represent "free" and hence metabolically active insulin, since the bioassay procedure measures glucose uptake by rat diaphragm directly from undiluted and untreated plasma.

Finally, a paramount causative role for circulating insulin antagonists has been championed by Vallance-Owen who recently theorized that all hereditary diabetes may be due to a substance bound to plasma albumin.[13] Although he finds the inhibitor even in normal plasma, its concentration is three or four times greater in diabetic patients. Since the amount of antagonist is the same not only in growth-onset and maturity-onset diabetics, but in "prediabetics" as well, the severity of clinical disease would not seem to evolve from increasing production of the substance. Instead, a constantly excessive amount of antagonist, elaborated for years during the "prediabetic" phase, is thought to impose a chronic hypersecretory drain which finally overpowers the beta cell. This intriguing concept is neither supported nor contested by the present data, since the demonstration of insulin activity in unaltered plasma does not rule out the simultaneous presence of anti-insulin factors.

SUMMARIO IN INTERLINGUA

Exhaustion del Reservas Insulinogene, in le Curso de Prolongate e Continue Stress Hyperglycemic, in Patientes con Diabete de Declaration a Etates Matur

Solutiones de 15 pro cento de glucosa esseva administrate per continue infusion intravenose durante cinque a septe dies a sex normal subjectos, a septe adulte diabeticos tolbutamido-responsive, e a sex adulte diabeticos tolbutamido-non-responsive. Le concentration sanguinee de glucosa, le activitate de insulina in le plasma, e le nette assimilation de hydrato de carbon esseva determinate a intervallos diurne. Un indice insulinogene, relationante le nivello del activitate de insulina in le circulation con le magnitude del stimulo glycemic, permitteva un comparation del capacitate insulino-secretori del diverse gruppos.

In subjectos non-diabetic, le nivellos medie diurne del glucosa sanguinee remaneva normal, e cargas diurne de hydrato de carbon amontante a un magnitude medie de 717 g esseva retenite totalmente. In ambe le gruppos diabetic, le augmentate glucosa sanguinee e le augmentate glycosuria permitteva acceptationes de glucosa amontante a solmente 88 pro cento (in tolbutamido-responsivos) e 56 pro cento (in tolbutamido-non-responsivos).

Le activitate de insulina in le plasma cresceva significativemente in omne le gruppos. Tanto in subjectos normal como etiam in diabeticos tolbutamido-responsive, augmentate nivellos appareva le prime die, se susteneva a alte titros durante le sequente dies, e monstrava un valor medie maximal le ultime die del infusion. Del altere latere, in le diabeticos tolbutamido-non-responsive, le maximo medie del activitate de insulina esseva attingite le secunde die, con—subsequentemente—un declino progressive que se terminava a vices in un disparition complete.

Comparate con un indice insulinogene de 100 pro cento, representante le maxime responsa secretori de subjectos normal, le correspondente indice *maxime* esseva 49 pro cento pro tolbutamido-responsores e 17 pro cento pro tolbutamido-non-responsores. Le ultime die del infusion, le capacitate pro un sustenite liberation de insulina esseva reflectite per indices insulinogene de 55 pro cento, 32 pro cento, e 0,1 pro cento in le respective gruppos.

Le datos indica que persistente hyperglycemia tende a exhaurir le reservas insulinogene in patientes con diabete de declaration a etates adulte e que un collapso betacytotropic occurre le plus rapidemente in patientes con severissime intolerantia clinic pro hydrato de carbon. Iste demonstration reinfortia le conception que diabete de declaration in maturitate e diabete de declaration in stadios crescential representa differente phases del mesme morbo. Le constatationes suggere que le lesion fundamental in hereditari diabete human es (1) carentia primari betacytic o (2) defective responsivitate de tissus peripheric al action de insulina o (3) un combination de ambes, lo que es possibilissime.

ACKNOWLEDGMENT

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MORTALITY FROM SELECTED CAUSES, 1961-1963

Industrial Policyholders, Metropolitan Life Insurance Company

Cause of Death	Annual Rate per 100,000 Policyholders*		
	1963	1962	1961
All Causes	741.4	690.7	688.0
Tuberculosis (all forms)	5.0	4.9	5.1
Communicable diseases of childhood	0.1	0.1	0.1
Acute poliomyelitis	†	†	†
Malignant neoplasms	160.1	148.7	148.3
Digestive system	50.5	47.4	47.3
Respiratory system	27.4	24.5	23.9
Diabetes mellitus	17.2	15.5	15.4
Diseases of the cardiovascular-renal system	391.9	367.9	368.7
Vascular lesions, central nervous system	71.2	66.2	67.0
Diseases of heart	289.9	274.6	273.8
Chronic rheumatic heart disease	11.6	10.7	11.3
Arteriosclerotic and degenerative heart disease	237.8	224.6	221.5
Diseases of coronary arteries	136.4	129.5	129.2
Hypertension with heart disease	26.8	26.9	28.5
Other diseases of heart	13.7	12.3	12.5
Nephritis and nephrosis	6.0	5.8	6.4
Pneumonia and influenza	22.5	18.1	17.6
Complications of pregnancy, childbirth	0.5	0.8	0.6
Suicide	6.9	6.5	6.3
Homicide	2.9	2.9	3.1
Accidents—total	35.3	33.9	32.9
Motor vehicle	16.0	15.2	14.3
All other causes	99.0	91.4	89.9

*These death rates relate to persons insured under Weekly or Monthly premium-paying industrial policies and Monthly premium-paying Ordinary policies for small amounts of insurance.

†Less than 0.05.

Note: Rates for 1963 are provisional.

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