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C^{14} Glucose Kinetic Studies in Normal, Diabetic, and Acromegalic Subjects[1]

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In the past few years several methods have been introduced for the study of the kinetics of C^{14} glucose in humans or laboratory animals. Among these methods, the most popular ones presently appear to be the priming dose-continuous infusion (1), the successive tracer injection (2), and the single tracer injection methods (3). The priming dose-continuous infusion method consists of giving an initial dose of C^{14} glucose and simultaneously starting a constant continuous infusion of this tracer. It provides a means of calculating various parameters for both the glucose compartment and the bicarbonate compartment, but the determination of an asymptote required for some of these calculations sometimes presents a difficulty. The successive tracer injection method is performed by giving injections of C^{14} glucose at various times, the time of each injection depending on the preceding events. This method was devised to study the characteristics of the glucose compartment. It has not been extended to include the bicarbonate compartment. The simplest method which allows the calculation of parameters for both the glucose and bicarbonate compartments is the single tracer injection method. It, however, relies on the steady-stateness of these two compartments, a situation not always attained in patients with abnormalities in carbohydrate metabolism. These methods along with the cautions required in their use are discussed by their respective authors.

The method used in the present study is a modification of the single tracer injection method introduced by Baker *et al* in 1954 (3). The technique which they used required the periodic collection of CO_2 via a face mask whereas the newer version, developed by Tolbert *et al* (4,5) allows "continuous" monitoring of expired CO_2 and $C^{14}O_2$. The theoretical model as presented by Baker *et al* had some minor gaps which were recently bridged (6). Further support of this model, when properly applied, will be presented in this article.

The present report, however, is concerned primarily with the results obtained when this method was applied to normal subjects (Table I), patients with either adult or juvenile type diabetes mellitus (Table II), and patients with active acromegaly (Table IV). The characteristic differences in glucose kinetics in the diabetics and in the acromegalics as compared to the normals will be indicated. Similarities between these groups will also be noted. It will be seen that the abnormalities in glucose kinetics which frequently accompany acromegaly are

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similar to those seen in diabetes mellitus but usually with a lesser degree of deviation from normal.

Preliminary results of glucose kinetic studies on patients after the administration of suppressive doses of heavy particle irradiation to their pituitary glands will also be presented. At the time of pituitary irradiation, these patients had either diabetes mellitus with retinopathy (Table III) or active acromegaly (Table V). It will be seen that the diabetic state which sometimes accompanies acromegaly can be reversed with heavy particle irradiation to the pituitary. The effects on adult-type diabetes are yet unclear. It appears, however, that the diabetic state is not improved in this disorder.

Included in this report is a study performed on a patient with Cushing's syndrome due to an adrenal carcinoma. Interestingly, this patient had a normal glucose kinetic study in spite of a markedly elevated excretion rate of urinary adrenocortical steroids.

THEORY AND METHOD

The method, in brief, consisted of giving a single tracer dose (10-15 μc) of universally labeled C^{14} glucose[1] intravenously and subsequently following the blood glucose specific activity, blood glucose concentration, expired CO_2, and expired CO_2 radioactivity for three to six hours (6). These studies were performed either after an overnight fast or, as in the case of some diabetics, immediately after breakfast preceded by a dose of insulin or an oral hypoglycemic agent. The diet of the acromegalic subjects contained more than 200 gm of carbohydrate. The diabetic subjects, however, were on individual diets as given in Table VII. The use of heavy particle pituitary irradiation in the treatment of diabetic retinopathy and acromegaly has been reported previously (7,8,9).

The theory is that of Baker *et al* (3,6). It is based on a unidirectional two compartmental (glucose compartment and bicarbonate compartment) steady-state model, in which glucose is oxidized to CO_2 by an "immediate oxidative pathway". The equations describing this model are:

$$a\ (t) = a_0\, e^{-\lambda_1 t}$$

$$b\ (t) = \begin{cases} a_0\, \lambda_2\, t\, e^{-\lambda_2 t}, & \text{for } \lambda_1 = \lambda_2 \\ a_0 \dfrac{\lambda_2}{\lambda_2 - \lambda_1}\ (e^{-\lambda_1 t} - e^{-\lambda_2 t}), & \text{for } \lambda_1 \neq \lambda_2 \end{cases}$$

where $\lambda_1 = \lambda_2$ if and only if $t_{max} = \dfrac{1}{\lambda_1}$, and where the quantities in these equations are defined to be:

a (t) = μc/g C in the glucose compartment at any time $t \geq 0$, ($a_0 = a\ (0)$).

b (t) = μc/g C in the bicarbonate compartment at any time $t \geq 0$.

λ_1 = fraction of the glucose compartment which turns over each minute.

λ_2 = fraction of the bicarbonate compartment which turns over each minute.

t = time in minutes. t = 0 is the time of injection of C^{14} glucose.

t_{max} = time when the specific activity of the bicarbonate compartment (or breath) reaches its maximum value.

[1]Obtained from Nuclear-Chicago Corporation.

a (t) is assumed to describe the actual situation in the glucose compartment. b (t) is the theoretical specific activity of the bicarbonate compartment assuming all of the CO_2 in this compartment comes from glucose. But, not all of the CO_2 in this compartment is derived from glucose. Hence the ratio between the experimentally observed breath specific activity, $E^{SA}_{CO_2}$, and this theoretical bicarbonate compartment specific activity, b (t), namely, $\frac{E^{SA\ (t)}_{CO_2}}{b\ (t)}$, is taken to be the fraction of CO_2 derived from glucose. The reader is referred to reference 6 for further details regarding the calculation of these and other quantities presented in the results. The words "pool" and "compartment" will be used synonymously.

RESULTS

The time required for uniform mixing of the injected radioactive glucose was defined to be the time when the exponential decay curve for blood specific activity fell on the straight line (using semilogarithmic paper) drawn through the later points. This was found to range from 15 to 60 minutes but was usually 30 minutes. Reichard *et al* (10), had similar results.

The glucose pool was considered to be in a steady state in all patients who had a constant blood glucose throughout the procedure. In all but seven instances, the variation in blood glucose was within 20 mg per cent. However, in these 7 studies, numbered 3, 16, 28, 32, 34 ("on insulin" study), 39, and 61, there was a change in blood glucose from 550 to 420, 180 to 70, 69 to 95, 340 to 240, 100 to 30, 200 to 110 and from 150 to 100 mg per cent, respectively, over the course of the procedure (3 to 6 hours).

In a few instances the blood glucose specific activity curves, plotted on semilog paper, could be better fitted using two straight lines rather than one. The point of intersection in these cases was between 90 to 180 minutes. The angle between the two lines was never more than 10 degrees.

Further support of assumption (A-7) (6), namely, that $E^{SA}_{CO_2}$ and b reach their maximum values at the same time, was provided by the data on patients who had steady blood glucose levels. t_{max}, the time at which $E^{SA}_{CO_2}$ had its maximum value, and $t_m = \frac{1}{\lambda_2 - \lambda_1}$. $\ln \frac{\lambda_2}{\lambda_1}$, the time at which b had its maximum value, differed, on the average, by only 2 per cent. This suggests that steady state conditions are reached between the bicarbonate compartment and the expired breath within the time interval $[0, t_{max}]$.

The results of the remainder of the experimental findings and calculations are presented in Tables I-V. In what follows, the ranges of variations of these parameters will be represented by intervals written as ordered pairs, [a, b], where a is the least member and b the greatest member of the interval. Numbers in parentheses, ( ), refer to the studies being discussed. Tables VI and VII provide the clinical background as well as some of the laboratory results on the patients studied.

(R-1) $t_{\frac{1}{2}}$: Half-life of C^{14}-glucose in the glucose pool.

TABLE I
NORMAL SUBJECTS

Study Number (different subjects)	*Bs (FBS) mg %*	$t_{\frac{1}{2}}$ *min*	*Glucose Pool Size*		*Glucose Turnover*		*Glucose Volume*	t_{max} *min*	$\left\langle \frac{d[CO^2]}{dt} \right\rangle$ *mg/min*
			P_G *g*	P_G^w *g/kg*	λ_1 *1/min*	T_G *g/kg/h*	V_G^w *% BW*		
6	79	90	21.5	0.364	0.0077	0.168	36.0	140	287
7	77	77	20.8	0.311	0.0090	0.168	42.0	95	302
9	82	78	16.6	0.236	0.0089	0.126	28.8	50	391
10	—	108	21.7	0.289	0.0064	0.111	——	120	373
12	61	95	23.8	0.370	0.0073	0.162	42.0	125	309
13	—	77	17.9	0.226	0.0090	0.122	——	125	305
28	81	88	20.4	0.232	0.0079	0.110	28.6	120	304
30	69	90	19.2	0.256	0.0077	0.118	37.1	100	317
31	71	117	15.6	0.215	0.0059	0.076	30.3	135	325
33	80	90	14.7	0.240	0.0077	0.111	30.0	112	265
48	94	97	17.2	0.240	0.0071	0.103	25.6	120	356
50	86	110	27.6	0.234	0.0063	0.089	27.2	130	487
51	88	112	18.3	0.192	0.0062	0.071	21.8	140	329
Average	79	95	19.6	0.262	0.0075	0.118	31.8	116	330

(excluding study ix for averages of the CO^2 data)

Table I continued

$E^{SA}_{CO^2}$ (t_{max}) $\mu C/gC$	$b(t_{max})$ $\mu C/gC$	$\%CO_2^G$ $\%CO_2$ *via glucose*	*Oxidation of Glucose to* CO_2		CO_2 *Turnover*		CO_2 *Pool Size* P_{CO_2}
			G_{CO_2} *mg/min*	$G^w_{CO_2}$ *g/kg/h*	λ_2 *1/min*	T_{CO_2} *g/kg/h*	*g/kg*
0.168	0.397	42.3	89.2	0.085	0.0065	0.294	0.758
0.153	0.538	28.7	88.0	0.054	0.0135	0.268	0.332
0.060	0.096	63.3	168.9	0.144	0.0380	0.333	1.460
0.107	0.528	19.8	50.4	0.040	0.0030	0.296	0.448
0.152	0.400	38.2	80.5	0.075	0.0083	0.288	0.581
0.150	0.450	34.0	70.8	0.054	0.0070	0.232	0.554
0.165	0.478	34.5	71.6	0.049	0.0090	0.207	0.383
0.165	0.604	27.3	59.1	0.047	0.0129	0.254	0.329
0.189	0.720	26.2	58.2	0.048	0.0092	0.268	0.486
0.250	0.716	34.9	63.1	0.062	0.0105	0.260	0.413
0.188	0.614	30.6	75.0	0.063	0.0096	0.302	0.524
0.090	0.401	22.4	74.5	0.038	0.0092	0.249	0.451
0.248	0.576	43.1	96.8	0.060	0.0082	0.204	0.414
0.169	0.535	31.8	73.1	0.056	0.0089	0.260	0.473

TABLE IIa

DIABETIC PATIENTS WITHOUT PITUITARY IRRADIATION AND OFF HYPOGLYCEMIC AGENTS

Study Number (different subjects)	*Bs (FBS) mg %*	$t_{\frac{1}{2}}$ *min*	*Glucose Pool Size*		*Glucose Turnover*		*Glucose Volume*	t_{max} *min*	$\left\langle \frac{d[CO^2]}{dt} \right\rangle$ *mg/min*
			P_G *g*	P_G^w *g/kg*	λ_1 *1/min*	T_G *g/kg/h*	V_G^w *% B W*		
3 (J)*	550	610	88.4	1.610	0.0011	0.118	29.0	120	303
15 (J)	472	381	90.8	1.320	0.0018	0.144	27.9	110	288
32 (J)	—	350	83.3	1.350	0.0020	0.160	—	250	259
39 (A)	200	447	43.5	0.660	0.0016	0.061	33.0	225	254
40 (A)	84	129	16.2	0.248	0.0054	0.080	29.5	135	254
41 (J)	167	200	26.6	0.426	0.0035	0.089	25.5	210	193
44 (J)	371	225	78.1	1.130	0.0031	0.210	30.4	155	338
61 (A)	127	198	30.4	0.496	0.0035	0.104	34.1	220	226
64 (A)	153	210	35.2	0.484	0.0033	0.096	31.6	125	300
76 (A)	120	280	33.8	0.442	0.0025	0.066	36.8	200	229
Average	249	303	52.6	0.817	0.0028	0.113	30.9	175	255

*Letters in parenthesis: (A) means adult-type diabetes, (J) means juvenile-type diabetes.

Table IIa continued

$E^{SA_2}_{CO^2}$ (t_{max}) $\mu C/gC$	$b(t_{max})$ $\mu C/gC$	$\%CO_2^G$ $\%CO_2$ *via glucose*	*Oxidation of Glucose to* CO_2		*CO_2 Turnover*		*CO_2 Pool Size* P_{CO_2}
			G_{CO_2} *mg/min*	$G^w_{CO_2}$ *g/kg/h*	λ_2 *1/min*	T_{CO_2} *g/kg/h*	*g/kg*
0.250	0.246	10.2	20.4	0.022	0.0280	0.336	0.200
0.183	2.250	8.1	16.0	0.014	0.0260	0.252	0.162
0.060	0.183	32.9	58.1	0.056	0.0071	0.419	0.989
0.126	0.406	31.0	53.8	0.049	0.0097	0.232	0.398
0.312	0.786	39.7	68.8	0.064	0.0099	0.236	0.395
0.148	0.452	32.7	43.1	0.041	0.0063	0.183	0.488
0.032	0.200	16.0	36.9	0.032	0.0116	0.293	0.419
0.145	0.381	38.1	49.1	0.048	0.0058	0.185	0.532
0.119	0.470	25.3	51.8	0.043	0.0159	0.249	0.216
0.167	0.450	37.1	57.9	0.046	0.0088	0.180	0.341
0.154	0.582	27.1	45.6	0.042	0.0129	0.257	0.414

TABLE IIb

DIABETIC PATIENTS ON INSULIN

Study Number (different subjects)	*Bs (FBS) mg %*	$t_{\frac{1}{2}}$ *min*	*Glucose Pool Size*		*Glucose Turnover*		*Glucose Volume*	$t_{max.}$ *min*	$\left\langle \frac{d[CO_2]}{dt} \right\rangle$ *mg/min*
			P_G *g*	P_G^w *g/kg*	λ_1 *1/min*	T_G *g/kg/h*	V_G^w *% B W*		
3	80	34	12.7	0.230	0.0099	0.281	29	70	405
15	98	71	15.4	0.224	0.0098	0.131	22	105	361
32		360	52.6	0.852	0.0019	0.099		170	280
34		164	34.0	0.398	0.0042	0.101		175	283
39	200	425	43.5	0.660	0.0016	0.064	33	190	252
41	109	325	31.2	0.501	0.0021	0.064	46	235	233
44	191	420	62.1	0.898	0.0017	0.089	47	320	320
Averages	135	257	35.9	0.538	0.0045	0.118	35	181	305

Table IIb continued

$E_{CO^2}^{SA}$ (t_{max}) $\mu C/gC$	$b(t_{max})$ $\mu C/gC$	$\%CO_2^G$ *%CO_2 via glucose*	*Oxidation of Glucose to CO_2*		*CO_2 Turnover*		*CO_2 Pool Size P_{CO_2}*
			G_{CO_2} *mg/min*	$G^w_{CO_2}$ *g/kg/h*	λ_2 *1/min*	T_{CO_2} *g/kg/h*	*g/kg*
0.185	0.475	39.0	109.5	0.120	0.0096	0.449	0.366
0.170	0.575	29.6	73.0	0.064	0.0089	0.316	0.589
0.131	0.344	38.1	72.8	0.07	0.0133	0.454	0.569
0.156	0.352	44.3	85.6	0.060	0.0074	0.199	0.446
0.109	0.421	25.9	44.5	0.041	0.0123	0.230	0.313
0.140	0.485	28.9	46.0	0.044	0.0075	0.223	0.492
0.074	0.237	31.2	68.2	0.059	0.0053	0.277	0.871
0.138	0.413	33.9	71.4	.066	0.0092	.307	0.521

TABLE III

DIABETIC PATIENTS AFTER PITUITARY IRRADIATION

Study Number (different subjects)	*Bs (FBS) mg %*	$t_{\frac{1}{2}}$ *min*	*Glucose Pool Size*		*Glucose Turnover*		*Glucose Volume*	t_{max} *min*	$\left\langle \frac{d[CO_2]}{dt} \right\rangle$ *mg/min*
			P_G *g*	P_G^w *g/kg*	λ_1 *1/min*	T_G *g/k/h*	V_G^w *%B W*		
34	255	209	83.3	0.976	0.0033	0.194	38.3	190	320
62 (40)*	127	195	34.4	0.528	0.0036	0.113	41.6	170	254
63	132	90	44.4	0.519	0.0077	0.240	39.0	165	324
69	127	240	59.9	0.771	0.0029	0.134	60.7	260	289
71 (40)	80	75	19.5	0.304	0.0092	0.168	38.0	160	132
78	78	151	33.8	0.332	0.0046	0.091	42.7	240	196
Average	133	160	45.9	0.571	0.0052	0.157	43.4	198	252
DIABETIC AFTER PITUITARY IRRADIATION ON CHLORPROPAMIDE									
63	120	129	23.1	0.270	0.0054	0.0087	22.3	170	295

*Figures in parentheses indicate corresponding pre-irradiation studies (see table IIa)

Table III continued

$E^{SA}_{CO^2}$ (t_{max}) $\mu C/gC$	$b(t_{max})$ $\mu C/gC$	$\%CO_2^G$ $\%CO_2$ via glucose	Oxidation of Glucose to CO_2		CO_2 Turnover		CO_2 Pool Size P_{CO_2} g/kg
			G_{CO_2} mg/min	$G^w_{CO_2}$ g/kg/h	λ_2 1/min	T_{CO_2} g/kg/h	
0.046	0.160	28.9	63.1	0.044	0.0079	0.225	0.478
0.188	0.399	47.1	81.7	0.076	0.0091	0.236	0.432
0.103	0.158	65.2	144.2	0.101	0.0047	0.227	0.805
0.097	0.198	48.9	96.5	0.074	0.0051	0.221	0.729
0.388	0.392	99.0	89.2	0.084	0.0030	0.124	0.689
0.206	0.259	79.5	106.4	0.062	0.0042	0.114	0.456
0.171	0.278	61.4	96.9	0.073	.0057	0.191	0.598
DIABETIC AFTER PITUITARY IRRADIATION ON CHLORPROPAMIDE							
0.143	0.438	32.7	66.0	0.046	0.0066	0.206	0.520

TABLE IV

ACROMEGALIC PATIENTS WITHOUT PITUITARY IRRADIATION

Study Number (different subjects)	*Bs (FBS) mg %*	$t_{\frac{1}{2}}$ *min*	*Glucose Pool Size*		*Glucose Turnover*		*Glucose Volume*	t_{max} *min*	$\left\langle \frac{d[CO_2]}{dt} \right\rangle$ *mg/min*
			P_G *g*	P_G^w *g/kg*	λ_1 *1/min*	T_G *g/kg/h*	V_G^w *% B W*		
8	108	117	52.1	0.527	0.0059	0.187	48.8	180	321
35*	92	133	38.4	0.443	0.0052	0.138	48.2	155	292
38	96	165	28.6	0.370	0.0042	0.093	38.2	165	224
45	76	98	26.2	0.311	0.0071	0.132	40.9	115	409
47	87	110	28.4	0.388	0.0063	0.147	44.6	150	418
49	95	134	25.0	0.260	0.0052	0.081	27.4	180	432
52	91	101	24.5	0.359	0.0069	0.148	39.5	115	397
55	95	118	18.4	0.324	0.0059	0.114	34.1	145	302
74	72	81	18.0	0.247	0.0086	0.127	34.3	140	199
75	99	118	34.7	0.402	0.0059	0.142	46.5	145	278
79	89.8	128	30.9	0.395	0.0054	0.128	44.0	170	238
Average	91	118	29.6	0.366	0.0060	0.131	40.6	151	319

*This study actually performed eight months after pituitary irradiation

Table IV continued

$E_{CO^2}^{SA}$ (t_{max}) $\mu C/gC$	$b(t_{max})$ $\mu C/gC$	$\%CO_2^G$ $\%CO_2$ *via glucose*	*Oxidation of Glucose to* CO_2		CO_2 *Turnover*		CO_2 *Pool Size* P_{CO_2}
			G_{CO_2} *mg/min*	$G^w_{CO_2}$ *g/kg/h*	λ_2 *1/min*	T_{CO_2} *g/kg/h*	*g/kg*
0.065	0.162	39.4	87.0	0.0528	.0055	0.196	0.602
0.104	0.290	35.9	71.5	0.049	.0078	0.202	0.431
0.134	0.437	30.6	46.9	0.0364	.0084	0.174	0.346
0.122	0.424	28.8	80.4	0.057	.0105	0.290	0.460
0.108	0.346	31.1	88.7	0.073	.0072	0.344	0.796
0.098	0.391	25.0	73.7	0.046	.0059	0.270	0.763
0.146	0.468	31.2	84.6	0.074	.0108	0.347	0.536
0.156	0.574	27.2	56.1	0.0593	.0079	0.319	0.673
0.249	0.042	16.9	23.0	0.0189	.0058	0.163	0.467
0.149	0.306	48.7	92.4	0.0642	.0080	0.193	0.405
0.257	0.309	83.2	135.2	0.1040	.0059	0.183	0.519
0.144	0.341	36.2	76.3	0.0577	.0076	0.244	0.545

TABLE V

ACROMEGALIC PATIENTS AFTER PITUITARY IRRADIATION

Study Number (different subjects)	*Bs (FBS) mg %*	$t_{\frac{1}{2}}$ *min*	*Glucose Pool Size*		*Glucose Turnover*		*Glucose Volume*	t_{max} *min*	$\left\langle \frac{d[CO_2]}{dt} \right\rangle$ *mg/min*
			P_G *g*	P_G^w *g/kg*	λ_1 *1/min*	T_G *g/kg/h*	V_G^w *% B W*		
16 (8)*	142	185	35.1	0.363	0.0037	0.082	25.5	185	325
45 (45)	77	104	24.0	0.261	0.0067	0.104	33.8	100	438
65 (35)	79	84	28.1	0.359	0.0083	0.178	45.4	120	376
68 (49)	87	108	30.5	0.305	0.0064	0.117	35.1	185	384
Average	96	120	29.4	0.322	0.0063	0.120	35.0	148	381

Table V continued

$E_{CO^2}^{SA}$ (t_{max}) *μC/gC*	$b(t_{max})$ *μC/gC*	$\%CO_2^G$ *%CO_2 via glucose*	*Oxidation of Glucose to CO_2*		*CO_2 Turnover*		*CO_2 Pool Size P_{CO_2}*
			G_{CO_2} *mg/min*	$G_{CO_2}^w$ *g/kg/h*	λ_2 *1/min*	T_{CO_2} *g/kg/h*	*g/kg*
0.057	0.356	16.2	35.8	0.022	0.0073	0.202	0.464
0.139	0.537	25.8	77.1	0.050	0.0143	0.278	0.324
0.112	0.308	36.4	93.4	0.071	0.0083	0.287	0.574
0.080	0.253	31.6	82.8	0.050	0.0046	0.232	0.841
0.097	0.364	27.5	72.3	0.048	0.0086	0.250	0.551

*Figures in parentheses indicate corresponding pre-irradiation studies (see table IV).

The radiobiological half life, $t_{\frac{1}{2}}$, of the glucose pool in diabetic subjects was strikingly different from normal in almost all instances. The normal range [77, 117] minutes, was relatively narrow with a mean of 95′. In sharp contrast, the juvenile diabetic patients without insulin therapy had $t_{\frac{1}{2}}$ values in the range [200, 610]. All individuals having $t_{\frac{1}{2}}$ values below the normal range were again juvenile diabetics but this time had received insulin and eaten breakfast. Only one diabetic patient (63) had a $t_{\frac{1}{2}}$ in the normal range but he had not only taken his usual dose of chlopropamide up to and including the morning of the test, but also had received pituitary irradiation 18 months prior to the test. However, when off medication for three days his $t_{\frac{1}{2}}$ was elevated above normal. Another adult diabetic subject (studies 40, 62, and 71, Fig. 1) had a slightly abnormal glucose tolerance test, a strikingly abnormal cortisone-modified glucose tolerance test and was well controlled on diet alone. She had a nearly normal $t_{\frac{1}{2}}$ before pituitary irradiation, but, 2½ years after irradiation her $t_{\frac{1}{2}}$ became definitely abnormal, rising from 129′ to 195′. At the time of this second study she was recovering from an episode of thrombophlebitis. Nine months later her thrombophlebitis had cleared and her $t_{\frac{1}{2}}$ value had returned to normal. Two other adult diabetic patients and one juvenile diabetic patient (69, 78, 34, respectively) had post pituitary irradiation studies, all with prolonged $t_{\frac{1}{2}}$ values.

The acromegalic patients tended to have normal or slightly elevated $t_{\frac{1}{2}}$ values. One (45) stayed essentially unchanged nine months after pituitary irradiation, one (8) developed a prolongation of his $t_{\frac{1}{2}}$ six months after irradiation, and two (35, 49), who had elevated $t_{\frac{1}{2}}$'s experienced a drop to normal in 3 7/12 and 1 1/12 years, respectively.

(R-2) P_G: glucose pool size in grams of glucose.

Eleven of our 13 normal subjects had P_G values in the range [14.5, 22.0] with the range for the whole group being [14.5, 28] and average 19.6. When insulin was withheld, all juvenile diabetic patients, except one (41), had markedly elevated glucose pool sizes, the highest being four times normal. These same patients on insulin had low to low normal glucose pool sizes. One adult diabetic patient (40) before irradiation and again 3¼ years after irradiation (71) and another adult diabetic patient (63) 1½ years after irradiation had normal glucose pool sizes. All other adult diabetic studies demonstrated elevated glucose pool sizes.

Acromegalic individuals had P_G values which ranged from high normal to definitely high values. Among the four acromegalic patients who had pre and post pituitary irradiation studies (see studies 8, 35, 45, 49 of Table IV and studies 16, 65, 45, 68 of Table V, respectively) two experienced a drop in their glucose pool size from high to normal ((8, 16) and (35, 65)), another remained unchanged in the normal range (45, 45), while the fourth had a rise in P_G from a normal value to a high value (49, 68).

(R-3) P_G^W: glucose pool size in g glucose/kg body weight.

This paralleled the glucose pool size in grams rather closely. The normal range was [0.19, 0.37].

(R-4) λ_1: fraction of the glucose pool which turns over each minute.

The normal group had λ_1 values in the interval [0.0059, 0.0090]. Only one diabetic subject (63) (with or without diabetic medication, before or after pitui-

tary irradiation) had a λ_1 value inside this range. Only juvenile diabetic patients who had received insulin the morning of the test were above 0.0090/min. The remainder were below 0.0059.

Acromegalic subjects had λ_1 values in the low to low normal range. The two, (35, 49), who had studies performed over one year following pituitary irradiation improved to normal.

(R-5) T_G: glucose turnover in g/kg/h:

For normal subjects, the range was [0.071, 0.168]; but, 10 out of 13 were in the much narrower interval [0.071, 0.126] with an average of 0.118 for the whole group. T_G values for juvenile diabetic patients without insulin replacement were almost always in the normal range indicating that their low fractional turnover per minute and their high glucose pool size resulted in a normal glucose turnover in terms of grams glucose leaving or entering the glucose pool per hour per kilogram of body weight. The one adult diabetic patient who had pre and post pituitary irradiation studies (40, 62, 71) had low, mid normal, and borderline high T_G values, in that order.

All acromegalic patients except two (8, 35) had normal glucose turnover rates. One of these had a high turnover rate before irradiation but a normal one 6 months later (8). The other had a normal T_G eight months after irradiation but a high turnover rate 3 7/12 years later, when he had evidence of mild hypopituitarism.

(R-6) V_G^W: Glucose pool's volume in per cent body weight.

V_G^W for normal individuals was in the range [21, 42]. This range also includes the V_G^W values for almost all other individuals studied. The acromegalic subjects, however, tended to have high normal V_G^W values whereas the diabetic patients tended toward low normal V_G^W values.

(R-7) t_{max}: the time in minutes required for the expired breath to reach maximum specific activity.

[95, 140] was the normal range. For diabetic patients, t_{max} tended to be above normal. All post pituitary irradiation studies on diabetic subjects were associated with elevated t_{max} values.

Acromegalic patients tended to behave as the diabetic patients with regard to t_{max} but with less divergence from normal. Pituitary irradiation was followed by a shortening of t_{max} in the two acromegalic patients whose post pituitary irradiation studies were performed 4 1/4 and 1 1/12 years following pituitary irradiation (35, 49). The patients studied six and nine months following irradiation experienced no change in t_{max} (8, 45).

(R-8) λ_2: fraction of the bicarbonate pool which enters and leaves that pool per minute.

Normal subjects had λ_2 values in [0.0030, 0.0135]. The only diabetic subjects outside this range were two nonirradiated juvenile diabetics (3, 15) and one adult diabetic (64) all of whom had elevated λ_2 values. The one diabetic patient (40) who had studies performed before and after pituitary irradiation had essentially no change in λ_2.

All acromegaly patients had λ_2 values in the normal range both before and after pituitary irradiation. However, two acromegalic subjects (8, 45) had an

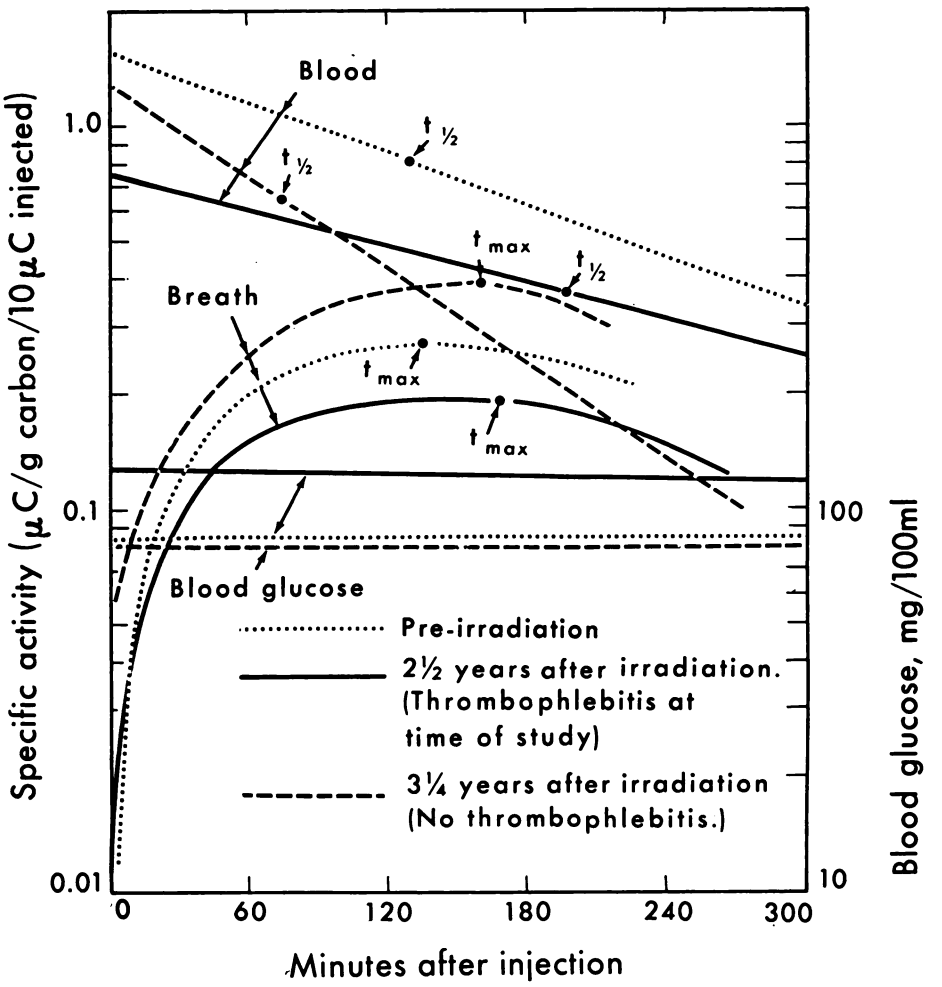

Fig. 1. Graphs of data obtained in three successive studies on a patient with adult type diabetes mellitus. These are studies numbered 40 t(pre-irradiation), 62 (2½ years post irradiation) and 71 (3¼ years post irradiation).

increase in λ_2 following pituitary irradiation, whereas, of the other two, one remained unchanged (35), and one had a decrease in λ_2 (49).

(R-9) $\left\langle \frac{d\,[CO_2]}{dt} \right\rangle$: mean mg CO_2 entering and leaving the bicarbonate pool each minute.

Normal values, with one exception, were in [265, 391]. Six out of ten diabetic subjects had values below 265. However, 8 out of 10 diabetic patients had studies resulting in $\left\langle \frac{d\,[CO_2]}{dt} \right\rangle \leq 300$ (Table IIa) whereas this was true for only 2 out of 13 normal subjects (Table I). Pituitary irradiation did not significantly alter $\left\langle \frac{d\,[CO_2]}{dt} \right\rangle$ in the acromegalic group. The lower value in study 71 on an adult diabetic patient is probably not valid.

(R-10) $E^{SA}_{CO_2}(t_{max})$: the experimental specific activity of expired CO_2 at t_{max}.

8 out of 13 studies on normal subjects resulted in values in the interval [0.150, 0.190]. If these values are taken as normal, then 10 out of 17 studies on non-irradiated diabetic patients produced values below normal and all but 3 acromegalic patients (55, 74, 79) either before or after pituitary irradiation, had values below normal. However, to include all normal subjects the range must be taken to be [0.060, 0.250] and this range includes nearly all the $E^{SA}_{CO_2}(t_{max})$ values. Still, one untreated juvenile diabetic patient off of insulin, (44) had a value below 0.060.

(R-11) $b(t_{max})$: the theoretical specific activity at t_{max}, of the bicarbonate pool.

$b(t_{max})$ had a wide spread for normal individuals, its range being [0.096, 0.720]. This range included all but one patient, an adult diabetic (40) who, following pituitary irradiation, reverted to a normal value. However, Table I shows that 12 of the 13 normal studies produced $b(t_{max}) \geq 390$ whereas from Table IIa it can be seen that 4 out of 5 untreated juvenile diabetic patients off of insulin had $b(t_{max}) < 0.390$. The one irradiated juvenile diabetic patient (34) had $b(t_{max}) < 0.390$ for both his "on insulin" and "off insulin" studies.

The acromegalic patients were split almost equally by $b(t_{max}) = 0.390$. Five studies resulted in values above and six studies resulted in values below 0.390. Pituitary irradiation had mixed effects on $b(t_{max})$ relative to this value. Among the four acromegalic patients who had both pre and post pituitary irradiation studies, two of the three (8, 35) with $b(t_{max}) < 0.390$ remained unchanged while the other (49) dropped 0.138 units. The one with $b(t_{max}) \geq 0.390$ (45) had a rise in $b(t_{max})$ by 0.113 units.

(R-12) $\%CO_2^G$: $\%CO_2$ derived from glucose.

If [20, 43] is taken as the normal range, then almost all studies resulted in normal $\%CO_2^G$ values. The ones digressing most significantly from this range were untreated juvenile diabetic patients off of insulin. They had low values. Pituitary irradiation had no significant effect on the value of $\%CO_2^G$ for the one adult diabetic patient (40) or for three of the acromegalic patients with sequential studies. The remaining acromegalic patients in this group had a drop in $\%CO_2^G$ to below normal.

(R-13) G_{CO_2}: The mg of glucose oxidized to CO_2 per minute.

Normal values, with one exception, were found to lie in the interval [50, 97] with a mean of 73.1. This range includes most other G_{CO_2} values. However, four out of five unirradiated juvenile diabetic patients had values below 50 when off of insulin, but when on insulin their G_{CO_2} values were higher and ranged from low normal to above normal. The one juvenile diabetic subject (34) who had a post-pituitary irradiation study had both "on insulin" and "off insulin" G_{CO_2} values in the normal range. One adult diabetic subject (40) developed a low G_{CO_2} 2 1/2 years after pituitary irradiation at which time she was convalescing from an episode of thrombophlebitis (62). Nine out of 13 normal individuals had $G_{CO_2} \geq 70$ whereas all 10 unirradiated diabetic subjects had $G_{CO_2} < 70$.

Almost all acromegalic patients had normal G_{CO_2} values before irradiation. In fact, 8 out of 11 pre-irradiation studies resulted in $G_{CO_2} \geq 70$. An acromegalic

patient with frank diabetes before irradiation (8) had a normal pre-irradiation G_{CO_2}, but, 6 months after irradiation, his G_{CO_2} had fallen to below normal values. Another acromegalic patient (35) who had diabetes (requiring 80 units of insulin) before irradiation but who, at the time of his first C^{14} glucose study, eight months after irradiation, was controlled on diet alone, had normal G_{CO_2} values for both his eighth month and 4 1/4 year post pituitary irradiation studies.

(R-14) $G^{W}_{CO_2}$: Oxidation of glucose to CO_2 in g/kg/h.

The results here were much like those for G_{CO_2}, the normal range being [0.038, 0.085] with average 0.056.

(R-15) T_{CO_2}: CO_2 turnover in g/kg/h.

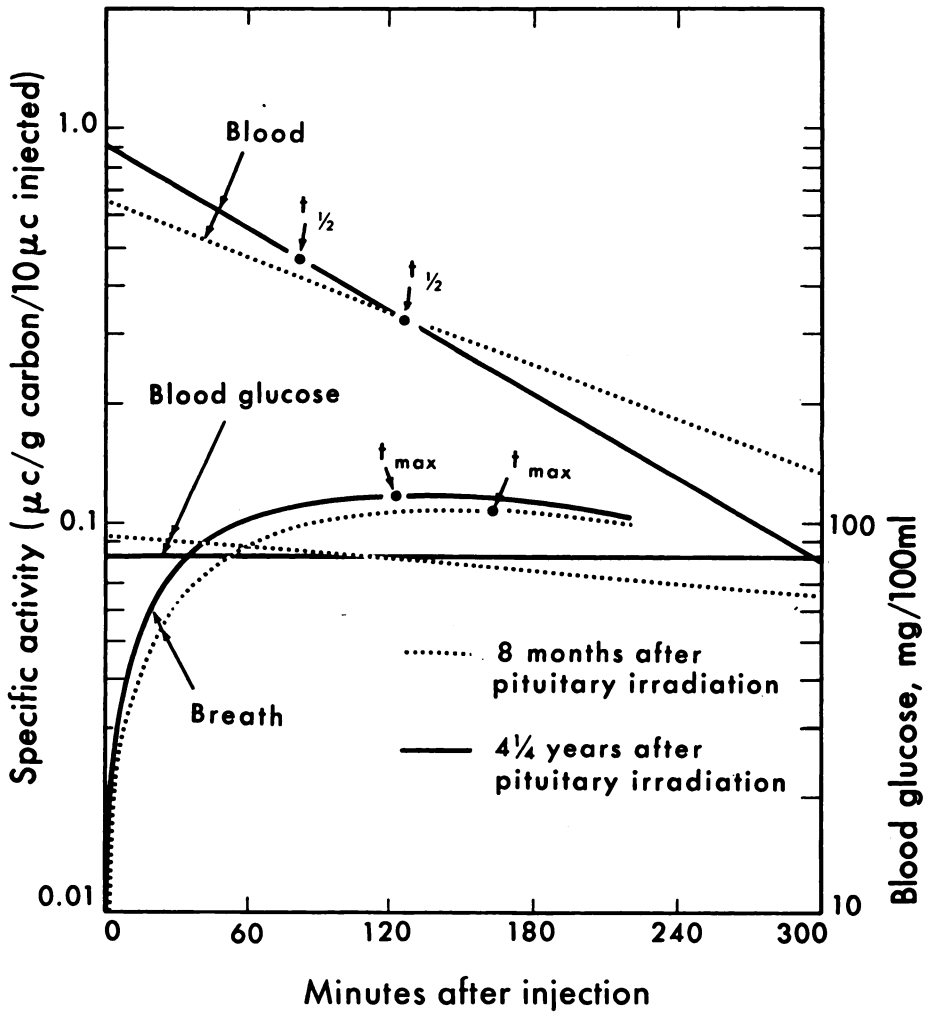

Fig. 2. Graphs of data obtained in two successive studies on an acromegalic patient. The first study, number 35, was performed 8 months after pituitary irradiation. The second study, number 65, was performed 4¼ years after therapy.

TABLE VI

DIABETIC PATIENTS, CLINICAL DATA

Study Number		*Age yrs*	*Wgt kg*	*Sex*	*Type of diabetes*	*Duration of diabetes years*	*Diet*		*Daily medication*	*Results of C^{14} glucose study*		*Years after pituitary irradiation*
Pre Pit irrad	*Post Pit irrad*						*cal*	*gm CHO*		*Off hypoglycemic agents*	*On hypoglycemic agents*	
3	—	57	55.0	♂	surgical pancreatectomy	1/6	—	—	insulin	abnormal	abnormal	0
15	—	48	68.6	♂	juvenile	21	1600	155	insulin	abnormal	abnormal	0
32	—	25	61.8	♀	juvenile	13	1200	—	insulin	abnormal	abnormal	0
39	—	35	65.9	♀	adult	13	1300	90	tolbutamide	abnormal	abnormal	0
40	see 62, 71 below	61	65.0	♀	adult	9/12	1200	100	none	abnormal		0
41	—	26	61.5	♀	juvenile	15	1800	—	insulin	abnormal	abnormal	0
44	—	40	69.1	♂	juvenile	21	2400	200	insulin	abnormal		0
61	—	47	61.3	♀	adult	14	1400	140	none	abnormal		0
64	—	55	72.7	♂	adult	10/12	1800	180	tolbutamide	abnormal		0
76	—	65	76.4	♂	adult	5 10/12	2100	114	tolbutamide	abnormal		0
—	34	37	85.0	♂	juvenile	23	2200	180	insulin	abnormal	abnormal	6/12
see 40 above	62	63	65.0	♀	adult	3 3/12	1200	100	none	abnormal		2 6/12

Table VI continued

—	63	50	85.0	♂	adult	11	1600	130	chlorpropamide	abnormal	abnormal	1 6/12
—	69	56	77.7	♂	adult	24	2000	150	none	abnormal		1
see 40 above	71	64	65.0	♀	adult	4	1000	100	none	abnormal		3 3/12
—	78	63	101.8	♂	adult	5	1200	92	none	abnormal		3 10/12

TABLE VII

ACROMEGALIC PATIENTS

Study Number		*Oral glucose tolerance test*	*Disease status*	*Yrs. after heavy particle irrad*	*C_{14} gluc study*
Pre-Pit irrad	*Post Pit-irrad*				
8	see 16 below	abnormal	active	received x-ray Rx to pituitary 4 years previously	abnormal
35	see 65 below	abnormal	active	8/12	abnormal
38		normal	questionable activity	0	abnormal
45	see 45 below	normal	active	0	normal
47		normal	active	0	normal
49	see 68 below	abnormal	active	0	abnormal
52		normal	questionable activity	1/12	normal

Table VII continued

Study Number		*Oral glucose tolerance test*	*Disease status*	*Yrs. after heavy particle irrad*	*C_{14} gluc study*
Pre-Pit irrad	*Post Pit-irrad*				
55		abnormal	active	0	normal
74		normal (flat)	active	3 months after surgical partial hypophysectomy	normal
75		abnormal	active	0	abnormal
79		abnormal	active	0	abnormal
see 8 above	16	abnormal	active	6/12	abnormal
see 45 above	45	abnormal	active	9/12	normal
see 35 above	65	abnormal (improved)	active	4 3/12	normal
see 49 above	68	abnormal	active	1 1/12	abnormal

The interval which includes T_{CO_2} values for all normal subjects is [0.204, 0.333]. However, 9 out of 13 studies on normal subjects resulted in T_{CO_2} values lying approximately in the interval [0.250, 0.300]. Only 3 out of 10 studies on diabetic subjects had T_{CO_2} values in this interval (Table IIa). The highest values of T_{CO_2} were obtained from diabetic patients on insulin (Table IIb). Pituitary irradiation resulted in a decrease in T_{CO_2} in the adult diabetic patient with sequential studies (40, 62, 71).

The acromegalic patients had T_{CO_2} values in the range [163, 347]. Pituitary irradiation resulted in no significant change in three cases (8, 45, 49) and a rise from below normal to normal values in one case (35).

(R-16) P_{CO_2}: The CO_2 pool in gCO_2/kg of body weight.

The normal range for P_{CO_2} was taken to be [0.329, 0.581]. Two untreated juvenile diabetic patients (3, 15) off of insulin had $P_{CO_2} < 0.329$ as did one adult diabetic (64). Pituitary irradiation resulted in a rise in this parameter in the one adult diabetic subject studied before (40) and after (62, 71) pituitary irradiation. Two other adult diabetics (63, 69), who were studied only after pituitary irradiation, also had high P_{CO_2} values.

Four acromegalic patients (8, 47, 49, 55) had high P_{CO_2} values before irradiation. Two of these (8, 49) had post irradiation studied (16, 68) and of these one (49, 68) had no significant change in T_{CO_2} while the other had a return to normal values (8, 16).

The one patient with Cushing's syndrome secondary to adrenal carcinoma had a normal glucose-C^{14} study, although two oral glucose tolerance tests were slightly abnormal. This patient had moderately elevated urinary 17-hydroxycorticosteroids and very high urinary 17 ketosteroids.

DISCUSSION

The parameters presented in the results will be divided into two classes. The first class will consist of those parameters whose values for the diabetic subjects differ from normal. The second class will consist of those parameters which show no significant difference in any of the groups of subjects studied.

The most distinctive members of the first class are $t_{\frac{1}{2}}$, P_G, P_G^W λ_1, and t_{max}. But also, since $E_{CO_2}^{SA}(t_{max})$, $b(t_{max})$, G_{CO_2}, and $\left\langle \frac{d\,[CO_2]}{dt} \right\rangle$ are of help in diagnosing abnormalities in glucose kinetics, they belong to this class. However, T_G, V_G^W, λ_2, $\%CO_2^G$, T_{CO_2}, and P_G are of no assistance in this regard, and, thus, do not belong to this class. Nonetheless, the fact that these latter quantities are normal, except in the severest diabetics after fasting, deserves some comment later.

Using the "diagnostic type" parameters, individuals with adult or juvenile diabetes mellitus can be distinguished from normal individuals in that when off therapy the diabetic patients have a prolonged $t_{\frac{1}{2}}$, an increased P_G and P_G^W, a diminished fractional turnover rate for the glucose pool, λ_1, and a delayed t_{max}. They also frequently have a low $E_{CO_2}^{SA}(t_{max})$, a low $b(t_{max})$, a low G_{CO_2} and a low $\left\langle \frac{d\,[CO_2]}{dt} \right\rangle$. All diabetic patients studied had an abnormal outcome to this test, abnormality being defined as having two or more of these parameters outside their normal range.

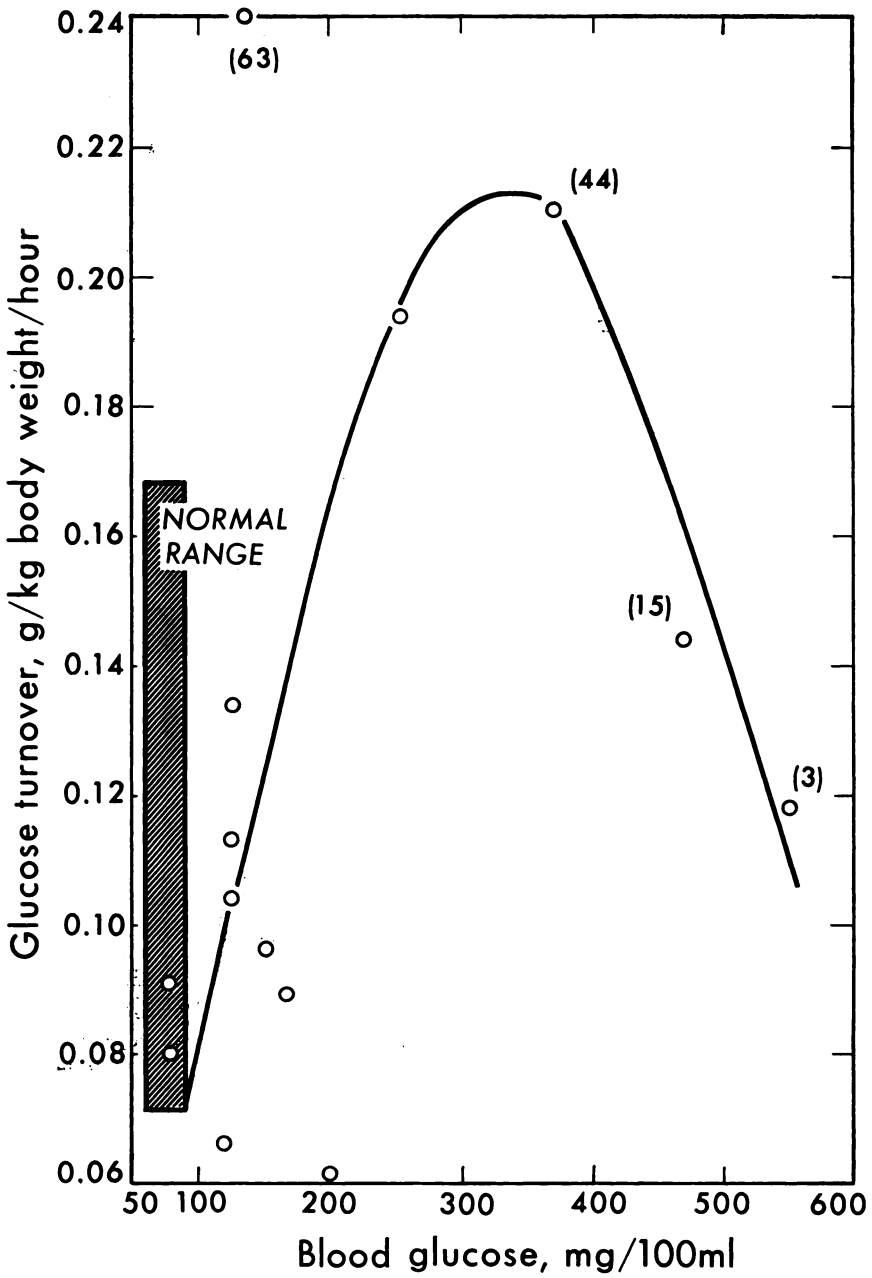

Fig. 3. A graph of T_G, the glucose turnover rate, versus B_g, the blood glucose concentration.

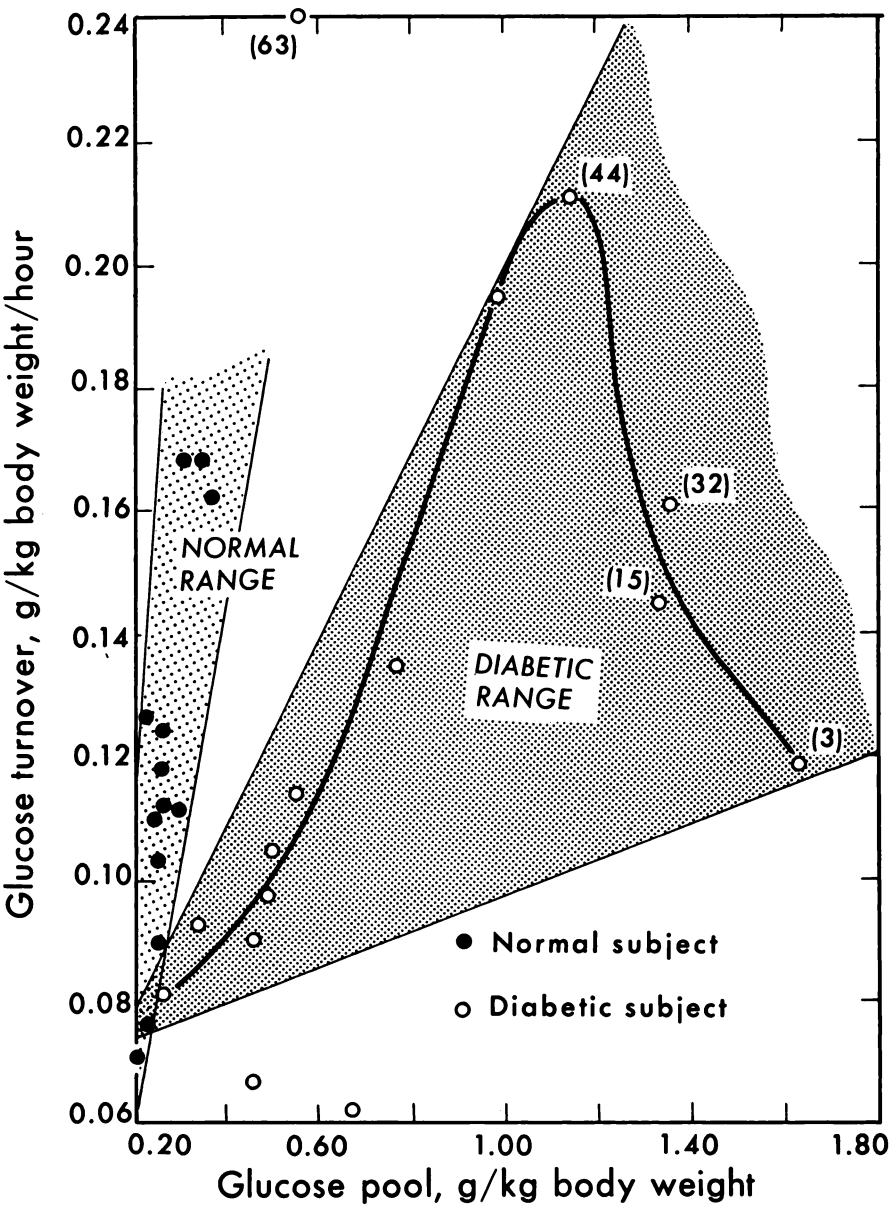

Fig. 4. A graph of T_G, glucose turnover rate, versus P_G^W, the glucose pool size.

The lowered λ_1 values in these diabetic patients were accompanied by elevated P_G^W values so that the glucose turnover rates, T_G ($T_G = \lambda_1 \cdot P_G^W \cdot 60$) were almost always in the normal range (see (R-5)). However, there was a general increase in T_G with increasing values of B_s or P_G^W over a limited range (see Figs. 3 and 4). This phenomenon is discussed by Soskin and Levine[11] who describe a linear relationship between fasting blood sugar concentration, B_s, in the range [100, 500] mg per cent, and dextrose utilization, T_G, in eviscerated dogs. For $B_s \geq 500$ mg per cent they display a nearly constant value for T_G. Although the present data are consistent with a linear relationship between T_G and B_s for a range B_s in [70,370], they do not support the constancy of T_G for larger values of B_s. In fact, there was a sharp decrease in T_G for values of $B_s \geq 370$ (Fig. 3). A plot of T_G vs P_G^W was even more revealing (Fig. 4). Again there was a general increase in T_G with P_G^W for diabetic subjects but this increase appeared to be non-linear. Normal subjects also had a general increase in T_G with P_G^W, the exact relationship being obscure. Furthermore, for the diabetic subjects, T_G reached a maximum (for P_G^W in the interval [1.000, 1.200]) and thereafter declined. These findings suggest that, directly or indirectly, glucose at high levels inhibits pathways envolved in its production or utilization.

Reichard *et al* (10) found T_G values to be decreased in "mild diabetes mellitus" whereas Shreeve *et al* (12) reported slightly elevated T_G values for such patients. The results (R-5) (Table IIa) in the present report lend support to those of Reichard *et al* in that T_G for adult type diabetic subjects prior to pituitary irradiation were in general in the low normal range. The one subject in this group who had postpituitary irradiation studies performed had an elevation of this parameter to a borderline high level. The cause for this rise in T_G is unknown. One may conjecture, on the basis of known growth hormone effects, that it was due to an increase in insulin sensitivity resulting from diminution in growth hormone (13).

The general decrease in oxidation of glucose to CO_2 in the diabetic subjects in spite of approximately normal values of T_G indicates that although glucose utilization is near normal, less of it is being converted to CO_2 by the "immediate oxidative pathway". This means that in diabetic individuals a larger portion of the glucose utilized is going by way of pathways other than the "immediate oxidative pathway", which probably consists of the hexose monophosphate pathway and the Embden-Meyerhof-Tricarboxylic acid pathway. One would thus expect a greater rate of appearance of C^{14} in fats and amino acids (14, 15).

The tendency toward a decreased expiratory specific activity, $E^{SA}_{CO_2}(t_{max})$ in the diabetic patients is consistent with the delay in reaching t_{max}. If G_{CO_2}, the oxidation of glucose to CO_2, is normal or less than normal, then the total amount of $C^{14}O_2$ expired in time t_{max} is normal or less than normal; hence, the area under the expiratory $C^{14}O_2$ curve must be normal or less than normal. Under these conditions a delay in t_{max} implies a lower $E^{SA}_{CO_2}(t_{max})$. The data in Table IIa or, in condensed form, Table IX support this statement.

Generally, diabetic subjects without therapy had lower $\left\langle \frac{d\,[CO_2]}{dt} \right\rangle$ values

than normal. Surprisingly, a depancreatized patient (3) and a brittle juvenile diabetic patient (15) had normal $\left\langle \frac{d\,[CO_2]}{dt} \right\rangle$ values. This will be discussed later. The cause for the lower CO_2 expiration rate in the remainder of the diabetics is unknown. It may, however, be hypothecated that it is due to a decrease in CO_2 production from glucose and/or an increase in CO_2 assimilation (*e.g.* CO_2 assimilation in fatty acid synthesis via acetyl coenzyme A).

Distinguishing acromegalic individuals from normal subjects on the basis of this glucose kinetic study was considerably more difficult than in the case of patients with diabetes mellitus. Although the changes in the two disorders were similar, they were less marked in the acromegalic subjects unless overt diabetes was present. Table VII shows that prior to pituitary irradiation all but two (38, 55) abnormal C^{14}-glucose studies were associated with abnormal oral glucose tolerance tests (using the criteria of Fajans and Conn[16]). In study (38) the glucose C^{14} test was abnormal whereas the glucose tolerance test was normal. This patient had questionable activity of her disease as measured by clinical and biochemical methods (which included a normal plasma level of growth hormone as assayed by C. H. Li). Study (55) on the other hand resulted in an abnormal glucose tolerance test and a normal C^{14} glucose kinetic study. Ikkos *et al* (17) found no correlation between decreased intravenous glucose tolerance and activity of acromegaly. As seen from Table VII the C^{14}-glucose studies as well as the oral glucose tolerance tests performed in the present study also did not correlate satisfactorily with activity of the disease.

This method of evaluating glucose metabolism, thus, appears to have diagnostic merit. It must, however, be emphasized that until a more precise method of measuring these parameters becomes available, each laboratory will have to determine its own set of standards for normal subjects. The values reported for these parameters by various investigators are listed in Table VIII. Although this method is simple to perform, it gives valid results only if the system remains in a steady state. In the fifty-two studies reported here the blood glucose levels during the test remained fairly constant except in seven cases. Furthermore, no perturbance such as insulin injection or appreciable glucose injection was made during the studies. The postpituitary irradiation studies were performed on individuals who may have had a new "steady-state" due to modified homeostatic control but no changes were induced during the test itself.

The parameters which are of little, if any, help in distinguishing normal, diabetic, and acromegalic individuals are T_G, V_G^W, λ_2, $\%CO_2^G$, T_{CO_2}, and P_{CO_2}. T_G was discussed earlier. V_G^W, the glucose space per kg body weight has been thought to correspond well with the extracellular fluid volume (1, 11). Hence, it is not surprising that all individuals had comparable values for this parameter. The remainder of these parameters refer to the bicarbonate compartment.

Since most patients were in a good nutritional state prior to the initiation of the test, the CO_2 compartments in most cases were normal. However, the overnight fast as well as abstinence from their daily dose of insulin, were sufficient to modify the bicarbonate compartments of two of the juvenile diabetic patients

TABLE VIII

Normal Subjects / *Investigators*	$t_{\frac{1}{2}}$ *min*	*Glucose Turnover* λ_1 *fraction/min*	T_G *g/kg/h*	P_G *g*	P_G^w *g/kg*	V_G *liters*	V_G^w *% B W*	$t_{max.}$ *min*	*Bicarbonate Turnover* λ_2 *fraction/min*	T_{CO_2} *g/kg/h*
Baker et al.[3]		0.0069	0.062		0.15		17		0.0086	0.27
Shreeve et al.[12]		0.0069	0.085		0.21		24		0.0084	0.27
Hlad et al.[18]							23.3			
Hlad et al.[19]							22.6			
Elrick et al.[20]							21.3			
Reichard et al.[10]		0.0064	0.120		0.31		30	120		
*Segal et al.[21] U–C^{14} 1–C^{14} 2–C^{14} 6–C^{14}								 100 127 107 145		
Pollycove[22]		0.0080	0.130		0.28		33		0.0090	0.27
Present study	95	0.0075	0.118	19.6	0.262		31.8	116	0.0089	0.26
Diabetes Mellitus Hlad et al.[19]							19.0			
Reichard et al.[10]		0.0058	0.109		0.51		29			

Table VIII continued

Shreeve et al.[12]										
Stable D.M.†		0.0019	0.10		0.87		26		0.0094	0.36
Labile D.M.		0.0030	0.19		1.08		30		0.0107	0.24
Present study	303	0.0028	0.113	52.6	0.817		30.9	175	0.0129	0.26
Acromegaly										
Present study	118	0.0060	0.131	29.6	0.366		40.6	151	0.0076	0.24
Hypophysectomized Subjects										
Ikkos et al.[13]		0.0107		16.3		17.6				

Normal Subjects *Investigators*	P_{CO_2} *g/kg*	$\left\langle \frac{d\,[CO_2]}{dt} \right\rangle$ *mg/min*	$E^{SA}_{CO_2}\ (t_{max})$ *μC/gC*	$b\ (t_{max})$ *μC/gC*	$G^{w}_{CO_2}$ *g/k/h*	$\%CO_2^G\ (t_m)$
Baker et al.[3]	0.54				0.038	20
Shreeve et al.[12]	0.53				0.055	
Hlad et al.[18]						
Hlad et al.[19]						
Elrick et al.[20]						25
Reichard et al.[10]						

*Figures taken from graphs presented in article.

†D.M. means Diabetes Mellitus.

Table VIII continued

Normal Subjects *Investigators*	P_{CO_2} *g/kg*	$\left\langle \frac{d\,[CO_2]}{dt} \right\rangle$ *mg/min*	$E^{SA}_{CO_2}\ (t_{max})$ $\mu C/gC$	$b\ (t_{max})$ $\mu C/gC$	$G^{w}_{CO_2}$ *g/k/h*	$\%CO^{G}_{2}\ (t_m)$
*Segal et al.[21] U–C^{14} 1–C^{14} 2–C^{14} 6–C^{14}						
Pollycove[22]	0.51				0.052	28
Present study	0.47	330	0.169	0.535	0.056	31.8
Diabetes Mellitus Hlad et al.[19]						
Reichard et al.[10]						22
Shreeve et al.[12] Stable D.M.† Labile D.M.	 0.72 0.40				 0.059 0.031	
Present study	0.41	255	.154	.582	0.042	27.1
Acromegaly Present study	0.55	319	0.144	0.341	0.058	36.2
Hypophysectomized Subjects Ikkos et al.[13]						

*Figures taken from graphs presented in article. †D.M. means Diabetes Mellitus.

TABLE IX

STUDIES HAVING PROLONGED t_{max} AND NORMAL OR LOW G_{CO_2}

Study	(34)		(32)			(41)		(39)		(44)		(61)
INSULIN	off	on	off		on	off	on	off	on	off	on	—
$E^{SA}_{CO_2}(t_{max})$	↓	n	↓	↓	−n	n	n	n	n	↓	↓	n

STUDIES HAVING NORMAL t_{max} AND NORMAL OR LOW G_{CO_2}

Study	(3)	(15)		(64)	(40)
INSULIN	off	off	on	—	—
$E^{SA}_{CO_2}(t_{max})$	↑ −n	n	n	n	↑

(3, 15). They experienced a lowering of their bicarbonate pool size probably due to metabolic acidosis resulting from poor diabetic control. In spite of this lowered bicarbonate pool they were able to maintain a normal output of CO_2, *i.e.*, $\left\langle \frac{d\,[CO_2]}{dt} \right\rangle$, by elevating their fractional turnover rates λ_2. These two patients also had markedly diminished $_{\%}CO_2^G$ values indicating, again, that much of their CO_2 was coming from nonglucose sources.

The effect of pituitary suppression on the diabetic state in acromegaly as measured by this method can best be exemplified by studies (35, 65) (Fig. 2) on the acromegalic patient who received a relatively large dose of α-particle radiation to the pituitary gland and who had the longest period, 4 1/4 years, between his irradiation and his kinetic study. Prior to irradiation this patient had frank diabetes and eight months after therapy he still had an abnormal kinetic study (35). However, approximately four years after therapy his kinetic study was normal (65).

Pituitary irradiation, however, did not produce such a clear effect on the adult diabetic patient studied before (40) and three years after a comparable dose of radiation (71) (Fig. 1). Both tests (40) and (71), were nearly normal but since each had two abnormal "diagnostic parameters", both were classified as abnormal. Nonetheless, there was a major distinction between the two tests. The first study revealed low T_G and λ_1 values whereas these parameters were elevated in the second study. This effect on T_G and λ_1 parallels the effect of pituitary irradiation on the acromegalic patient discussed in the last paragraph.

SUMMARY

The results obtained by using the single injection tracer method of Baker *et al.*, as modified by Tolbert *et al*, for the study of glucose kinetics in humans are presented for normal subjects, diabetic patients, and acromegalic patients. The latter two categories contain individuals who had studies performed pre and/or post heavy-particle irradiation to the pituitary gland. The results indicate similar deviations from normal for both the diabetic and the acromegalic patients. These deviations are more marked in diabetes mellitus than in uncomplicated acromegaly and consist of prolongation of the radiobiological half-life of glucose C^{14}, diminution of the fractional turnover rate of glucose, enlargement of the glucose pool size, and lowering of the oxidation rate of glucose to CO_2.

The deviations in acromegaly can be reversed by heavy particle pituitary irradiation. However, the effect of pituitary irradiation on the C^{14} glucose kinetic pattern of adult diabetic subjects seems to be an elevation in glucose turnover without significant improvement in the diabetic state. Further studies are required on irradiated diabetic and acromegalic subjects before more definite statements can be made.

The rise in glucose turnover which accompanies the rise in blood glucose appears to be limited, a decline in turnover being observed for blood glucose values above 370 mg/100 ml.

Further support for the model of Baker *et al* was obtained through the agreement of the theoretically predicted t_{max} and the actually observed t_{max} for the CO_2 specific activity curves.

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