and ^{42}K the measurement of samples containing both of these isotopes is comparatively easy (Tait and Williams 1952). The use of ^{22}Na also represents a considerable financial saving compared with ^{24}Na, because the frequent shipments and high wastage due to radioactive decay are avoided.

The main advantage of the present method lies in the fact that complete collection of all excreta is unnecessary, and the possibility of loss of sodium in sweat does not have to be considered. The method thus lends itself particularly well to environmental studies. Measurements on healthy volunteers are greatly facilitated; clinical studies can now be made in the antenatal and outpatient clinics instead of in the metabolic ward, and the patient is not subjected to inconvenience or to emotional stress. The whole-body counting-apparatus is a relatively inexpensive attachment to the now widely available radioactivity-measuring equipment and can be varied considerably to meet different requirements. Thus it is relatively simple to adapt the apparatus for measurements on bed patients. Apart from electrolyte studies, the technique is generally applicable to any problem where the absorption or retention of a gamma-emiting radioactive isotope in the body is of interest.

Radiation Dosage

The 2·6-year half-life of ^{22}Na gives rise to some misgivings about the radiation dosage received by the subject. However, the effective half-life in the body is determined by the excretion-rate and is about 2 weeks. There is no evidence of any permanent retention. The currently accepted figure for the maximal permissible radiation dose-rate for continuous exposure is 0·3r per week (International Commission on Radiological Protection 1954), and the maximal permissible body-burden of ^{22}Na corresponding to this dose-rate can be calculated (Mayneord and Sinclair 1953). For a person weighing 70 kg. this amounts to about 50 μC. In the present studies it has not been found necessary to exceed this figure at any time, and measurements were usually made at about half this activity level. It therefore appears that, so far as radiation dosage is concerned, observations could be continued on the same person indefinitely.

A. H. James (personal communication) has pointed out, however, that the possibility of the incorporation of appreciable amounts of ^{22}Na in the "non-exchangeable" bone-sodium in cases where mineralisation of bone tissue is occurring has not been excluded. The use of this isotope in late pregnancy with a viable fœtus, or in growing children, is thought to be inadvisable until the results of further experimental studies are known.

Summary

The fraction of a tracer dose of a gamma-emitting isotope which remains in the body after a given time can be measured by a simple Geiger-Müller counter system.

Using ^{22}Na this technique permits direct measurement of the biological decay-rate and serial measurements of total exchangeable sodium. The biological half-life for healthy people is about 11 days. The standard error of a single measurement of total exchangeable sodium is ±3%.

About 10% of the total exchangeable sodium takes several days for complete equilibration; uncertainties due to this and to calibration errors caused by changes in shape or size of the subject can be reduced by suitably fractionating the administered tracer dose.

Body-sodium measurements may be continued indefinitely on the same person without exceeding the permissible maximum of radiation dosage figure of 0·3r a week.

The technique is simple and enables studies to be made on hospital outpatients. The whole-body counting-technique is applicable in a wide variety of other clinical investigations.

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LOW-FAT DIET AND THERAPEUTIC DOSES OF INSULIN IN DIABETES MELLITUS

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THERE is no indication that healthy people taking a diet rich in carbohydrates are especially liable to diabetes; in fact numerous observations show improvement of carbohydrate tolerance following its greater intake. The Staub-Traugott effect is a classical example of this in acute experiments. As a long-term effect diabetes mellitus is not especially common among the huge and mainly carbohydrate-eating populations of the world—e.g., the Chinese—except the rich and the sedentary among them who partake of large quantities of fat as well and encourage obesity by overeating.

Although it is theoretically possible that in such circumstances the islets of Langerhans can be exhausted, there is no experimental proof that this happens. Allan (1923) showed that the relationship between the carbohydrate ingested and the insulin necessary to metabolise it was approximately logarithmic; hence the strain on the insulin mechanism is relatively small. Moreover it is impossible to improve to any great extent nervous hypoglycæmia by treatment for months with a diet containing a very large quantity of carbohydrates.

Even diabetics tolerate a high-carbohydrate diet.

Strouse and Soskin (1932) found that increased intake of carbohydrate from 72 to 290 g. in isocaloric diets of diabetics did not increase the demand on insulin, and the glycosuric effect remained more or less the same.

Jackson and Kenefick (1942) recorded similar findings in diabetic children.

Rabinowitch (1949) claimed that inclusion of 20–80 g. of sucrose in a diabetic diet definitely reduced the insulin requirements.

Soffer and Gabrilove (1951) cite a man, aged 65, who had diabetes for fifteen years and took 50–60 teaspoonfuls of sucrose in various forms in addition to his normal diet throughout his illness without deteriorating further in any way, his insulin requirements remaining constant at 40 units of protamine-zinc insulin daily. This diabetic never had

ketosis or pyogenic infections despite glycosuria equivalent to 50–60 g. of glucose.

Ellis (1934), who treated some cases of severe diabetes with 600 g. of glucose daily in lieu of restricted diet and on identical doses of insulin, found that, instead of deteriorating in any way, some of the patients showed increased carbohydrate tolerance. In one case this effect was striking: after 21 days' treatment the insulin requirements were reduced from 192 units to 9 units daily.

Fat, however, depresses the insulin mechanism. Himsworth (1934, 1935) confirmed the findings of earlier workers that a high-carbohydrate diet increases sugar tolerance whereas a high-fat diet decreases it, and showed that the result was solely due to the increased amount of carbohydrates in the diet. Each unit of insulin in these circumstances metabolises a greater amount of glucose (see above).

Since these findings the tendency has been to abandon high-fat low-carbohydrate diets in the treatment of diabetes and to give a diet containing a normal or a smaller than normal amount of fat, a normal amount of carbohydrate, and a normal amount of protein with adequate insulin. The findings described here suggest that, if fat is reduced still further to the minimum, insulin begins to exert its curative effect, most patients can be stabilised progressively on diet alone, and some patients are to all intents and purposes cured. Apparently, when a diet very low in fat is given, the diabetogenic stimulus is minimised, and insulin in adequate amounts can then cure diabetes, as has been shown experimentally by Haist et al. (1940) and Lukens and Dohan (1942).

Methods

Selection of Patients

All the cases were of insulin-sensitive diabetes. Of the 80 patients 6 were female and 74 male; and 17 were 5–23 lb. overweight for their age, height, body-frame, and sex, the remaining 63 being from normal to 45 lb. underweight. Except 1 child aged 13 and 2 men aged 66–80, the patients were aged 26–58. Ketonuria was found in 14 and glycosuria alone in 66. 23 apparently had no symptoms, and of the remaining 57 patients 2 were picked up semicomatose and 55 complained of symptoms ranging from weakness to all the classical symptoms of diabetes mellitus. None of them had any septic complications.

Apart from the initial glucose-tolerance test on each patient it was impossible to estimate the blood-sugar level frequently, because of the cost. Accordingly only patients with an approximately normal renal threshold were selected for treatment to enable day-to-day observations to be made on the urine. Where the fasting blood-sugar level was higher than 190 mg. per 100 ml. and the normality of renal threshold could not initially be decided, results of single blood-sugar estimations and of urine examinations done two hours after a meal at intervals while the diabetic state was coming under progressive control with treatment helped to determine whether the renal threshold was normal or not. The results of the initial glucose-tolerance tests are given in table I to give an idea of the types of cases treated.

Diet

The patients without ketosis were allowed unrestricted high-carbohydrate diet without insulin for the week before the initial glucose-tolerance test. Subsequently they were put on a diet of required caloric value for them for treatment purposes. This diet contained 20–30 g. of fat and 120–150 g. of protein, and the rest of the caloric requirement was made up by carbohydrates excluding free sugar. The caloric value was based on energy requirements and calculated for a shift of the body-weight towards 5–10 lb. below normal at the rate of 2–3 lb. increase in the underweight and a similar decrease in the overweight per month. Apart from the patients who were grossly underweight and received as much as 4000–4500 calories a day, the caloric value of the diet in the remaining cases was 1600–2200 calories. Subsequently, with improvement in the diabetic process, however, many patients started losing weight on their original diets, and the caloric value had to be increased accordingly. There were three main meals: breakfast, luncheon, and dinner, of about $^2/_8$, $^3/_8$, and $^3/_8$ of the total caloric value and given at 8 A.M., 1 P.M., and 8 P.M. respectively. Minor variations for bed tea, afternoon tea, and a bedtime drink were allowed for convenience and satisfaction of patients.

TABLE I—RESULTS OF INITIAL GLUCOSE-TOLERANCE TESTS

Case no.	Blood-sugar (mg. per 100 ml.)					
	Fasting	After 50 g. of glucose				
		½ hr.	1 hr.	1½ hr.	2 hr.	2½ hr.
1	266	296	333	400	366	..
2	192	201	258	333	289	..
3	108	228	263	202	138	..
4	222	296	333	320	307	..
5	117	216	230	142	133	..
6	100	238	254	153	111	..
7	275	339	363	322	285	..
8	324	400	476	392	380	..
9	212	234	276	300	284	..
10	614	666	676	644	634	..
11	216	245	312	298	250	..
12	192	250	312	306	288	..
13	363	373	416	408	370	..
14	190	250	296	322	307	..
15	228	245	312	285	253	..
16	126	222	258	266	250	..
17	180	278	307	279	232	..
18	439	454	570	400	328	..
19	184	275	294	294	250	..
20	276	362	400	384	362	..
21	220	380	430	440	330	..
22	173	272	312	254	182	..
23	470	533	579	579	500	..
24	266	307	363	333	285	..
25	151	166	216	210	198	..
26	285	230	339	320	289	..
27	187	200	261	296	314	..
28	199	234	266	292	250	..
29	174	205	280	286	266	222
30	190	333	423	533	333	313
31	235	333	400	500	400	333
32	152	222	272	272	260	166
33	272	375	333	272	250	..
34	250	428	500	428	375	..
35	375	423	500	500	430	375
36	110	200	300	280	250	170
37	160	300	280	280	260	240
38	110	186	200	220	170	120
39	253	381	454	400	388	..
40	160	262	296	315	285	..
41	142	250	275	238	198	..
42	230	312	347	281	247	..
43	86	166	224	216	202	..
44	250	360	408	372	333	..
45	146	198	235	222	209	..
46	173	186	198	238	205	..
47	347	398	421	444	400	..
48	123	258	320	285	205	..
49	111	181	194	208	200	..
50	420	500	518	487	470	..
51	117	208	250	253	234	..
52	416	500	571	512	487	..
53	125	186	242	258	250	..
54	117	186	216	228	204	..
55	145	230	250	228	181	..
56	212	307	420	400	374	..
57	186	250	266	275	242	..
58	115	173	220	228	168	..
59	95	190	228	210	166	..
60	111	235	250	228	129	..
61	400	420	500	532	470	..
62	121	228	275	258	200	..
63	148	258	275	250	234	..
64	222	270	320	347	370	..
65	116	216	280	260	208	..
66	138	190	235	258	228	..
67	119	186	224	222	216	..
68	216	296	400	357	333	..
69	125	266	228	200	142	..
70	600	726	800	888	1000	..
71	125	242	266	285	296	..
72	96	204	235	275	228	..
73	150	230	325	280	240	..
74	172	184	240	242	222	..
75	97	186	228	218	166	..
76	87	161	258	242	155	..
77	114	163	213	205	164	..
78	128	232	222	222	166	..
79	435	..	..	..	..	..
80	520	..	..	..	..	..

Method of Administration and Dosage of Insulin

The patients who had been on diet for 7–10 days and still had glycosuria were put on relatively large doses of insulin calculated to leave a slight excess after counteracting the glycosuria completely. The initial dose of insulin was approximately determined by allowing a unit of insulin for each gramme of glucose excreted in the urine in twenty-four hours and adding 5–10 units of extra insulin to this amount. This dose counteracted the glycosuria in most cases except the severest, which needed somewhat higher doses.

Calculated in this way the initial dose of insulin was between 30 units in milder cases to 120 units in the severer ones, and was given as protamine-zinc insulin half an hour before breakfast. When the patient had been free from glycosuria for 48–72 hours the dose of insulin was reduced by 5–10 units till the patient was sugar-free again for the same length of time. This was repeated till either no insulin was required or the minimal dose of insulin had been reached. This procedure, which progressively increased carbohydrate tolerance, was applied to 10 patients, who became just sugar-free on diet alone. They received 20 units of protamine-zinc insulin initially to be reduced by 5 units every five days till none was to be given.

TABLE II—FINAL RESULTS OF TREATMENT IN 7 CASES

Case no.	—	Blood-sugar (mg. per 100 ml.)					
		Fasting	After 50 g. of glucose				
			½ hr.	1 hr.	1½ hr.	2 hr.	2½ hr.
1	Initial	266	296	333	400	366	..
	Final	90	172	156	115	92	..
24	Initial	266	307	363	333	285	..
	Final	90	126	160	97	96	..
44	Initial	250	360	408	372	333	..
	Final	90	148	160	153	142	100
79	Initial	435	Not done, patient had severe ketosis				
	After 9 weeks	168	177	204	209	190	157
	Final	103	180	165	146	113	..
80	Initial	520	Not done, patient had severe ketosis				
	After 9 weeks	114	172	212	208	180	..
	Final	88	170	177	167	101	76
48	Initial	123	258	320	285	205	..
	Final	108	206	258	210	129	..
68	Initial	216	296	400	357	333	..
	Final	128	210	190	175	150	..

There was never any danger of excessive dosage of insulin. The initial amounts given were only slightly above the doses which counteracted glycosuria completely. Reduction by 5–10 units at a time subsequently within a few days generally allowed some glycosuria after one or more meals before being controlled again. Hypoglycæmic reactions were further avoided by adequate spacing, in time and quantity, of meals. It will be noticed that the caloric values of luncheon and dinner were the same, and dinner was late. This helped to prevent trouble from nocturnal hypoglycæmia even when the initial dose of protamine-zinc insulin was 120 units.

Urine was tested for glycosuria before breakfast and two hours after breakfast, luncheon, and dinner every day. All the samples had to be sugar-free for 48–72 hours before the insulin dosage was reduced.

Results

Of the 80 patients 50 became sugar-free in 3–6 weeks and did not require any more insulin, and 14 (cases 8, 13, 21, 27, 31, 34, 39, 44, 47, 52, 56, 64, 68, and 73) showed slight irregular glycosuria on some days and not on others, which could be controlled adequately with

TABLE III—VARIATIONS IN GLUCOSE TOLERANCE ASSOCIATED WITH INTAKE OF FAT

Date	Blood-sugar (mg. per 100 ml.)					
	Fasting	After 50 g. of glucose				
		½ hr.	1 hr.	1½ hr.	2 hr.	2½ hr.
Oct. 10, 1949	520	Not done, patient had severe ketosis				
		After very low-fat diet				
Dec. 18, 1949	114	172	212	208	180	..
Feb. 9, 1950	100	140	180	160	150	90
March 9, 1950	110	165	190	150	125	80
April 10, 1950	112	175	180	170	150	100
June 17, 1950	96	140	165	140	95	80
July 7, 1950	86	115	145	120	80	85
Aug. 9, 1950	90	105	130	95	90	..
		After indiscretion with fats				
Sept. 9, 1951	160	380	280	250	200	..
		After reversion to very low-fat diet				
Sept. 29, 1951	115	220	260	240	160	112
Sept. 23, 1951	67	120	137	129	101	75
		With 50–60 g. of fat				
April 28, 1952	78	153	167	172	166	141
May 5, 1952	88	170	177	167	101	76

10 units of protamine-zinc insulin. Of these 14 patients 8 (cases 8, 13, 21, 34, 47, 52, 56, and 68) improved subsequently and did not require any insulin by 18 weeks, and the remaining 6 (cases 27, 31, 39, 44, 64, and 73) continued to show irregular glycosuria.

Case 31 agreed to undergo treatment with œstrogen therapy in spite of the risks and was given 25 mg. of stilbœstrol on alternate days for 3 weeks. He became considerably worse, and œstrogen had to be stopped. He was re-treated with diet and insulin for 4 weeks before he could be restored to the original state.

10 patients (cases 5, 6, 38, 43, 59, 60, 75, 76, 77, and 78) who became sugar-free on diet alone (see above) showed considerable increase of carbohydrate tolerance after 20 days' insulin treatment. They acquired an additional reserve of 150–400 calories.

The 6 patients with severe diabetes (cases 10, 18, 23, 50, 61, and 70) initially required 80–120 units of protamine-zinc insulin, but at the end of 6 weeks they could be controlled with 20–40 units. After 18 weeks' treatment they still required about the same or a smaller amount.

All these cases have been followed up on diet alone for from 6 months to 5 years. Because of the cost involved, as already pointed out, it was only possible to do serial glucose-tolerance tests subsequently in 7 patients (cases 1, 24, 44, 48, 68, 79, and 80). In 18–26 months 5 of them (cases 1, 24, 44, 79, and 80) have returned to well within normal and for all purposes are apparently cured. They now take fat more liberally, but it is limited to 50–60 g. daily. The remaining 2 patients (cases 48 and 68) have

TABLE IV—VARIATIONS IN GLUCOSE-TOLERANCE CURVES

Date	Blood-sugar (mg. per 100 ml.)					
	Fasting	After 50 g. of glucose				
		½ hr.	1 hr.	1½ hr.	2 hr.	2½ hr.
Oct. 10, 1952	435	Not done, patient had severe ketosis				
Dec. 23, 1952	140	Not done, patient had myocardial infarction				
Jan. 8, 1953	167	Ditto				
Feb. 27, 1953	168	177	204	209	190	157
April 17, 1953	110	149	164	188	167	160
May 15, 1953	134	168	195	187	162	111
July 7, 1953	130	184	185	151	106	..
Sept. 12, 1953	123	189	174	146	90	..
Oct. 3, 1953	110	202	165	155	109	..
Nov. 18, 1953	121	184	167	123	106	..
Dec. 12, 1953	123	189	169	129	97	..
Feb. 6, 1954	126	172	207	172	138	92
April 17, 1954	121	186	166	135	77	..
May 15, 1954	116	184	174	148	102	..
July 9, 1954	111	192	173	153	119	..
Aug. 6, 1954	103	180	165	146	113	

glucose-tolerance curves suggesting very mild diabetes. The results obtained in these 7 cases are summarised in table II.

In addition there is an interesting 8th case, a woman now aged 37, whose initial records have been lost. In December, 1950, she required initially 20 units of protamine-zinc insulin. After 8 weeks' treatment she required none. After nearly 4 years of continuous low-fat diet she has turned up with hypoglycæmic symptoms and a glucose-tolerance curve of fasting 59, 1/2 hr. 71, 1 hr. 90, 1 1/2 hr. 110, 2 hr. 88, and 2 1/2 hr. 70 mg. per 100 ml.

The results in these 8 cases are significant. In the last case with hypoglycæmic symptoms it appears that the diabetic tendency has been lost. There is evidence from records of case 80 (table III) that, unless the low-fat diet is kept up for a long time, the diabetic tendency reappears; but it can be recontrolled.

The glucose-tolerance curves undergo the following changes of improvement: (1) lowered fasting sugar, (2) reduced hyperglycæmia with delayed fall, (3) moderate hyperglycæmic reactions, and (4) within normal curves. These changes may be more or less progressive (table III) or may show slight variations from time to time (table IV).

With the return of glucose tolerance to normal in the long run there was a concomitant fall in blood-cholesterol level.

With improvements in symptoms, the glycosuric condition, and general health in a short space of 3–6 weeks, most patients did not mind the comparatively slight inconvenience of adjusting themselves to the low-fat diet and were fully coöperative.

Summary

80 patients with insulin-sensitive diabetes were treated with low-fat optimal caloric diets containing 20–30 g. of fat, 120–150 g. of protein, and the rest carbohydrate and progressively diminishing therapeutic doses of insulin.

50 of them became sugar-free in 3–6 weeks, and 8 in 18 weeks, and did not need any more insulin. 6 needed 10 units of insulin daily, and in 6 cases the original requirement of 80–120 units was reduced to 20–40 units.

7 cases were checked with serial glucose-tolerance tests for 18–26 months. 5 of them showed return to normal, and 2 to almost normal. Another case in which hypoglycæmia developed, is described.

10 patients who had become sugar-free on diet alone showed increased carbohydrate tolerance.

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". . . The most obvious characteristic of present-day standards is their tentative and uncertain nature, and the degree of variation observable within quite small groups in the population. The 'official' mores to which the individual might turn for guidance are far from clear in relation to such matters as marriage, divorce, sex relations, and parenthood, and the various sources of authority differ greatly among themselves. . . . The modern individual finds himself in a painful dilemma. On the one hand he feels himself to be under no very rational compulsion to obey any one set of rules or observe any particular customs. On the other hand he is not convinced that these rules and customs have no validity and, especially if he finds himself in trouble, is likely to feel at least some guilt for having infringed them. He is at once unwilling to accept external rules and unhappy over the consequences of accepting responsibility for his own decisions."—Social Casework in Marital Problems. FAMILY DISCUSSION BUREAU. London: Tavistock Publications. 1955; p. 164

MYLERAN IN CHRONIC MYELOID LEUKÆMIA

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'Myleran' (1 : 4-dimethanesulphonyloxybutane)

$$\begin{matrix} CH_3SO_2O \\ CH_3SO_2O \end{matrix}\!\!\rangle (CH_2)_4$$

(Haddow and Timmis 1953) is an effective palliative in chronic myeloid leukæmia (Galton 1953a and b, Bollag 1953, Hansen 1954, Turesson 1953, Wilkinson 1953, Petrakis et al. 1954). In its ability to relieve symptoms, to reduce the size of spleen and liver, and to improve the blood picture, particularly the hæmoglobin level, it compares well with radiotherapy, and has the advantages of ease of administration and freedom from side-effects. Myleran is ineffective in acute leukæmias and in chronic myeloid leukæmia in myeloblastic relapse. Previous reports have described short-term observations. We now record the effects of repeated courses of myleran and of maintenance therapy in chronic myeloid leukæmia.

Clinical Material

The trial was started in September, 1950. 31 patients, including the 19 already reported (Galton 1953a), had begun treatment by March, 1954. Table I and fig. 1 show the types of myleran therapy used in new patients and in those previously treated by X rays, urethane, nitrogen mustard, or ^{32}P.

TABLE I—METHODS OF ADMINISTRATION OF MYLERAN IN 31 PATIENTS WITH CHRONIC MYELOID LEUKÆMIA

—	Courses of myleran only	Maintenance therapy after one or more courses	Maintenanc therapy only	Total
Myleran only	5 (1*)	2 (1*)	5	12
Previous X rays, ^{32}P or drugs other than myleran	9 (4*)	4 (2*)	6	19
Total	14	6	11	31

* More than 1 course.

Dosage

Administration is by tablets of 2 mg. and 0·5 mg. In August, 1951, we gave up the "short intensive" courses of treatment in which 100–150 mg. was given in 1–6 days, because severe bone-marrow depression, fatal in 1 case, occurred in 3 patients. The standard dose for adults has since been 0·06 mg. per kg. of body-weight daily (about 4 mg.). An initial loading dose of 20 mg. was used a few times (fig. 4) but was found unnecessary. The first 20 patients received one or more courses of myleran. 8 died within a year of the only course, 7 having received "short intensive" therapy. 11 patients received 1–3 subsequent courses (0·06 mg. per kg. of body-weight daily); maintenance therapy (0·5–4·0 mg. daily) was eventually given to 6 of them. In 11 other patients maintenance therapy was given immediately after an initial period on standard dosage.

Interrupted Therapy

Treatment was stopped when the clinical and hæmatological improvement seemed to justify it, or when the leucocyte-count was thought to be falling too steeply,