

THE VITAMIN B COMPLEX AND FASTING
BLOOD-SUGAR LEVELS.

An investigation into the changes in fasting blood-sugar levels of diabetic and non-diabetic patients following the intravenous injection of aneurin, riboflavin and nicotinamide. With a review of relevant literature, and a note on diabetic neuritis.

C. M. Wylie, M.B., Ch.B.

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Note. The writer's own investigations are underlined.

INTRODUCTION

The use of the long-acting insulins now enable most diabetics to live comfortably on one injection daily. The desire has not lessened, however, for an oral preparation which could obviate the troublesome injections. Attempts to produce an insulin preparation which could be absorbed from the bowel have been unsuccessful and seem almost hopeless. Attention has therefore been directed to other drugs which might have a beneficial effect.

Because aneurin, riboflavin and nicotinamide are essential for carbohydrate metabolism, numerous investigations were carried out on these vitamins. Results were so conflicting that it was not until recently that the position gradually became clearer. Since opinions are still not unanimous, however, it seemed that further investigations would not be without value.

The fasting blood-sugar level of each individual is stated to be remarkably constant (Lichtwitz). Diabetics, as one would expect, show a greater variation. It is obviously necessary, however, when investigating the blood-sugar changes produced by injections of vitamins, that control investigations should also be carried out simultaneously on subjects who have not been given these injections.

For reasons of convenience, a modified Folin and Wu's procedure was used to estimate the blood-sugar levels. This method gives results which are ten to thirty mg.% higher than the true figures, due to the presence in the filtrate of reducing substances such as thioneine and glutathione. The difference between this and the true figure is sufficiently constant to make the readings quite satisfactory for showing changes in the blood-sugar levels.

Oxalated and fluorized venous blood was used. Although this usually contains five mg.% less glucose than arterial blood, it shows the same changes in blood-sugar levels as the arterial blood.

The sugar estimations were usually carried out about six hours after taking the blood specimens. Since the glucose level of correctly fluorized blood remains constant for seven days (Van der Walle and Noeridin) no change could have occurred in this short period.

The method used was as follows: 0.1 ml. of oxalated and fluorized blood was added to 3.5 ml. distilled water. 0.2 ml. each of 10% sodium tungstate and of $2/3$ N. sulphuric acid was added. These accurately neutralised each other to form tungstic acid which precipitated the blood proteins. The mixture was filtered after standing for ten minutes.

Two ml. of the filtrate and 2 ml. of the alkaline copper solution in a Folin and Wu's tube were placed in a boiling water bath for six minutes. The copper sulphate was reduced to cuprous oxide in amounts proportional to the concentration of glucose. The addition of 2 ml. of the sodium phosphomolybdate solution dissolved the cuprous oxide to produce an intensely blue molybdenum salt.

The colour developed was not rigidly proportional to the blood-sugar concentration when the difference between the concentrations was very marked. Two standard solutions were therefore prepared to ensure accurate results, one with 100 mg. glucose per cent, and one with twice that amount. These were used to produce the standard blue solutions which were compared in the colorimeter with the unknown solutions.

One has noticed in some previous papers on similar investigations, that some of the biochemical results seemed to be remarkably inaccurate. Let us take one of these papers as an example (Kodicek).

In the second paragraph of the experimental section, the writer states: "The fasting levels of blood-sugar of normals and diabetics without any treatment do not change appreciably during such a short experimental period."

Table 1 of that article gives figures for the changes in the blood-sugar levels in diabetics after the intravenous

injection of 2 mg. of aneurin.

The fasting sugar of Patient 1 dropped from 318 to 218 mg.% in one hour.

That of Patient 5 dropped from 163 to 83 mg.% in one hour, and was 200 mg.% an hour later.

The blood-sugar of patient 6 rose by 67 mg.% in 30 minutes.

Patient 8's sugar level dropped from 144 to 75 mg.% in thirty minutes.

The fasting sugar of Patient 13 rose by 157 mg.% in one hour.

That of Patient 18 rose from 106 at 30 minutes to 245 mg.% at 60 minutes.

Kodicek's statistical analysis of that table shows that aneurin does not affect the fasting blood-sugar values of diabetics. One must presume that the writer was satisfied with a considerable degree of inaccuracy from the biochemists, as such relatively enormous changes could not really occur in diabetics in the absence of any cause.

The present investigator therefore decided to carry out the biochemical work himself. Whenever a difference of more than ten mg.% was found between two consecutive specimens, the estimations were repeated to verify this change.

On numerous occasions during the course of the investigation, the blood-sugar estimation was repeated five times

on the same blood specimen to determine the accuracy of the investigator's technique. Table I shows ten typical sets of readings.

TABLE I

	Blood-Sugar Values Obtained On Same Blood Specimens. Mg.%					Mean	Standard Deviation
1	76	86	77	83	79	80	4.2
2	121	132	130	110	112	121	10.0
3	335	355	345	363	359	351	11.4
4	232	243	253	263	246	247	11.6
5	144	138	141	148	139	142	4.1
6	82	78	76.5	87.5	73	79	5.6
7	108	128	114	128	122	120	8.9
8	68	63	58	68	61	64	5.0
9	86	86	85	85	88	86	1.2
10	234	239	217	233	230	231	8.3
Average Standard Deviation							7.0

The standard deviation of these readings seemed to be a suitable way of comparing them with those in the following tables. It was noticeable that the standard deviation increased considerably as the blood-sugar levels reached diabetic figures. It is evident from this table that an average standard deviation of 7.0 can be obtained with

blood-sugar levels which are quite constant.

To determine how much of the error of estimation was due to inaccuracies in reading the colorimeter, the readings on various occasions were repeated five times on the same blue solution, the colorimeter scale being moved after each reading. Table II shows that this error becomes important with high sugar levels.

TABLE III

	Figures to Indicate Error in Reading Colorimeter.					Mean.	Standard Deviation.
1	240	236	232	234	235	235	3.0
2	208	200	200	202	204	203	3.3
3	208	212	204	210	209	209	3.0
4	180	182	180	182	183	181	1.4
5	235	232	230	236	231	233	2.6
6	210	208	210	220	216	213	5.0
7	61	61	62	62	62	62	0.7
8	102	101	102	101	103	102	0.9
9	88	86	89	88	87	88	1.2
10	96	98	97	99	97	97	1.2
Average Standard Deviation							2.2

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- Van der Walle and Noeridin, 1933. \emptyset Geneeskund. Tijdschr. Nederland., Indie 73, 380.

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- Cameron, A.T. and White, T.D. 1946. Practical Biochemistry.
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\emptyset . Not consulted in the original.

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THE CONTROL INVESTIGATIONS.

THE CONTROL INVESTIGATIONS

In the investigation about to be described, the following procedure was used: The patient had been fasting for approximately fifteen hours. The first blood sample was taken, and the intravenous injection of the vitamin preparation immediately given. Further blood samples were removed after thirty minutes, one hour, two and three hours.

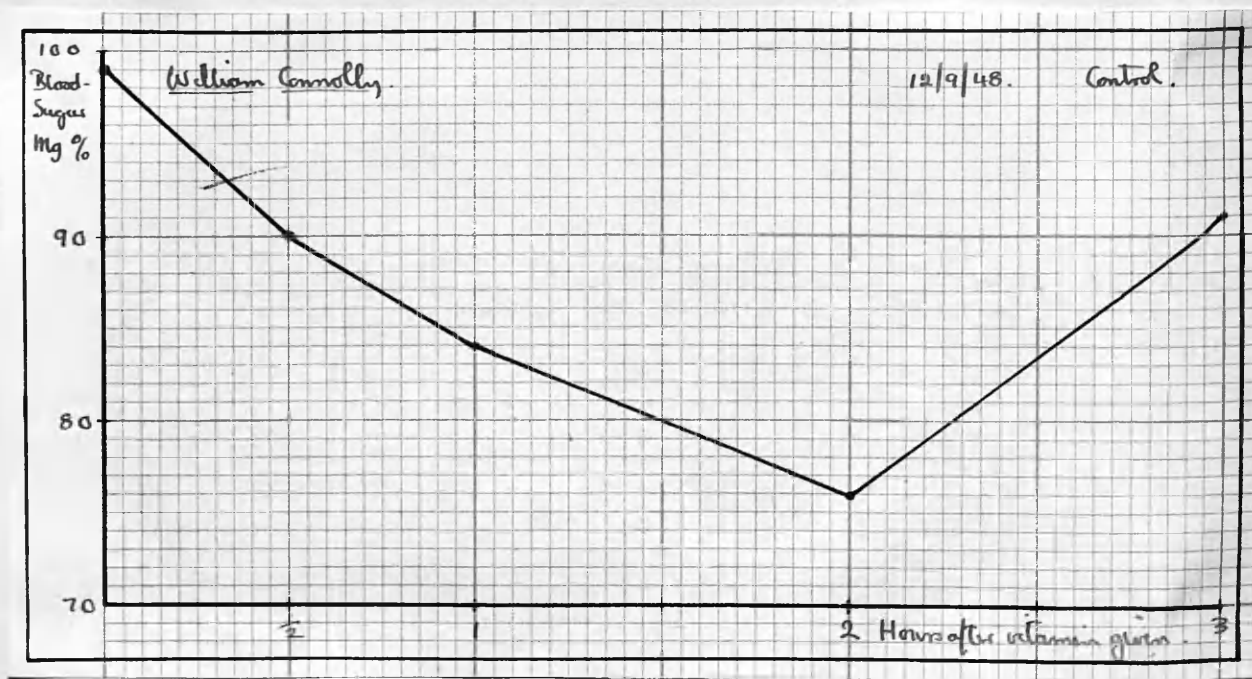
This was carried out on ten non-diabetic patients, omitting the vitamin injection, as a control investigation. Table III shows the results obtained.

TABLE III

Patient's Initials.	Blood-Sugar Concentration Mg.%					Mean	Standard Deviation
	Time in Hours After Investigations Commenced.						
	0	$\frac{1}{2}$	1	2	3		
W.C.	99	90	84	76	91	88	8.6
D.B.	118	113	110	116	113	114	3.1
J.M.	98	88	81	82	83	86	7.0
J.F.	120	109	116	112	101	112	7.0
G.R.	109	92	94	95	108	100	8.2
I.M.	92	97	84	80.4	93	89	6.9
R.D.	120	114	111	115	114	115	3.3
M.B.	90	103	101	109	106	102	7.3
M.D.	97	92	90	91	98	94	3.7
H.H.	84	86	90	87	84	86	2.5
Average Standard Deviation							5.8

The standard deviation seemed to be quite a convenient method of comparing the controls with the other subjects, as it gave a measure of the variation in the blood-sugar values occurring during the period of three hours. The average standard deviation of 5.8 showed that on the whole the fast-ing blood-sugar levels of the controls remained fairly constant.

The results of this control investigation, with comments, are given in graphical form in the following pages.

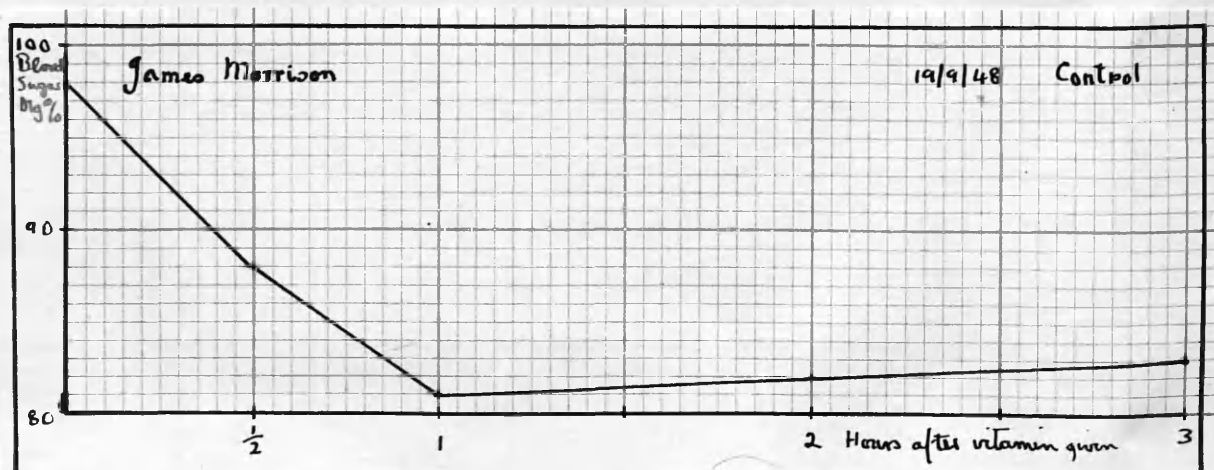


W.C., aged 31, had an enlarged liver and spleen, with ascites, oedema and albuminuria. His skin was pigmented, but there was

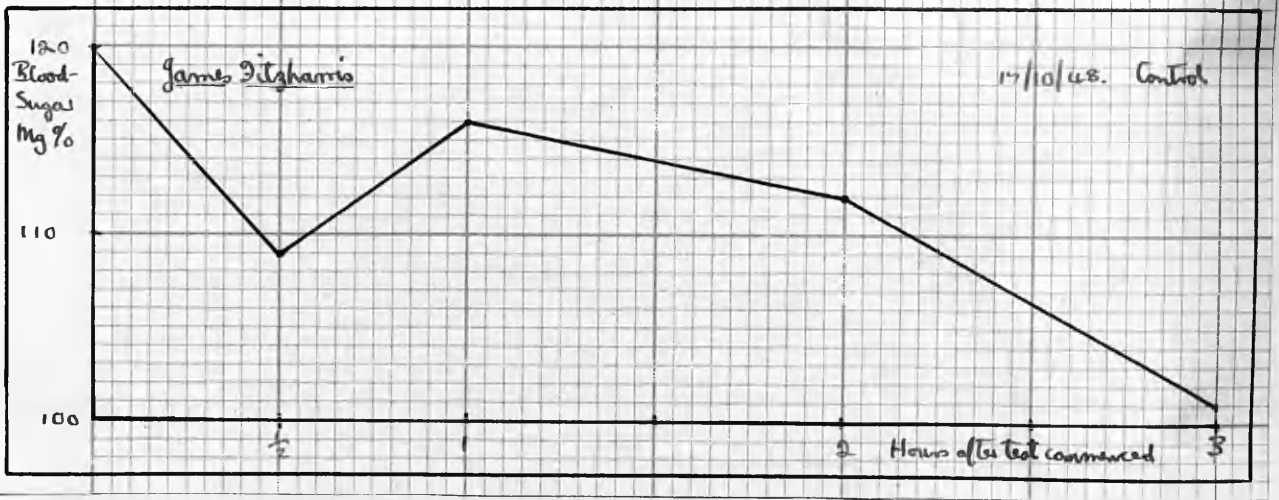
no glycosuria. Histological examination after death confirmed the diagnosis of haemochromatosis, with cirrhosis of the liver. The cirrhotic liver may have been responsible for the unstable fasting blood-sugar level shown here, which was confirmed by repeating the estimations.



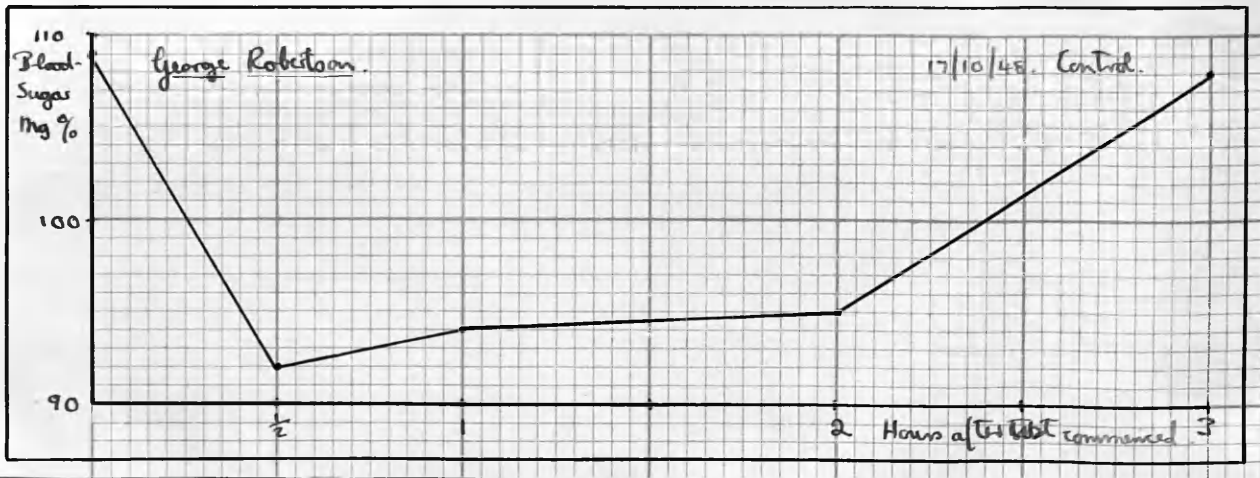
D.B., aged 45, had a bronchogenic carcinoma with secondary subcutaneous nodules.



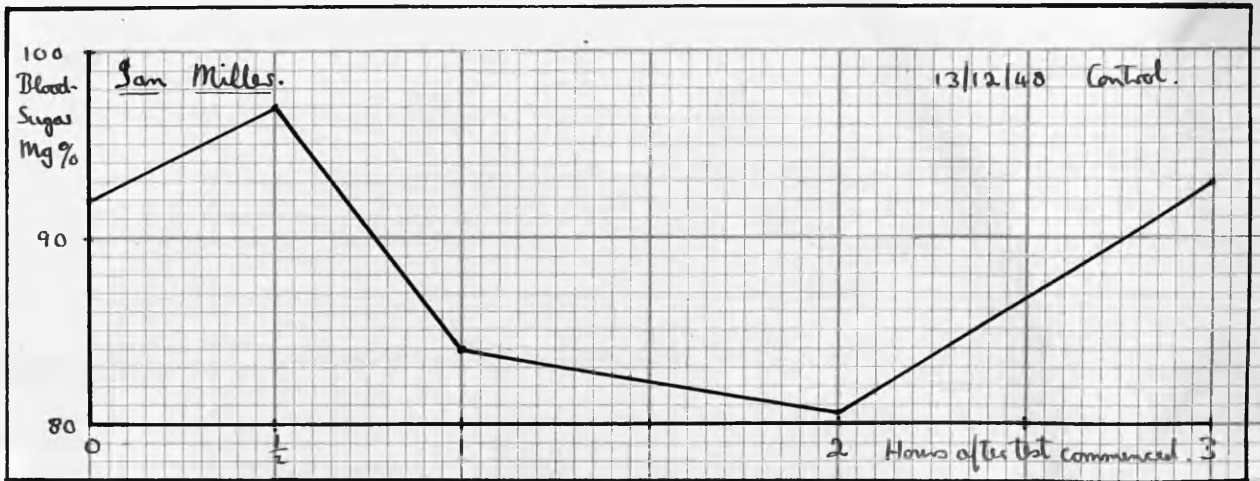
J.M., aged 63, had a severe congestive heart failure with oedema of the legs and enlargement of the liver.



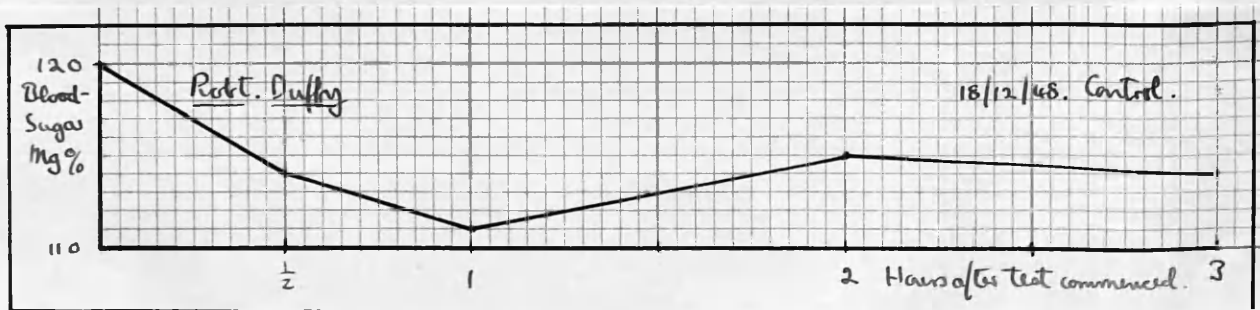
J.F., aged 51, had a chronic sinusitis and mild atypical pneumonia.



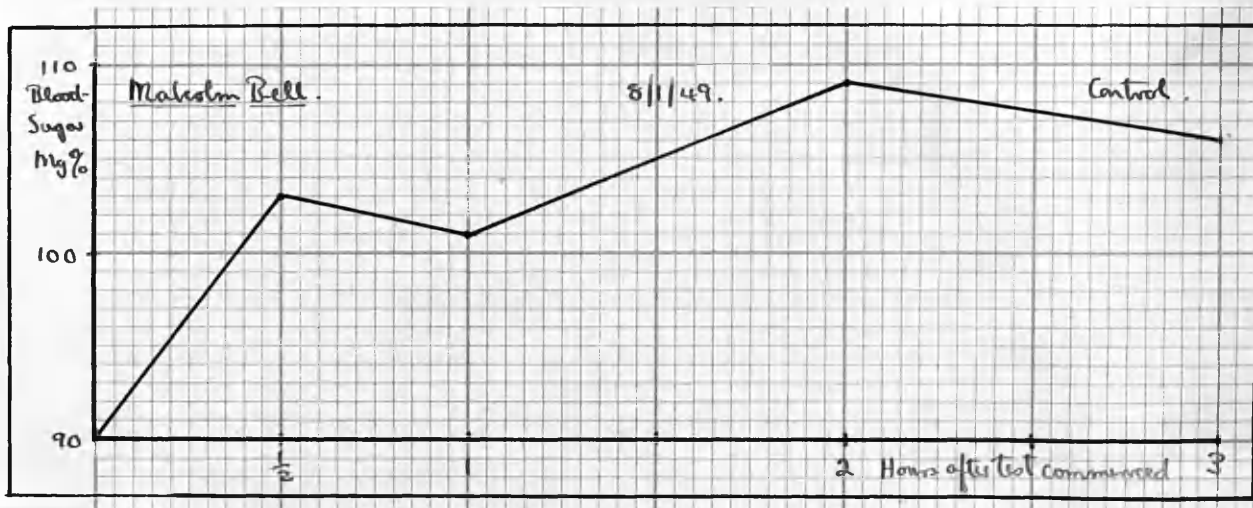
G.R., aged 28, showed signs of early disseminated sclerosis.



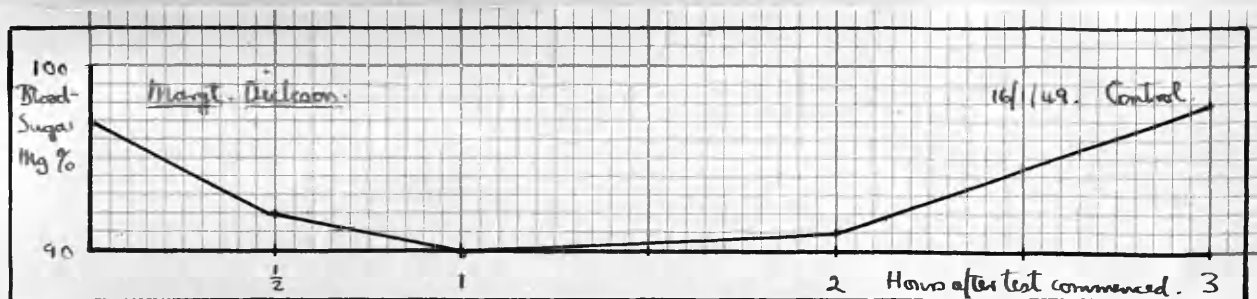
I.M., aged 20, had a unilateral bronchiectasis of two years' duration.



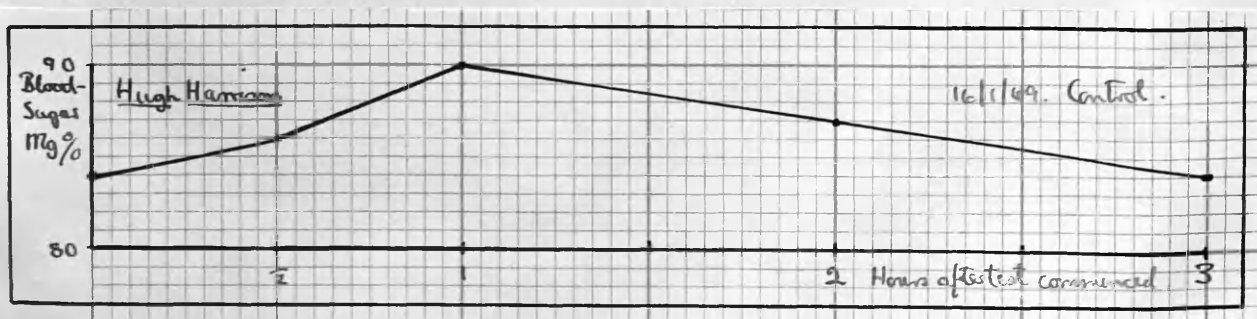
R.D., aged 54, showed slight signs of bronchiectasis on screening the chest, but turned out to be quite healthy.



M.B., aged 65, had the symptoms of a small coronary thrombosis.



M.D., aged 34, was a very obese woman who had occasionally shown a slight glycosuria.

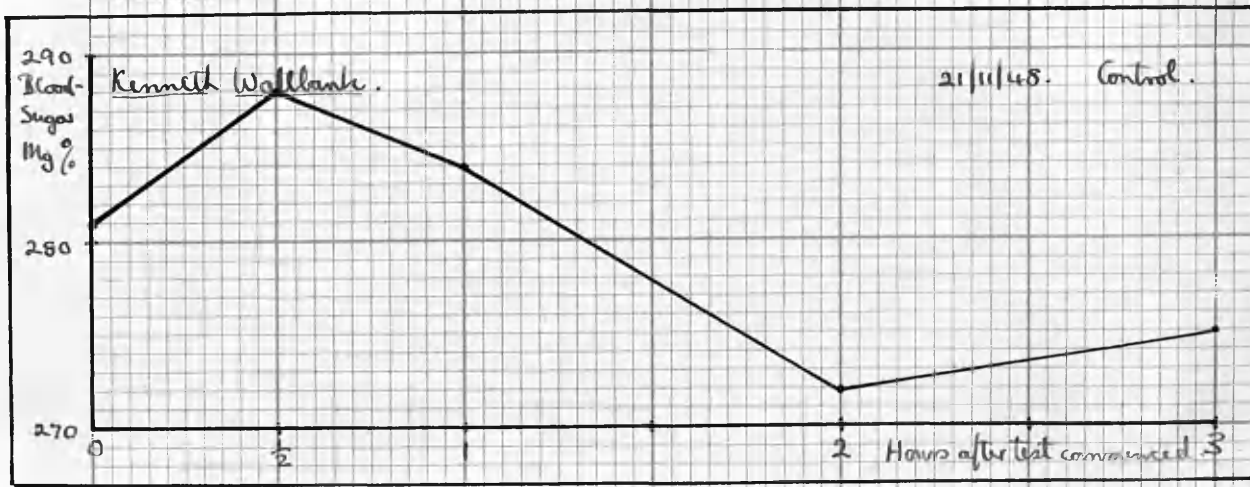


H.H., aged 38, was a haematemesis case with a long history of peptic ulcer symptoms.

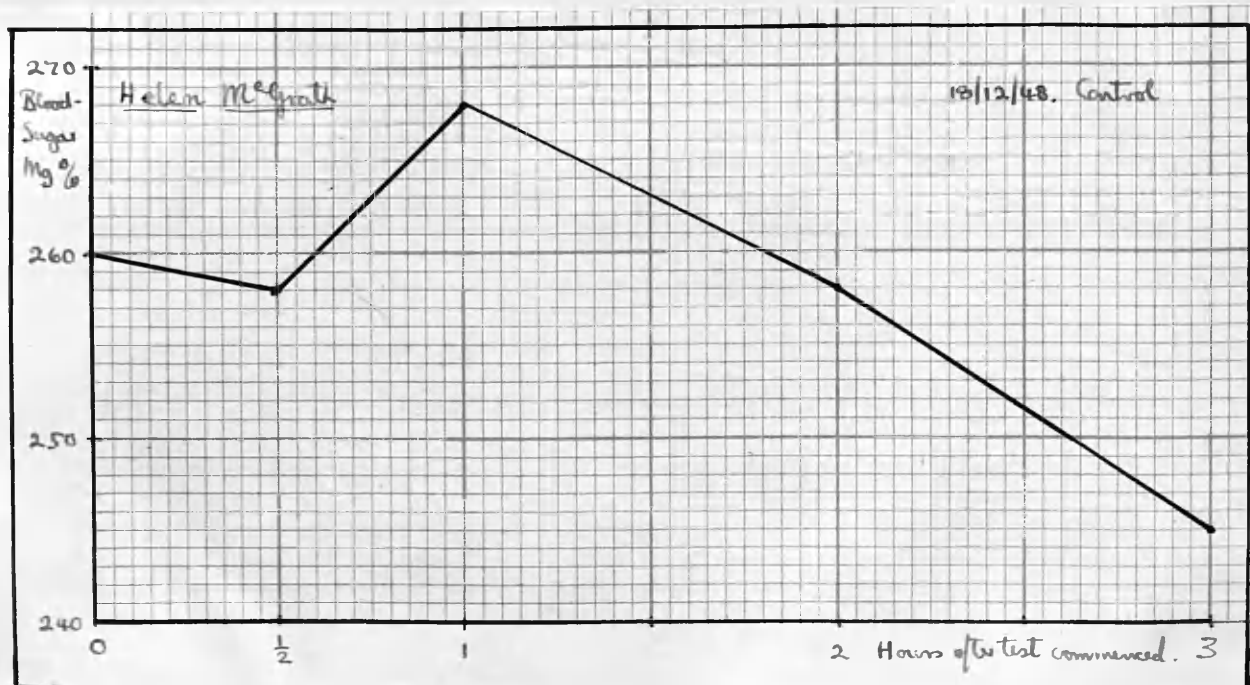
The results obtained from the four diabetics used as controls are given in Table IV. This is followed by the same results given in graph form. The diabetics, in addition to having been fasting for about fifteen hours, had received no insulin for at least 26 hours.

TABLE IV

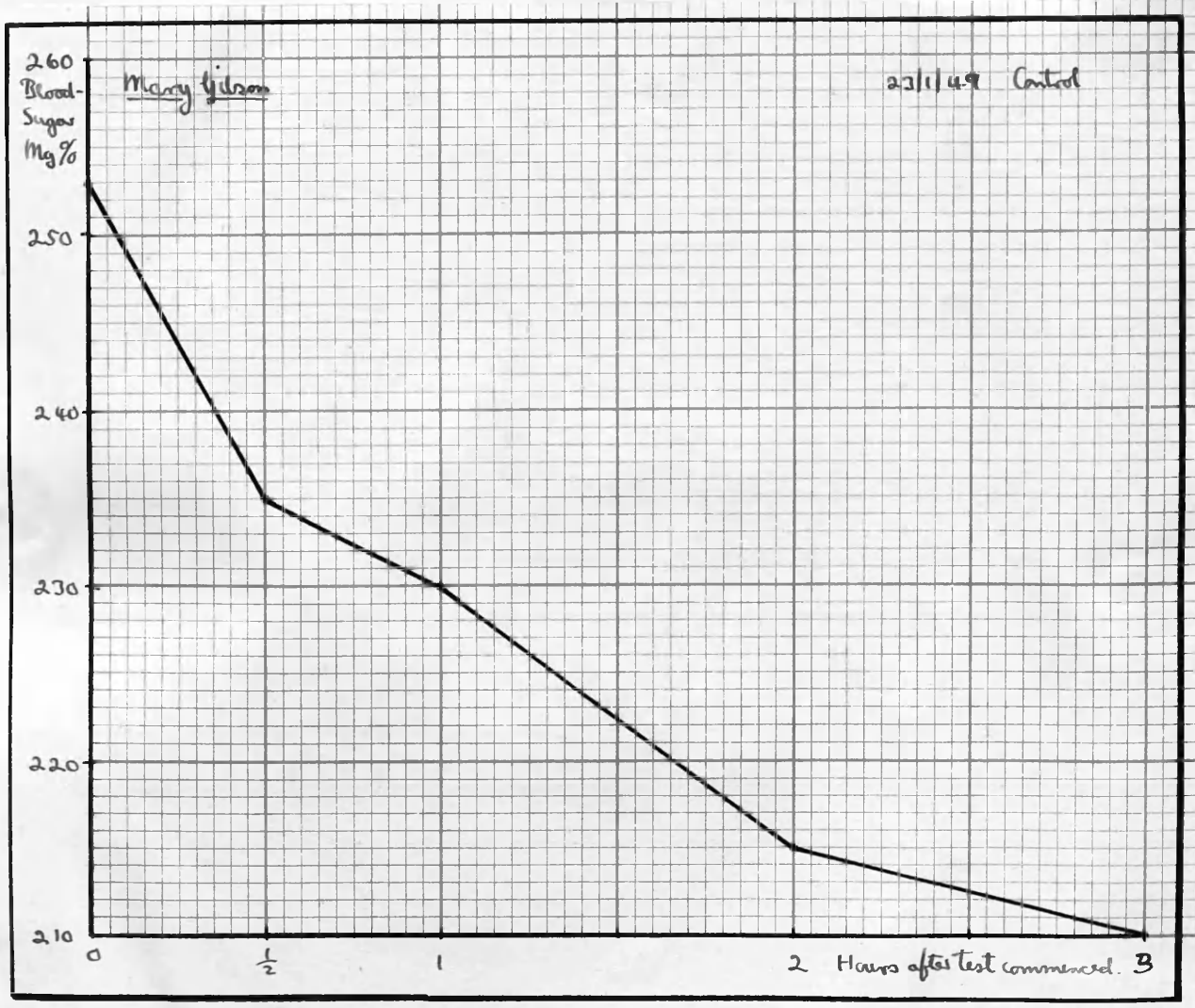
Patient's Initials.	Blood-Sugar Concentration Mg.%					Mean	Standard Deviation
	Time in Hours After Investigation Commenced.						
	0	$\frac{1}{2}$	1	2	3		
K.W.	281	288	284	272	275	280	6.2
H.M.	260	258	268	258	245	258	8.2
M.G.	253	235	230	215	210	229	17.1
V.G.	260	253	253	241	245	250	7.5
Average Standard Deviation						10.7	



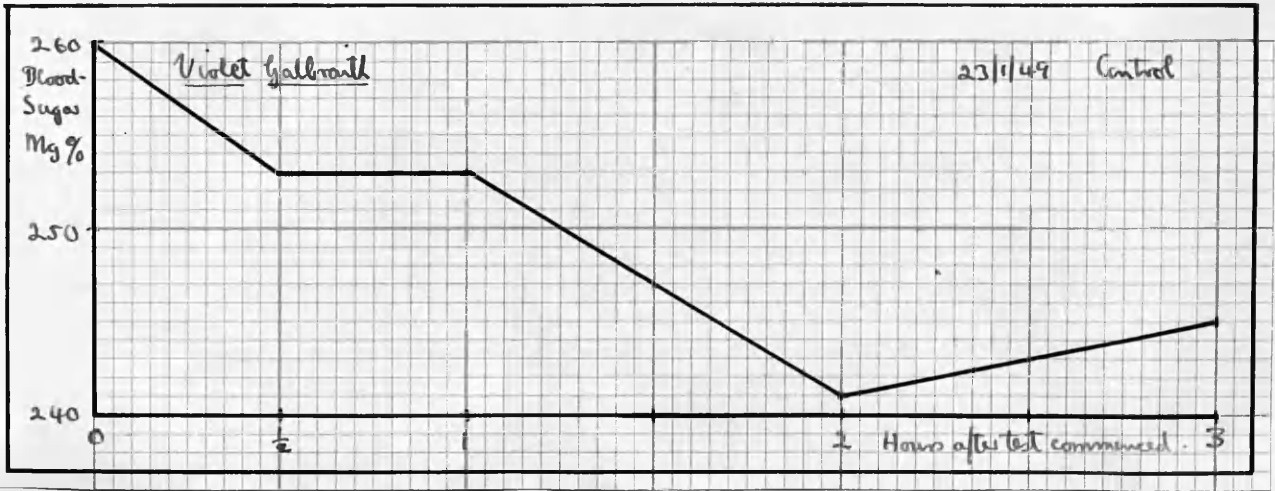
K.W., aged 25, had been a diabetic for four years, fairly well controlled on a 16 line diet with 30 units S.I. and 15 units P.Z.I. daily. (see page 20)



H.M., aged 64, had been treated by diet for glycosuria for two years.



M.G., aged 51, was getting 20 units S.I. daily for her diabetes of four years' duration.



V.G., aged 42, had been getting a small dose of P.Z.I. daily for her diabetes of twelve years' duration.

What precautions were taken to ensure that previous administered PZI had ceased to be effective at time of test?

THE CARBOHYDRATE METABOLISM

THE CARBOHYDRATE METABOLISM.

This might now be a suitable stage at which to describe briefly the processes occurring during carbohydrate metabolism, and to discuss why the B vitamins might aid this metabolism in diabetes mellitus.

The digestive juices of the stomach, small bowel and pancreas break up the carbohydrate food material into the three monosaccharides - glucose, galactose and fructose. These are absorbed, mainly in the small bowel, by two methods:

(1) Phosphorylation - the coupling of the monosaccharide with phosphoric acid to produce a hexose-phosphate. This occurs as soon as the monosaccharide has diffused into the intestinal wall. (This process is depressed by phloridzin. Since reabsorption of glucose from the renal tubules occurs by phosphorylation, phloridzin thus produces a renal glycosuria).

(2) Diffusion alone across the mucous membrane into the blood stream. This takes place only to a small extent.

The fructose and galactose are converted to glucose and glycogen in the liver. The glucose is disposed of in three main ways:

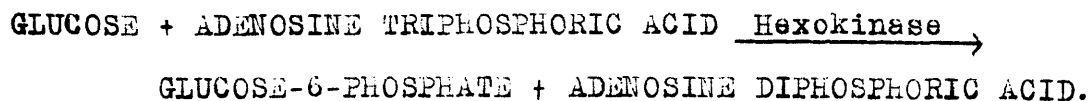
(a) Transformation into fat. There is increasing evidence that more glucose is stored as fatty acids than as glycogen. It is thought probably that the conversion of glucose to fatty acids takes place mainly, if not entirely,

via hexose-phosphates and pyruvic acid, but there is not yet any definite evidence of this (Young). It is known that aneurin is necessary for this process, and probably also insulin.

(b) Conversion to liver and muscle glycogen is the second method; and finally

(c) Oxidation.

Rôle of Insulin. The phosphorylation of glucose through the action of an enzyme called hexokinase may be demonstrated diagrammatically as follows:



This process may be essential for the passage of glucose through the membranes of cells. The metabolism of glucose within the cell may be impossible without it.

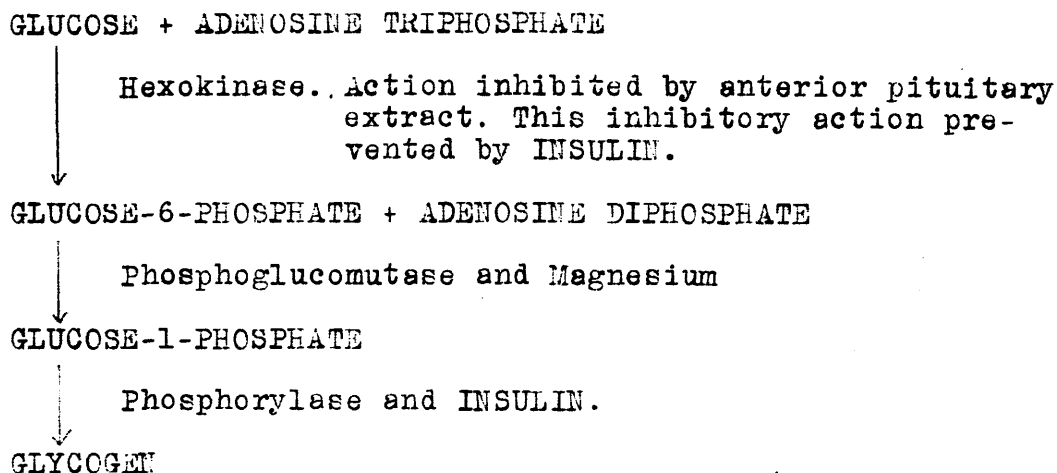
Certain freshly prepared anterior-pituitary extracts can depress this action of hexokinase in-vitro; and this depressive action can be prevented by the in-vitro addition of insulin to the system. The depressive action can be prolonged by a secretion of the adrenal cortex.

That the main action of insulin in-vivo is this release of hexokinase from pituitary inhibition is not certain, however. Insulin exerts, for instance, a greatly exaggerated hypoglycaemic action in hypophysectomised animals who have therefore no hexokinase inhibitor.

A recent and so far unconfirmed report shows that insulin promotes the formation of glycogen from glucose-1-phosphate in liver slices under certain conditions. Hexokinase does not appear to take any part in this procedure.

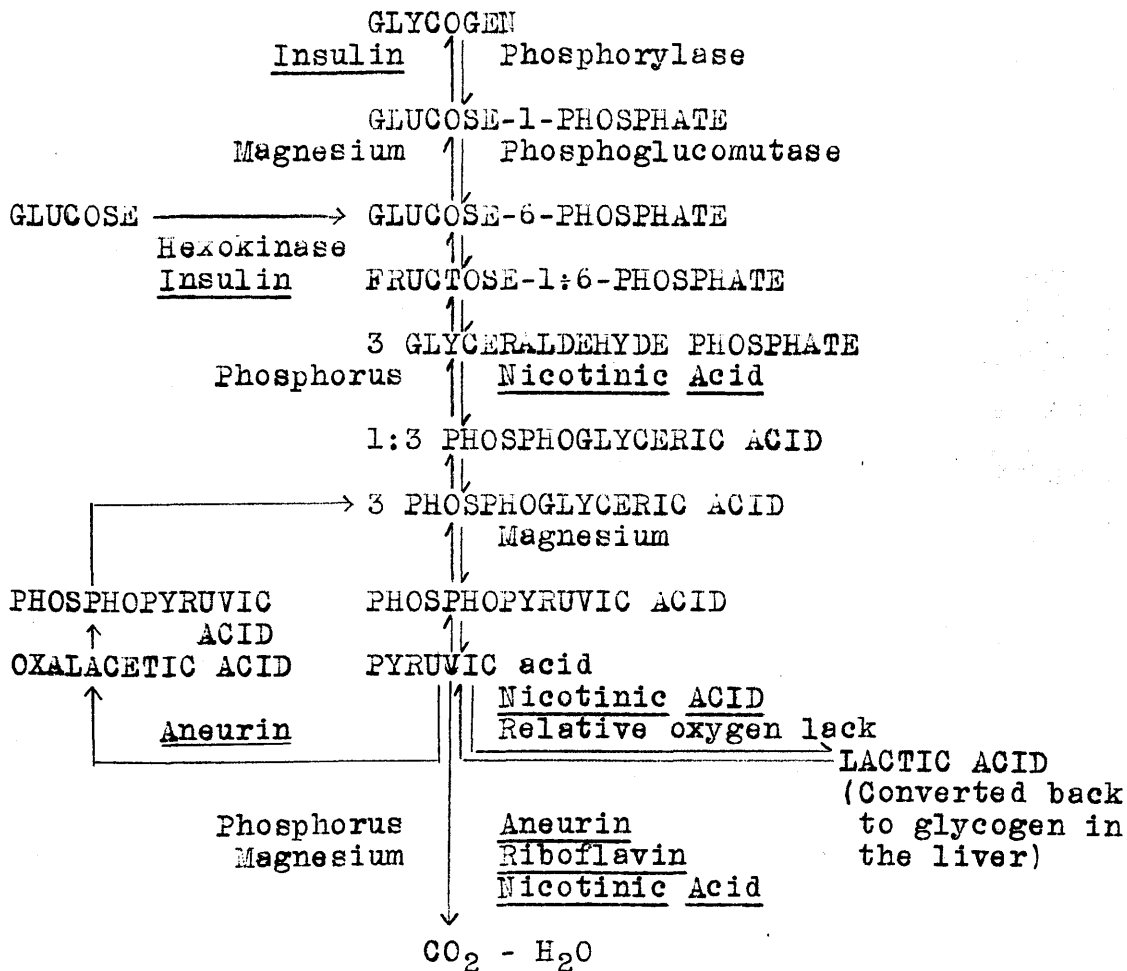
Although insulin greatly facilitates the transformation of glucose to glycogen, this can proceed at a lessened rate in the total absence of insulin. The site of action is probably higher than the pyruvic acid stage in carbohydrate metabolism. It promotes the formation of pyruvic acid, and thereby increases the rate of oxidation of carbohydrate. Insulin may also facilitate the formation of fat from carbohydrate.

The rôle of insulin in glycogen formation may be summarised diagrammatically as follows:



Rôle of Vitamin B Complex. This will be discussed separately in later parts of the paper. The following figure (adapted from Wohl's Dietotherapy, 1945, P 57) shows the relative

stages in the carbohydrate metabolism at which insulin and the B vitamins act. The substances indicated alongside the arrows are necessary for the reactions to occur in both directions.



It can thus be seen that there is no point known at present at which insulin and any of the B complex vitamins act together. There is therefore no theoretical reason why a deficiency of insulin could be remedied by an increased dosage of any or all of the vitamin B complex.

GMW/RM.



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Dr. C.M. Wylie,
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Renfrewshire.

Dear Dr. Wylie,

Having reviewed the reports of the readers of your Thesis I think I ought to advise you to abandon any idea of modifying the present thesis and rather to start out on a completely new subject.

Yours sincerely,

G. M. Wishart

Dean of the Faculty of Medicine.

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Young, F.G. 1948. Lancet 2, 955

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Wright, S. 1943. Applied Physiology. 7th Ed.

WHY THE VITAMIN B COMPLEX MAY BE BENEFICIAL IN
DIABETES MELLITUS

WHY THE VITAMIN B COMPLEX MAY BE BENEFICIAL IN

DIABETES MELLITUS

There have been many conjectures made on this subject, and some of them could not be taken too seriously. The more likely and interesting ones might briefly be discussed here.

(1) The vitamins may help to control the nutrition of the β cells of the islets of Langerhans. There is no evidence at present that this is correct. In addition, the B complex is claimed to have a beneficial effect on depancreatized animals, who presumably have no remaining islet tissue.

(2) The abnormal carbohydrate metabolism when insulin is deficient may necessitate an increased intake of the B vitamins, or might interfere with their utilization.

(3) An inadequate intake of B complex may occur in many diabetics due to the substitution of foods poor in the complex for prescribed foods with a richer content.

(4) Severe arteriosclerosis may require a higher concentration of aneurin in the blood, to provide sufficient vitamin to the nerves, than in subjects with normal arteries (Naide). This seems a very unlikely theory. The arterioles would probably have to be so narrowed that gangrene had set in before the vitamin supply to the nerves was impaired. The capillaries, unaffected by the arteriosclerosis, would still allow the vitamins to diffuse out quite normally.

(5) The polyuria in untreated and poorly treated diabetics may cause increased excretion of the vitamins.

(6) There might be a stage in the carbohydrate metabolism at which both insulin and any of the B vitamins acted, so that a deficiency of insulin could be remedied by an increase in the necessary vitamin. Thus, the B vitamins might exert an action similar to insulin in preventing the anterior pituitary inhibition of hexokinase activity and the resulting disruption of carbohydrate metabolism. There is, unfortunately, no evidence that this occurs, and careful examination of the stages of carbohydrate metabolism known at present does not show any point at which the two groups act together.

(7) They might raise the renal threshold for glucose and thus diminish the glycosuria. There has never been any reliable indication that this occurs; and even with the glycosuria diminished, the abnormal carbohydrate metabolism would continue, which is much more important in the severe diabetic.

At present, therefore, the two most likely theories seem to be:-

(a) The diminished vitamin B content of the diet, and the excessive excretion of the vitamins may cause the B vitamin content of the diabetic's body to be below normal.

(b) The diabetic may contain normal amounts of the B vitamins, but the abnormal metabolism may require larger quantities than usual for these vitamins.

Reference. Naide, M. 1939. Am.J.M.Sc. 197, 766.

VITAMIN B₁ AND BLOOD SUGAR LEVELS

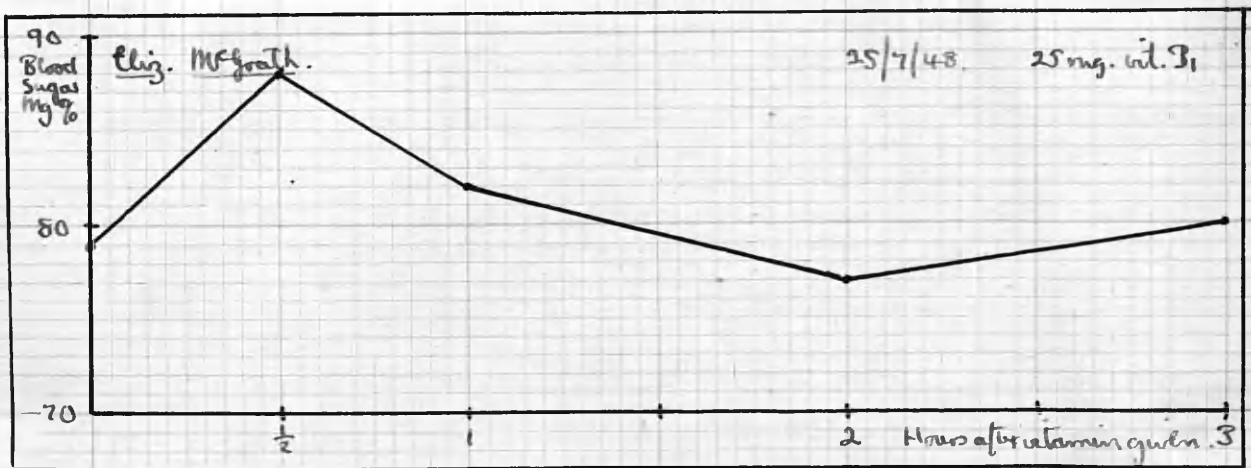
VITAMIN B₁ AND BLOOD-SUGAR LEVELS

The effect of an intravenous injection of aneurin hydrochloride was determined on eighteen non-diabetic patients. Fifteen of them were given 25 mg. of the vitamin, and three received 100 mg. The doses are indicated on the individual graphs, which follow Table V summarising the results of this part of the investigation. The average standard deviation of 5.2 indicates that aneurin does not have any significant effect on the fasting blood-sugar concentrations of non-diabetic persons.

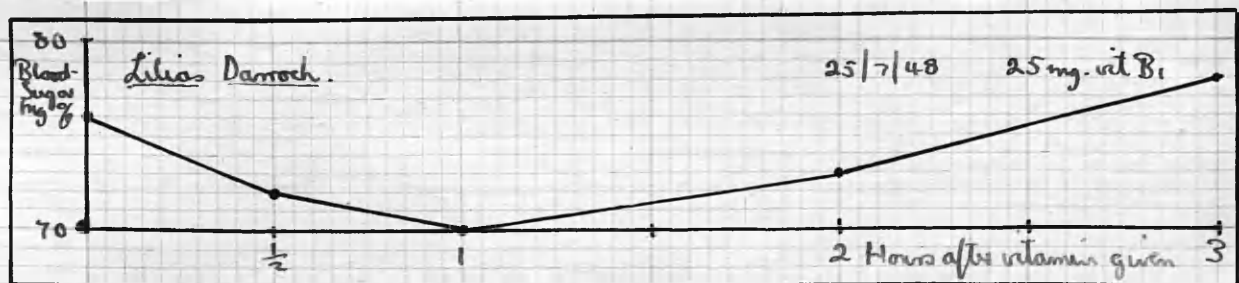
Six diabetics were also given injections of aneurin. Table VI, summarising their results, is followed by their blood-sugar curves in graph form. The average standard deviation of 7.3 suggests that vitamin B₁ does not affect the fasting sugar levels of diabetics.

Table V

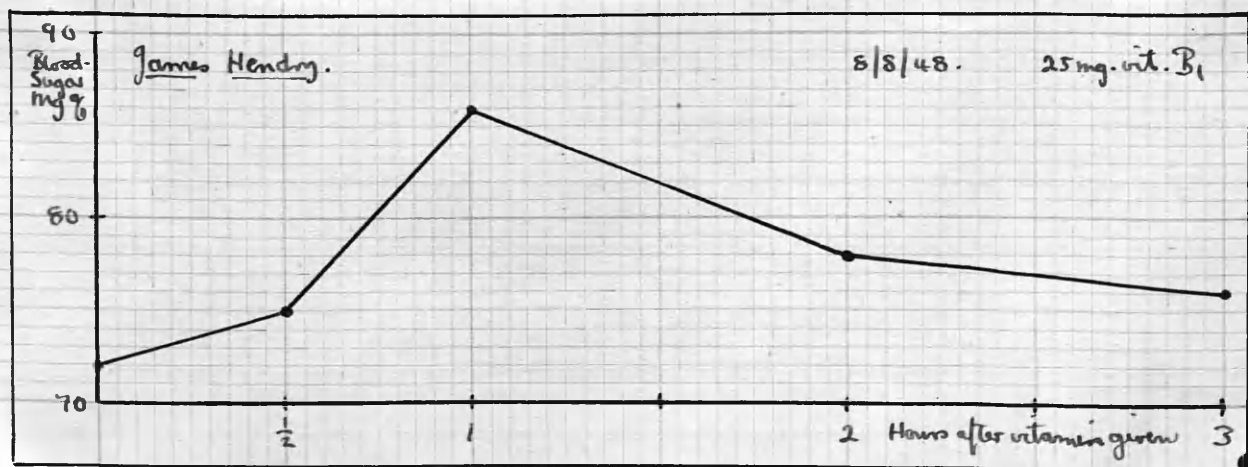
Patient's Initials.	Blood-Sugar Concentration Mg.%					Mean	Standard Deviation
	Time in Hours after Investigation Commenced.						
	0	$\frac{1}{2}$	1	2	3		
E.M.	79	88	82	77	80	81	4.2
L.D.	76	72	70	73	78	74	3.2
J.H.	72	75	86	78	76	77	5.3
E.B.	87	83	94	98	97	92	6.5
H.M.	100	97	100	98	99	99	1.3
J.B.	99	92	96	98	88	95	4.6
J.S.	84	78	72	71	81	77	5.6
W.R.	107	99	97	109	112	105	6.5
M.M.	119	116	87	82	84	98	18.6
T.M.	118	108	112	106	101	109	6.4
W.C.	111	119	116	112	103	112	6.1
J.C.	82	86	78	76	81	81	3.9
J.M.	118	114	116	103	101	110	7.9
T.C.	92	99	100	90	87	94	5.7
J.C.	101	104	108	114	118	109	7
W.A.	104	101	101	94	102	100	3.8
W.C.	94	92	90	92	82	90	4.7
J.C.	100	102	102	102	102	102	0.7
Average Standard Deviation							5.2



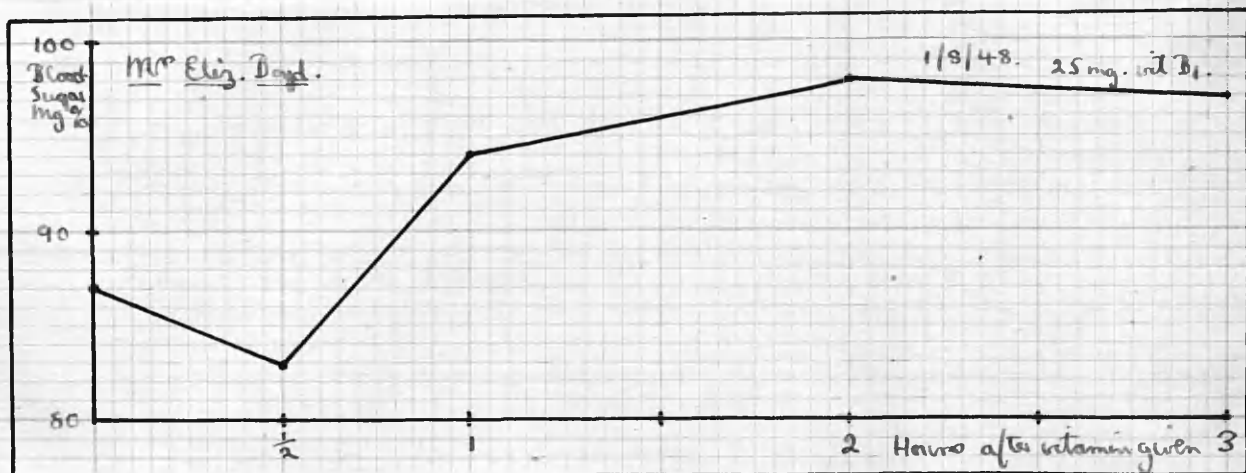
E.M., aged 58, had an acute exacerbation of chronic nephritis.



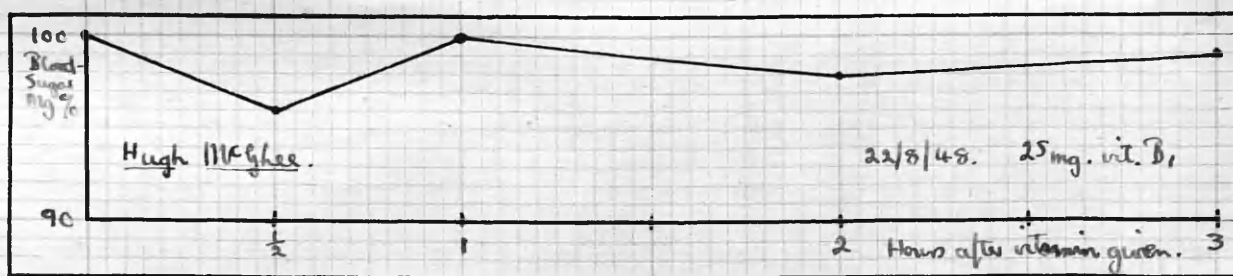
L.D., aged 45, had rheumatoid arthritis for several years.



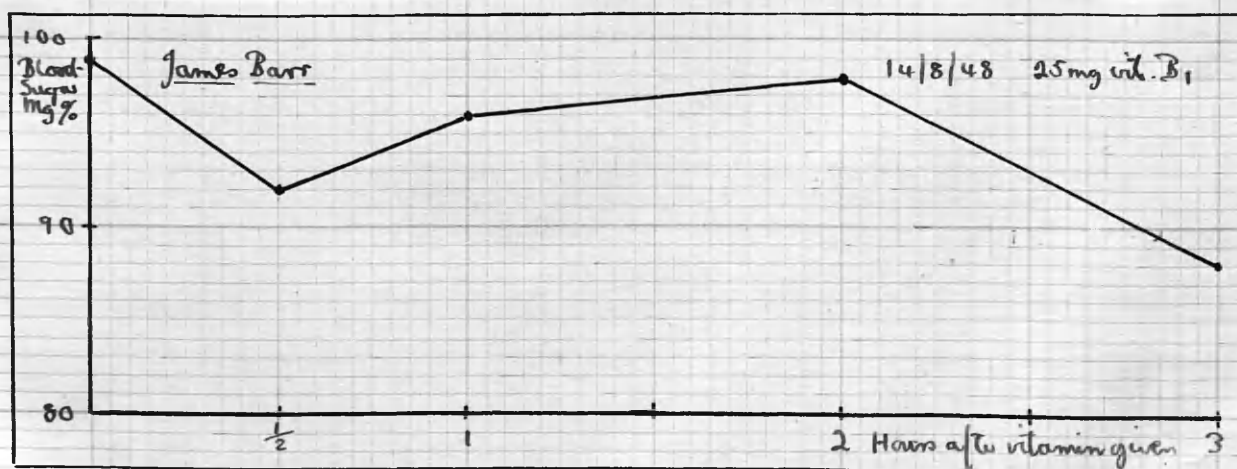
J.H., aged 27, had a mild acute rheumatoid arthritis.



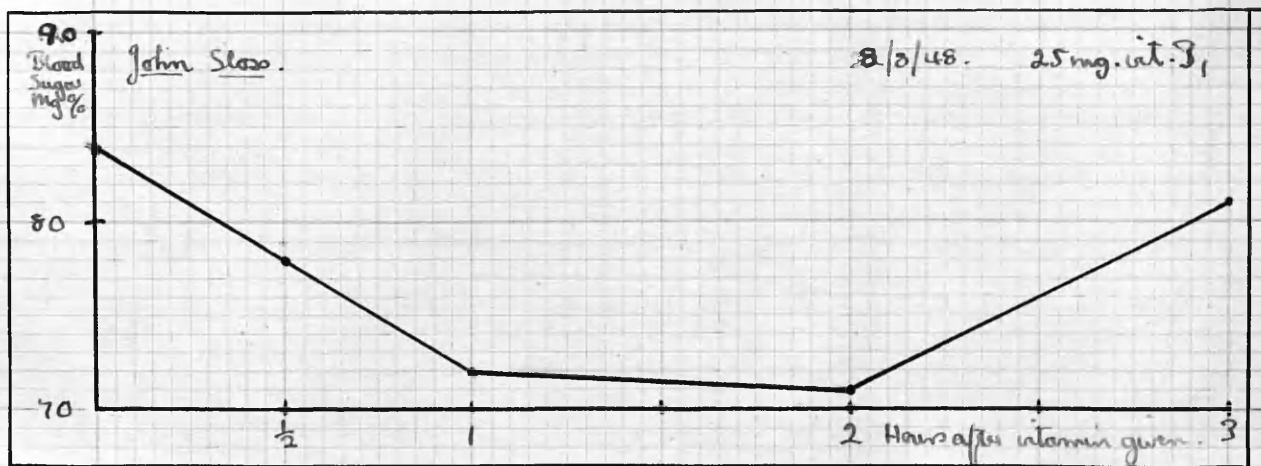
E.B., aged 59, was a case of chronic congestive heart failure of some months' duration.



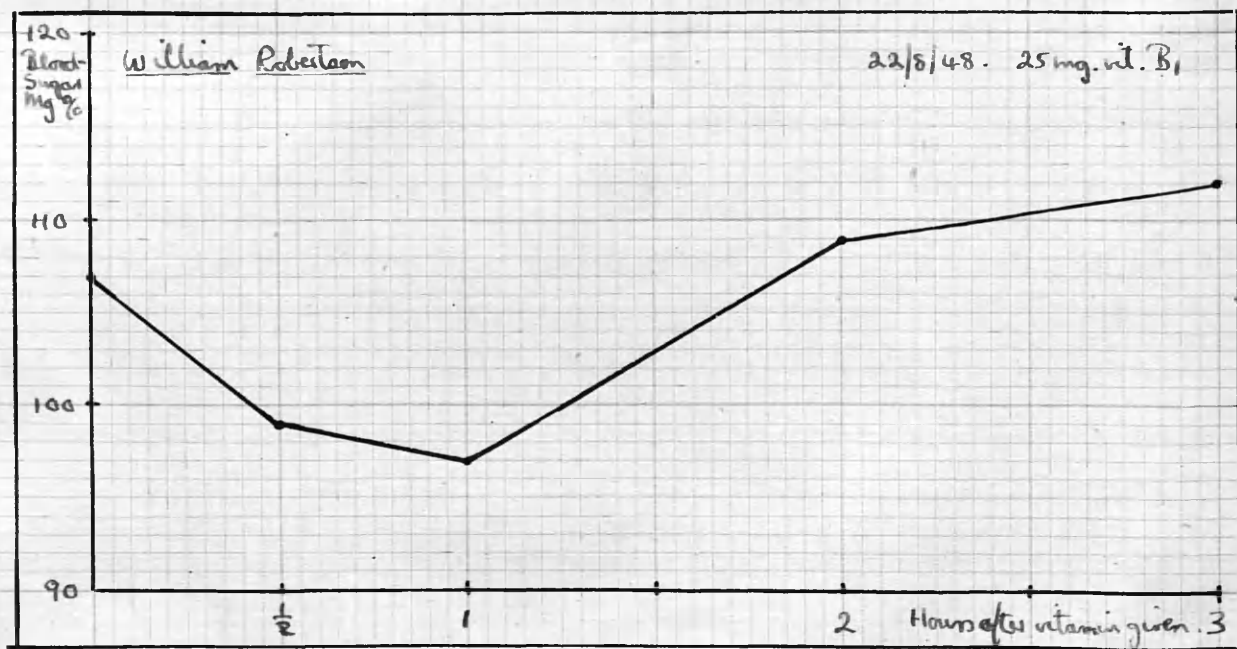
H.M., aged 46, had auricular fibrillation with mitral stenosis and congestive heart failure.



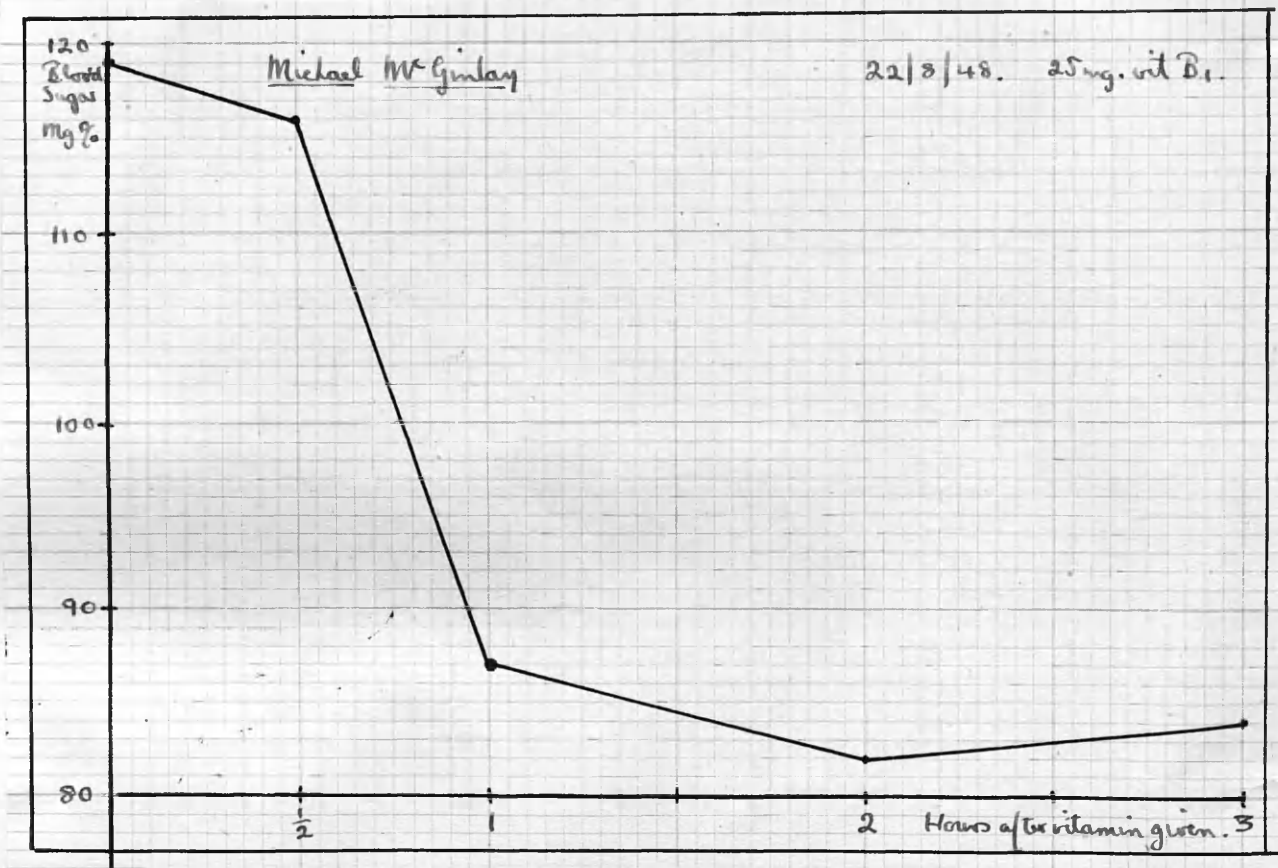
J.B., aged 22, had a mild chronic gastritis.



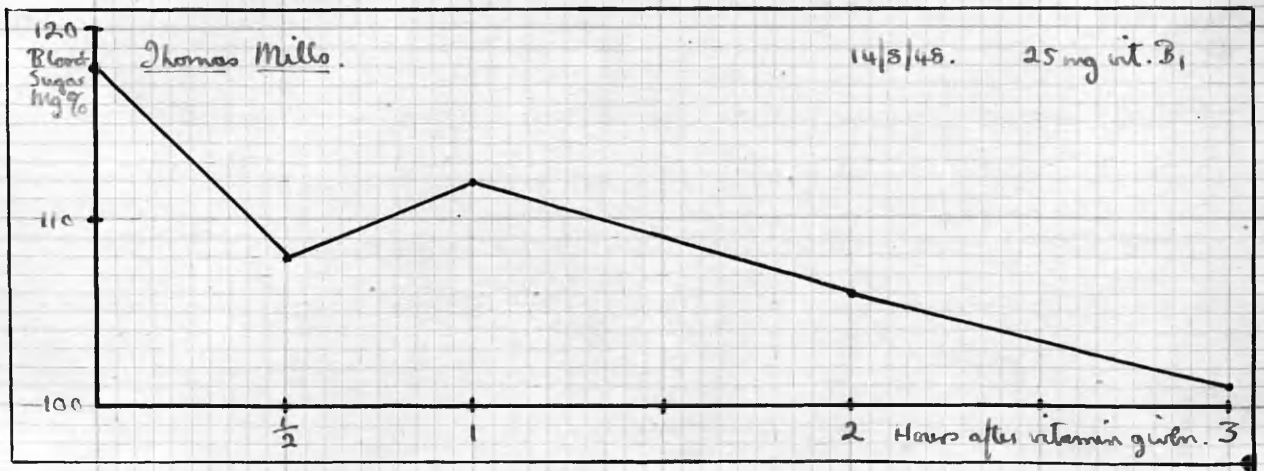
J.S., aged 50, was a syphilitic case with aortic incompetence.



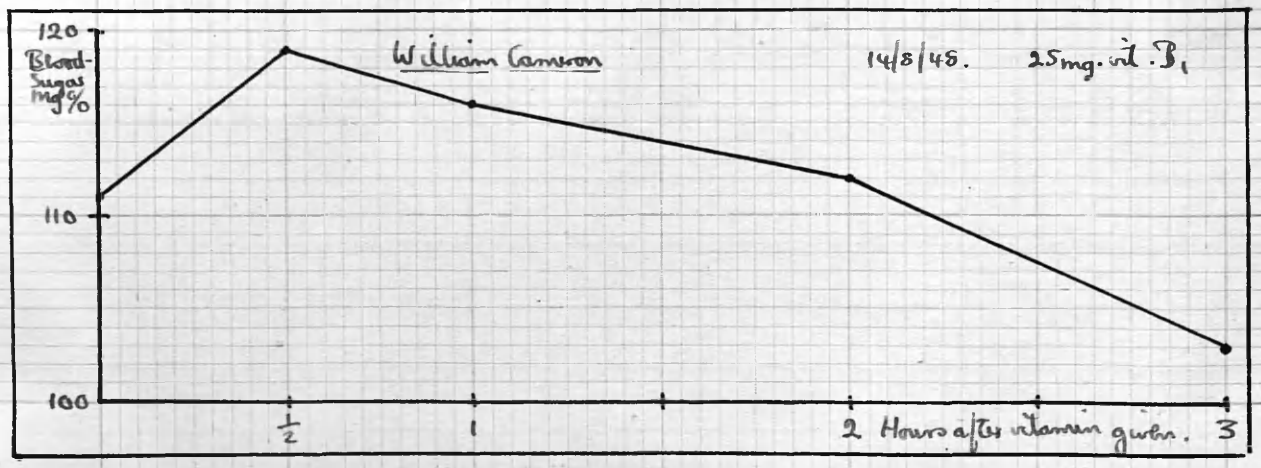
W.R., aged 50, was recovering from a subarachnoid haemorrhage.



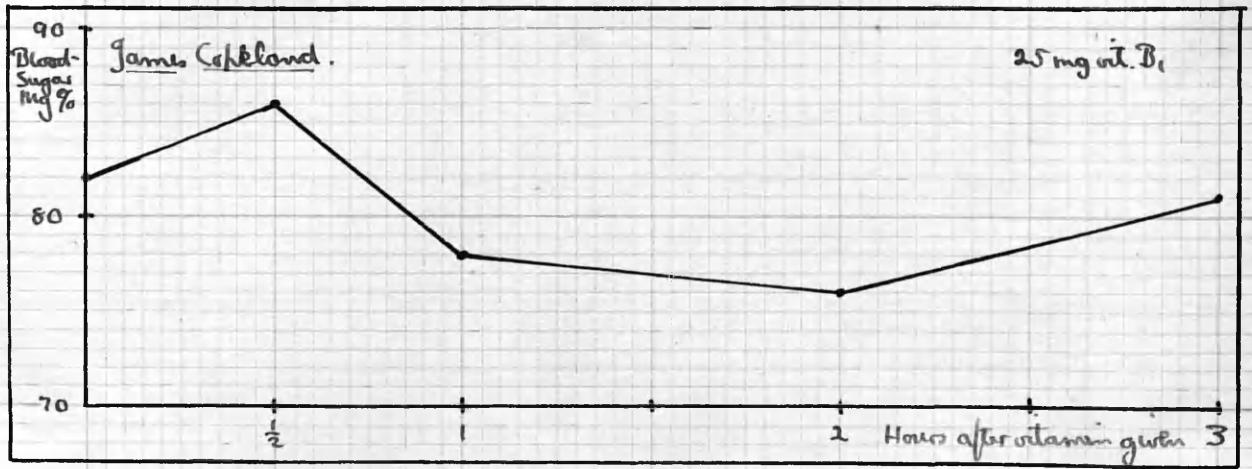
M.M., aged 37, had a cerebral thrombosis with a weak positive W.R. The marked fall in blood-sugar was confirmed, but could not be attributed definitely to the vitamin injection, as cerebral lesions do sometimes disturb the carbohydrate metabolism.



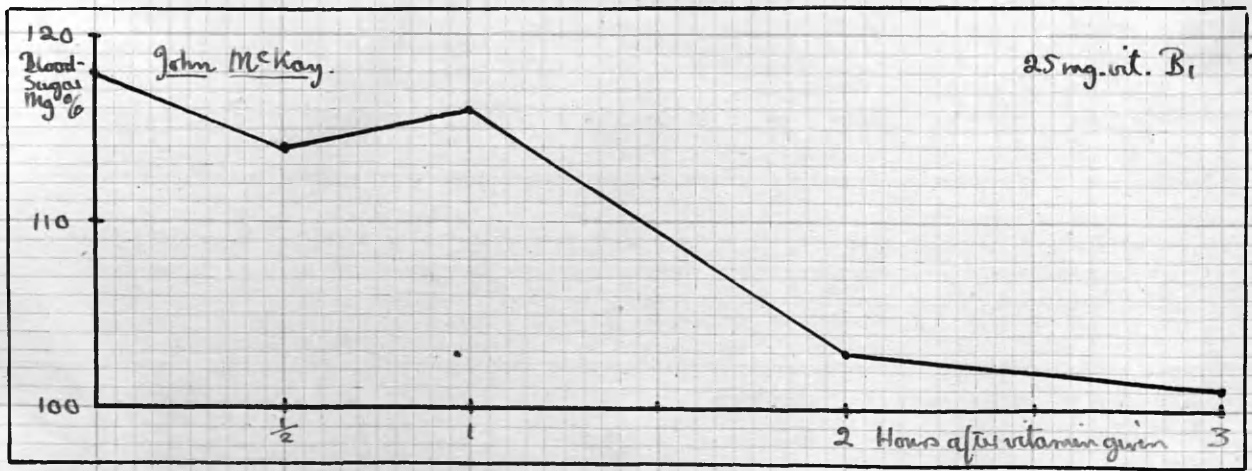
T.M., aged 65, had a mild congestive heart failure.



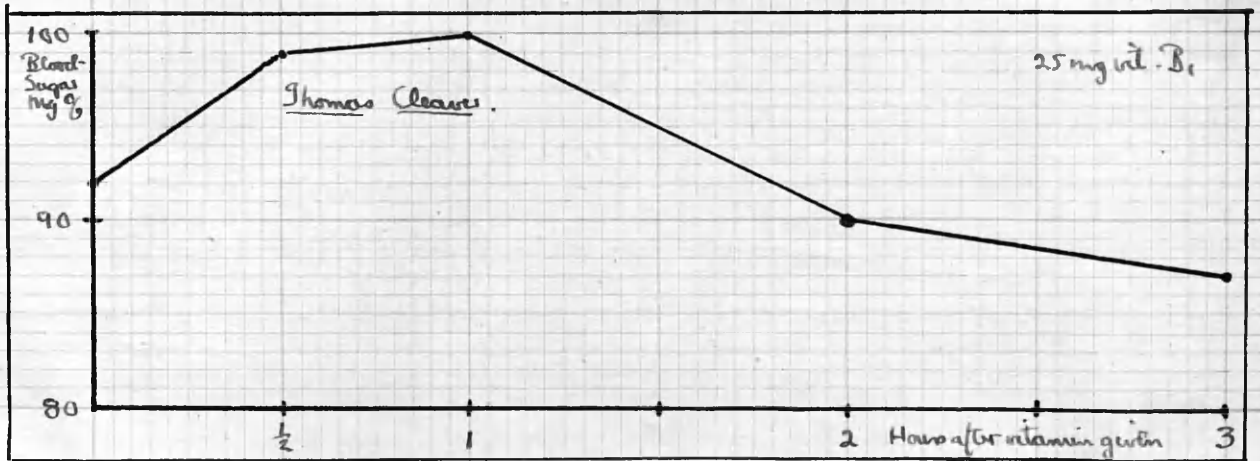
W.C., aged 53, had a slow auricular fibrillation for four years.



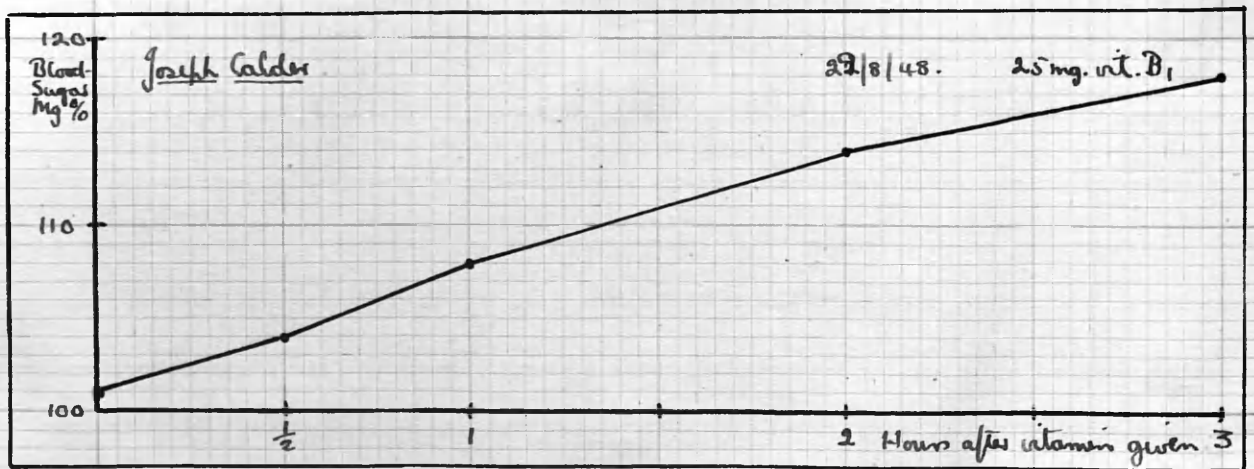
J.C., aged 55, had a mild coronary thrombosis.



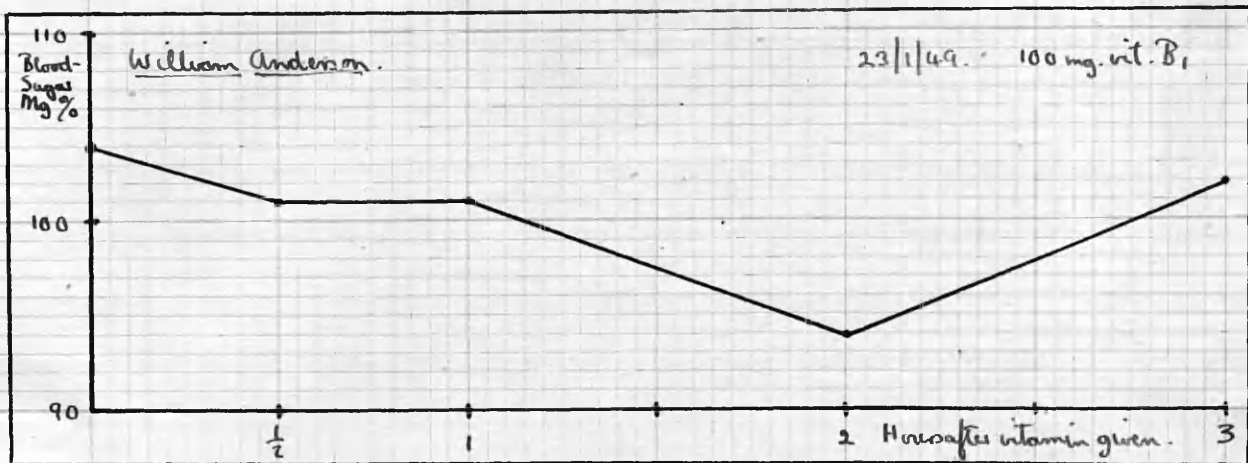
J.M., aged 54, had a small coronary thrombosis.



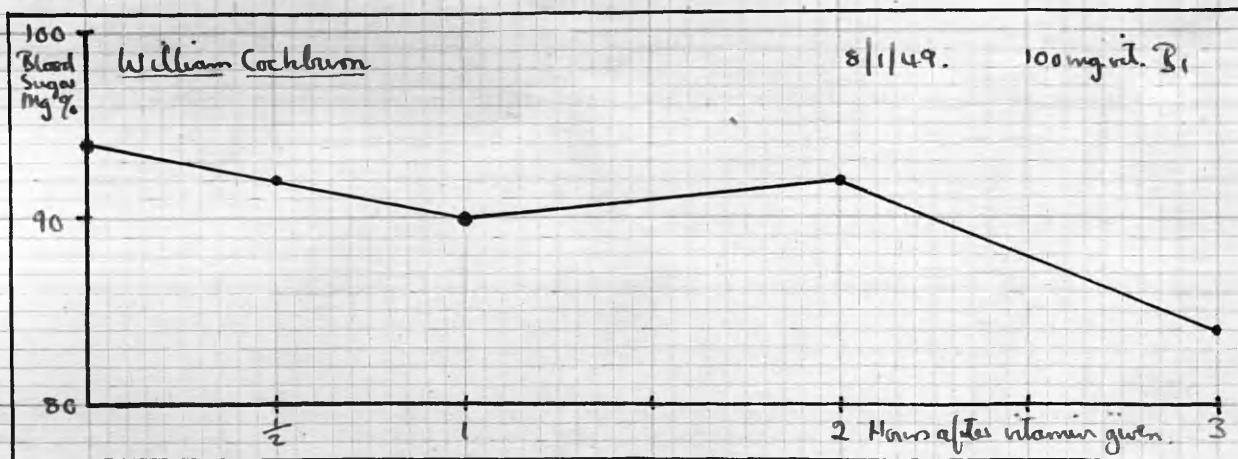
T.C., aged 34, was found to have nothing abnormal.



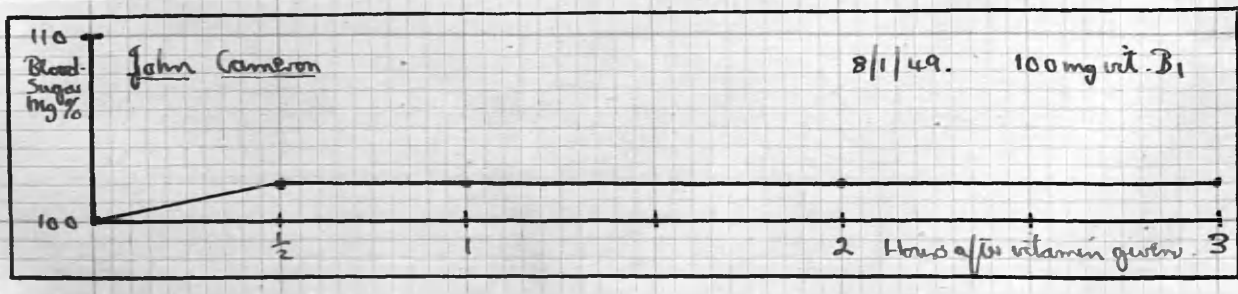
J.C., aged 16, had an acute rheumatic fever.



W.A., aged 31, had recurring attacks of left sciatic pain for many years.



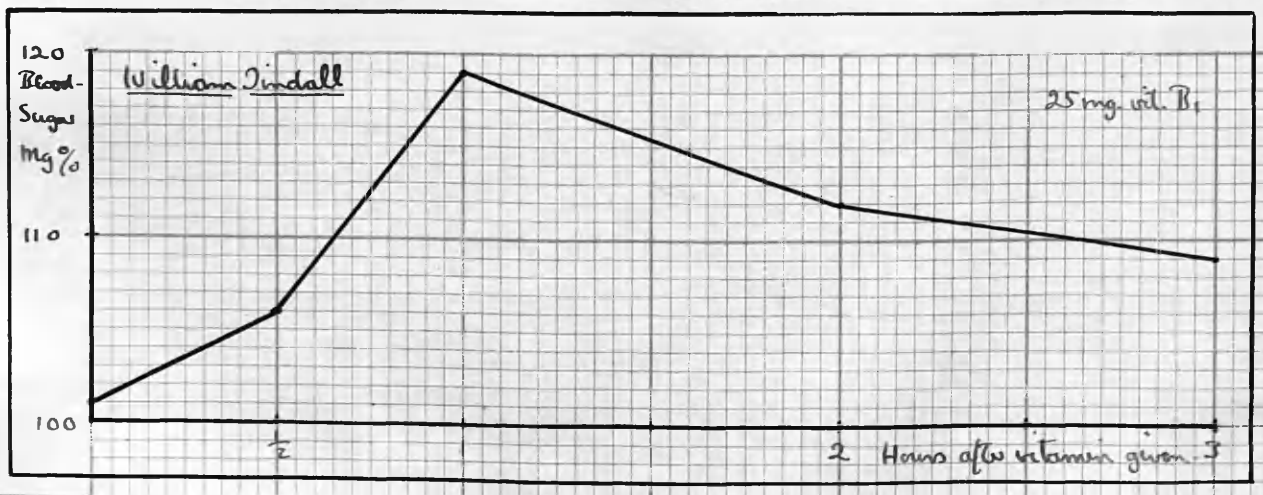
W.C., aged 54, had recurring attacks of sciatica for 30 years.



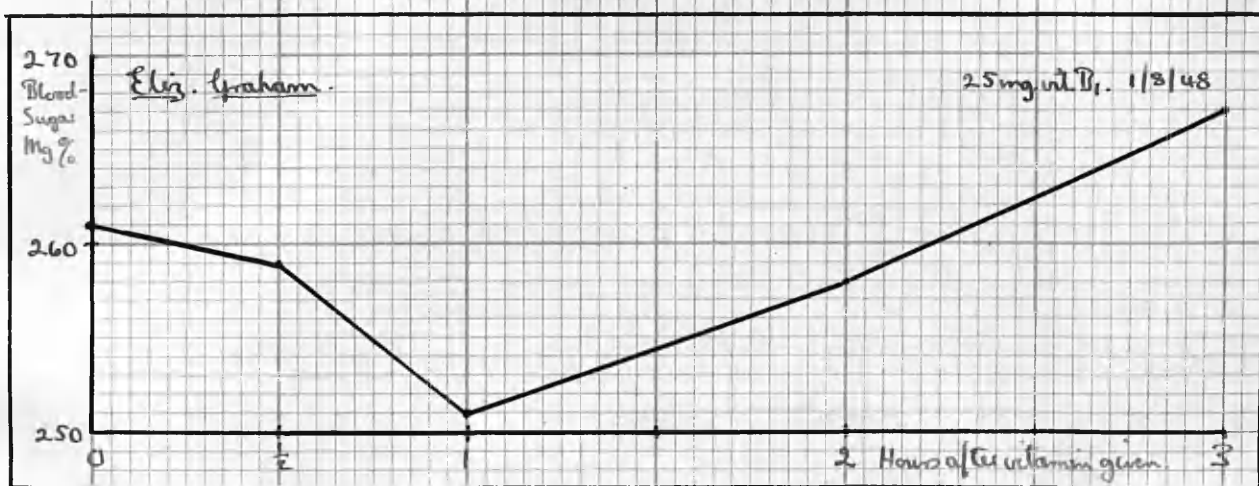
J.C., aged 38, had mild attacks of diarrhoea of uncertain origin.

Table VI

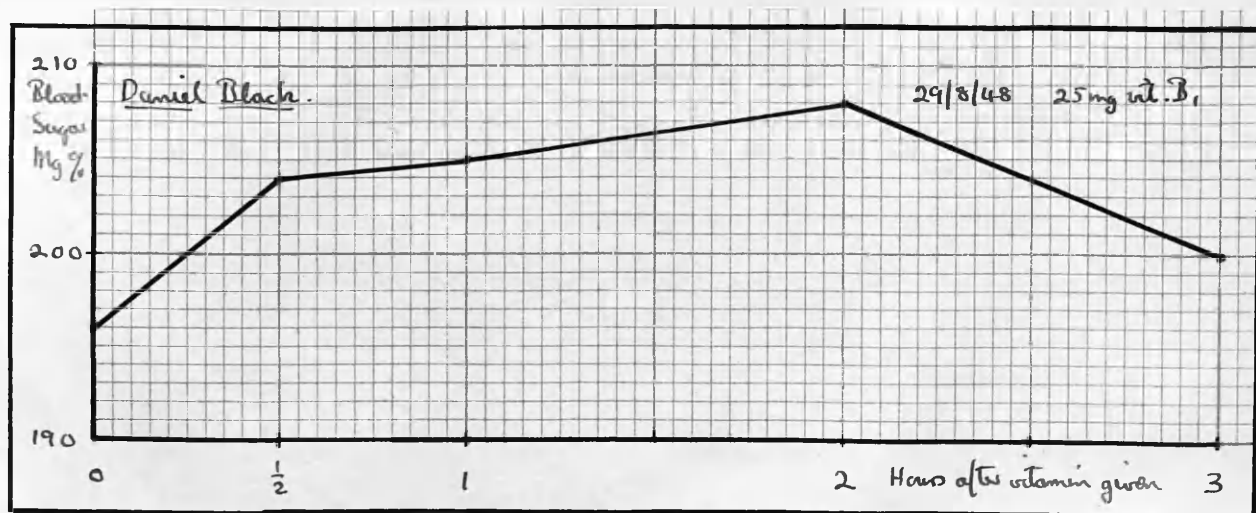
Patient's Initials.	Blood-Sugar Concentration Mg.%					Mean	Standard Deviation
	Time in Hours After Investigation Commenced.	0	$\frac{1}{2}$	1	2		
W.T.	101	106	119	112	109	109	6.8
E.G.	261	259	251	258	267	259	5.8
J.M.	162	169	176	192	197	179	5.0
D.B.	196	204	208	208	200	203	5.2
A.L.	123	125	116	120	130	123	5.3
C.M.	156	164	152	156	150	156	5.4
Average Standard Deviation						7.3	



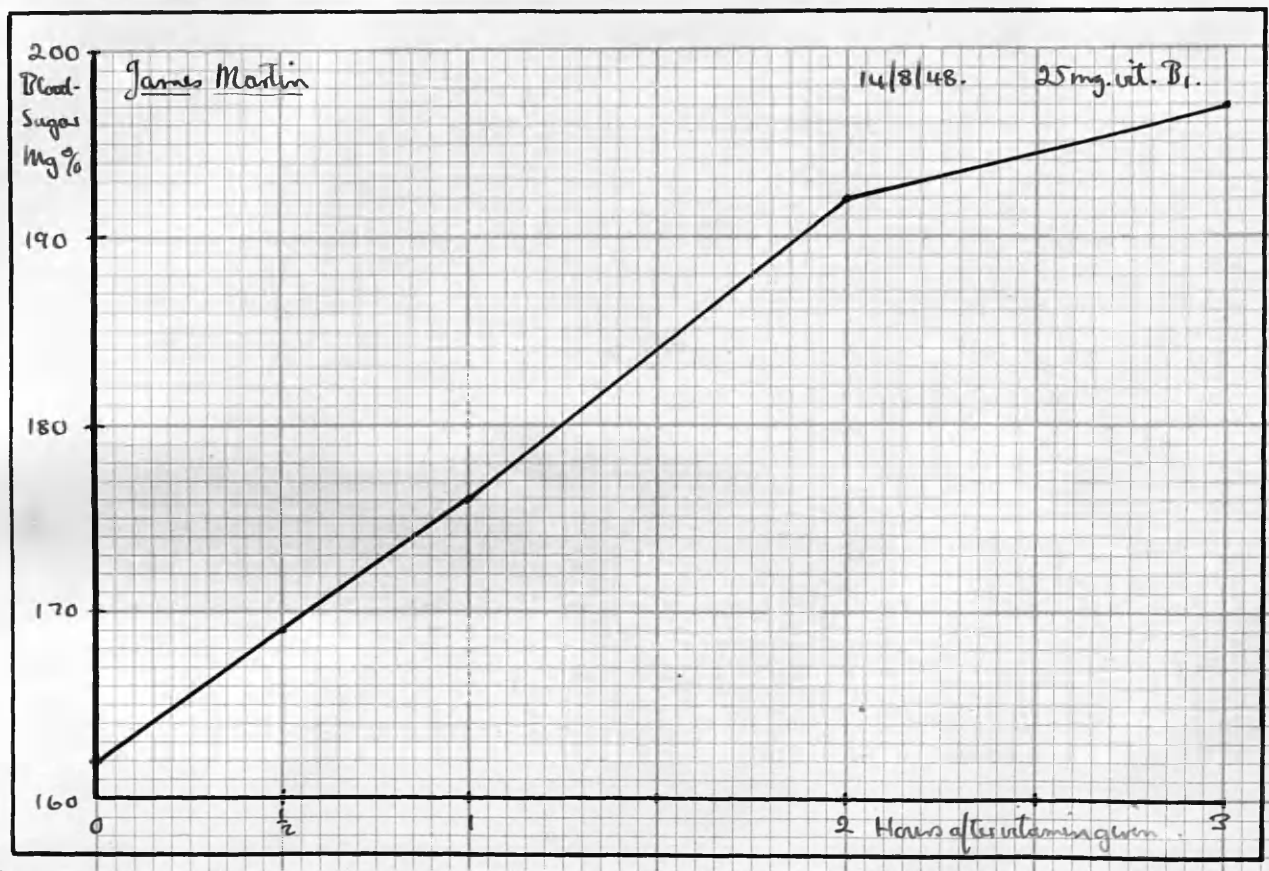
W.T., aged 63, was a mild diabetic receiving ten units S.I. twice daily.



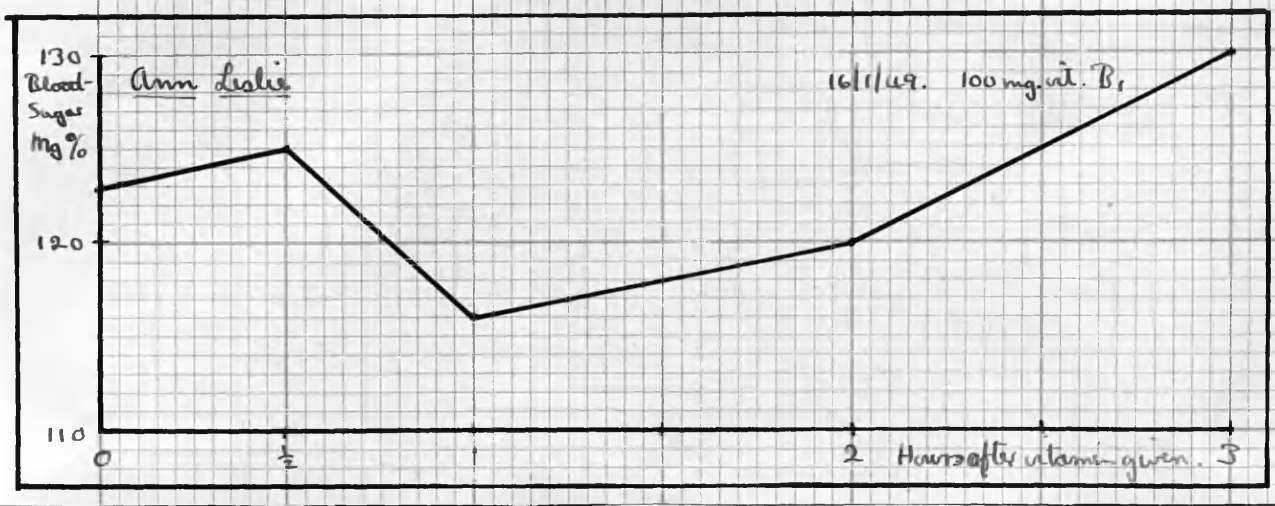
E.G., aged 27, had been receiving no insulin for her severe diabetes of four months' duration.



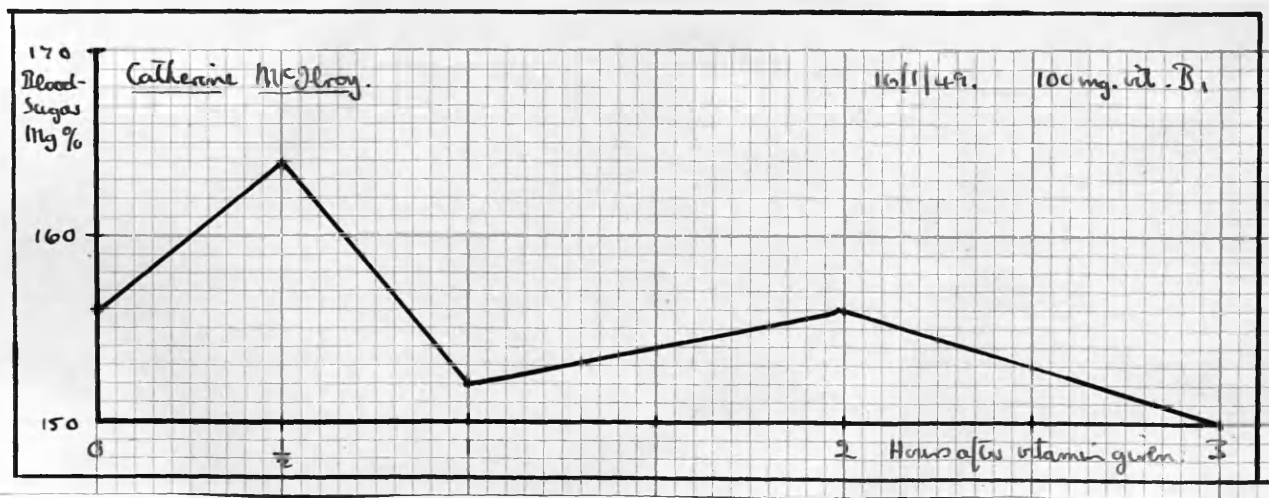
D.B., aged 35, was an acute diabetic who was not yet on insulin.



J.M., aged 19, was admitted twenty hours previously in hypoglycaemic coma. The insulin still seemed to be having some effect when this test was carried out. He was receiving 50 units S.I. and 30 units P.Z.I. daily for his diabetes of three years' duration.



A.L., aged 55, was a mild, obese diabetic who did not require insulin.



C.M., aged 47, had not yet been started on insulin for her glycosuria which had been discovered accidentally two weeks previously.

PHARMACOLOGY OF VITAMIN B₁

It is unfortunate that measuring the excretion of aneurin after large doses have been given is not a reliable method of estimating the degree of saturation of the body.

Aneurin is excreted in the urine, and much of it is washed out when a diuresis occurs in such conditions as untreated or badly treated diabetes mellitus. When used therapeutically, it must be given at least once a day to maintain an adequate concentration. Appreciable amounts of the vitamin are contained in perspiration.

A minimum of 1.35 mg. is required for a normal 3,000 Calorie diet. More vitamin B₁ is required in such physiological states as increased muscular activity, rapid growth, pregnancy and lactation. The raised basal metabolic rate in hyperthyroidism and infective conditions also increases its requirement. A satisfactory diet should therefore contain two mg. aneurin daily if possible.

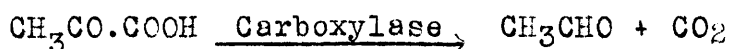
The carbohydrate content of the diet is an important factor in determining the daily requirements. The aneurin requirement is very small on a diet consisting entirely of protein and fat, and animals show signs of vitamin deficiency only when carbohydrate is added.

Vitamin B₁ is phosphorylated mainly in the liver and kidneys by enzymes through the agency of adenosine-triphosphate. The coenzyme cocarboxylase is formed. This is the coenzyme for the enzyme carboxylase.

ADENOSINE TRIPHOSPHATE + VITAMIN B₁ Phosphorylase →

ADENYLIC ACID + COCARBOXYLASE (VITAMIN B₁ PYROPHOSPHATE)

Carboxylase possibly consists of a protein, cocarboxylase and magnesium. It is the enzyme which causes decarboxylation of pyruvic acid to form carbon dioxide and acetaldehyde.



Coccarboxylase is also believed to be concerned in the synthesis of carbohydrate from lactic and pyruvic acids, in glycogenesis, and in the conversion of fructose to glucose in the liver. Aneurin is also necessary for the formation of fat from carbohydrate.

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- | | |
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ANEURIN AND BLOOD-SUGAR LEVELS OF ANIMALS.

ANEURIN AND BLOOD-SUGAR LEVELS OF ANIMALS.

Conflicting reports have been published on the effects of vitamin B₁ on the glucose metabolism of different animals. Summaries of the more relevant of these papers will now be given.

Demole and Silberschmidt found that the administration of 0.1 to 4 mg. vitamin B₁ had no effect on the blood-sugar level of normal rabbits, nor on the temporary hyperglycaemia produced by injecting glucose.

Magyar, on the other hand, found that aneurin given with an injection of glucose or galactose increased the rate of disappearance of the sugar from the blood of rabbits. It had no effect on the fasting blood-sugar, but usually intensified the hypoglycaemic action of insulin when injected at the same time. The same intensifying action was found with human diabetics. He suggested that vitamin B₁ assisted the cells of the body to take up sugar from the blood. It did not, he believed, increase the pancreatic output of insulin.

Liotta suggested that the vitamin seemed to normalise the blood-sugar of rabbits and pigeons. It had a hypoglycaemic effect after the administration of glucose, and intensified the blood-sugar reducing effect of insulin. The vitamin did not much influence the fasting blood-sugar.

Lowering of the blood-sugar with small doses, and hyperglycaemia with larger doses, were the findings of Ortoleva, working on rabbits. Roux found that injection of aneurin pyrophosphoric ester caused a 20 to 40% decrease in blood-sugar after a delay of about seven hours.

Janes and Brady found that aneurin deficiency had no definite effect on the blood-sugar levels of normal and alloxan-diabetic rats. The liver aneurin content of alloxan-diabetic rats was approximately one-third that of the average value found in normal animals (Bisceglie).

Glycogen was found to be absent from B₁-avitaminotic rats. Injections of vitamin B₁ and glucose brought about an accumulation of liver glycogen (Tonutti and Wallraff).

Lowry and Hegsted showed evidence that alloxan-diabetic rats required less vitamin B₁ than normal controls. They had no increased tendency to develop signs of aneurin deficiency, and the vitamin's action was not perceptibly impaired. Their study, therefore, did not support the theory that diabetic neuritis was due to aneurin deficiency.

Experimental vitamin B₁ deficiency did not effect carbohydrate tolerance, as judged by glucose tolerance tests, in either normal or diabetic rats, unless the degree of deficiency was extreme when the giving of aneurin appeared to improve carbohydrate tolerance (Styron et al.).

In normal rats, Lepkovsky et al. also found that glucose

tolerance was impaired only in the later stages of aneurin deficiency.

Inclusion of vitamin B₁ in the diet of albino rats, who were on diets deficient in various combinations of the vitamin B factors, increased the hypoglycaemic response to insulin. Variations in the intake of other vitamin B factors did not markedly alter the sugar tolerance of the rat (Burke and M^CIntyre).

Wein had found, contrary to the experience of most workers, that rats deprived of the vitamin B complex showed a greater hypoglycaemic reaction to insulin than those animals receiving a normal diet.

Harper observed a decrease in the rate of absorption of glucose from the intestine of aneurin deficient rats, with diminished hepatic glycogenesis and glycogenolysis. There was no significant difference in their blood-sugar levels.

Working with dogs, Chesler et al. found impaired glucose tolerance with both a mild and a severe aneurin deficiency. The post-absorptive blood-sugar level was high, and both lactic and pyruvic acids accumulated in the blood.

One or two mg. vitamin B₁ were daily injected subcutaneously for a month into guineapigs on a normal diet. Blood-sugar estimations at intervals of ten days showed a steady

rise. By the end of thirty days they were 120 to 125% of the original values. A marked reduction occurred in the liver glycogen content of these animals. These findings of Morelli and D'Ambrosio obviously contradict those of many other workers.

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ANEURIN IN NORMAL PERSONS AND DIABETICS.

ANEURIN IN NORMAL PERSONS AND DIABETICS.

The investigations on human beings have also given just as variable results. A summary of many of these papers will now be given.

Monauni claimed that intravenous aneurin raised the blood-sugar level when subnormal, and lowered it when it was elevated. De Lucia and Moreli found that the intravenous administration of vitamin B₁ reduced the blood-sugar of healthy persons, but had irregular results in those with liver disturbances. In diabetics, Ijiri believed that injections of vitamin B₁ slightly lowered the blood-sugar.

Wilson also experimented on healthy human subjects, however, and observed that the intravenous injection of ten mg. aneurin had no effect on the fasting blood-sugar level. The action on the fasting blood-sugar of ten units soluble insulin subcutaneously was intensified by the intravenous injection of twenty mg. vitamin B₁. The blood-sugar reached a lower level, and took longer to rise to its previous level. Three intramuscular injections each of ten mg. vitamin B₁ at twelve-hourly intervals before the insulin, had a similar intensifying effect. An intravenous injection of twenty mg. aneurin given simultaneously with an oral dose of glucose caused a distinctly greater rise of the blood-sugar level in six out of seven subjects for a period of 1½ hours after the dose; two hours after the dose the blood-sugar values

were the same, whether the vitamin had been given or not. These experiments, the author suggested, indicated that vitamin B₁ not only intensified the action of insulin, but also hastened the absorption of sugar.

Kodicek studied the effect of aneurin on the blood-sugar of 32 diabetics. The vitamin, either alone or in combination with insulin, did not affect the fasting blood-sugar of the patients nor increase the action of insulin. He gave ten mg. aneurin daily for four weeks to two diabetics with no improvement in their sugar tolerance or insulin requirement. While agreeing that a partial deficiency of vitamin B₁ is likely to be an incidental accompaniment of diabetes, he could not confirm that the use of aneurin to increase the sugar tolerance in diabetics was justified.

Six diabetics, previously stabilised on a constant diet with a constant dose of insulin, were studied by Dienst. They were given orally 240 units of vitamin B₁ per day in a proprietary preparation containing the vitamin B complex and vitamin C. The carbohydrate tolerance of every patient was improved to a degree corresponding with the effect of ten to twenty units of insulin a day. Smaller doses of the preparation had no effect. Fluctuations of the blood-sugar level were reduced, and the frequent severe hypoglycaemic reactions in two patients disappeared when the extra vitamins were given.

Sendrail and Marceillac gave both vitamin B₁ and C to ten diabetic cases. They concluded that ascorbic acid exerted a more rapid action than vitamin B₁ on the sensitivity of the individual to insulin. The two vitamins together seemed to reduce the glycosuria before the blood-sugars fell, as if the renal threshold for glucose had been raised.

Vorhaus et al. claimed "an increased utilisation of carbohydrates" in six out of eleven diabetics who were given orally ten mg. vitamin B₁ daily for four weeks. The facts that many of the patients lost weight and that their diets were changed during the experimental period made this investigation of little value.

A later report by Vorhaus admitted that the majority of diabetics did not benefit from aneurin administration. Only in those who showed some signs of deficiency was the vitamin of value.

In a series of ten well-controlled cases, three mg. daily of aneurin in addition to that received in the food had no significant effect on the blood-sugar of diabetics (Kaufman). He concluded that this vitamin was not indicated as a routine measure for diabetics.

Smith and Mason kept two severe diabetics on vitamin B₁ deficient diets. A third was given injections of glucose, with and without the addition of vitamin B₁. They were unable to find that aneurin had any effect on the intensity of

diabetes, or on the sensitivity of diabetics to the action of insulin.

Sciclounoff gave vitamin B₁ orally and parenterally to 35 diabetics. Twelve showed improvement of symptoms lasting for periods of several days up to some months. The rise in blood-sugar following glucose injections was stated to be less marked after the vitamin's administration. He believed that aneurin was at least a useful addition in the treatment of diabetic acidosis.

Williams et al. studied four subjects on a low aneurin diet for a prolonged period. In three, the blood-sugar tolerance curves reached diabetic levels. The curves returned to normal after administration of the vitamin. They had previously reported the same findings on four other subjects.

Bueding et al. gave similar findings. The average blood-sugar curve following glucose ingestion by fifteen aneurin-deficient subjects was significantly higher and more prolonged than that of 23 controls. In most, the blood-sugar level rose above the renal threshold.

Trasoff and Bordin found improved carbohydrate tolerance in five out of fifteen diabetics receiving 2 to 10 mg. vitamin B₁ daily. A careful analysis showed that the improvement could not be attributed, however, to the vitamin therapy. Similar results were reported by Costa and Mosuello.

Mosonyi and Aszodi claimed that the injection of five

mg. aneurin into diabetics produced an initial hyperglycaemia followed by a protracted fall in the blood-sugar level. The initial hyperglycaemia was abolished by the simultaneous administration of 300 mg. vitamin C. They gave seven moderate diabetics 300 to 2,000 mg. vitamin C and one to ten mg. vitamin B₁ daily. Daily blood and urinary sugar values were determined. It was found that the maintenance dose of insulin could be reduced after a few days. Sometimes the patient was able to keep the urine sugar-free without insulin for several weeks. Due to the variable dosage and poor control of their patients, however, their conclusions were not convincing.

Wilder believes that the diabetic probably requires more vitamin B₁ than is easily obtained in a mixed diet. He considers that additional doses of aneurin and riboflavin are of little value, except in cases with a previously deficient intake of these vitamins.

Von Drigalski also believed that the results of experiments on animals with B-avitaminosis could not be applied to human diabetes. After a poorly controlled investigation of ten diabetics, he believed that aneurin had no influence on the glycosuria, blood-sugar levels or insulin requirement.

To summarise these findings, one might say that although many reports have suggested that aneurin lowered the blood-sugar levels of diabetics and rendered them more sensitive

to insulin, numerous other papers have failed to confirm this. Treatment of diabetics with aneurin, therefore, will probably never be of any great practical value.

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RIBOFLAVIN AND BLOOD-SUGAR LEVELS.

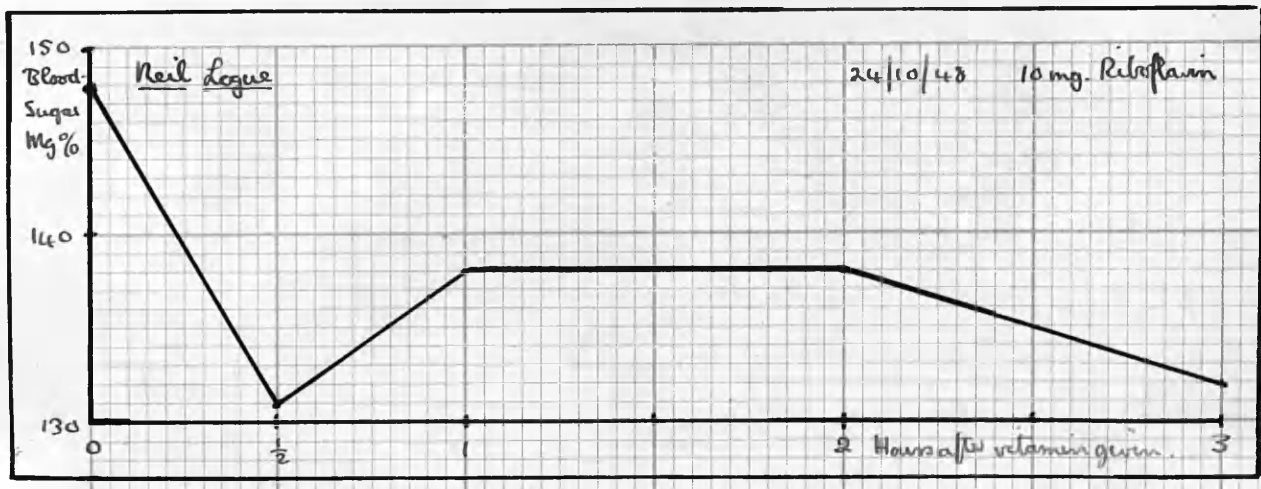
RIBOFLAVIN AND BLOOD-SUGAR LEVELS.

Since no important investigations have been published on the effect of riboflavin alone on diabetics, and since theoretically it seemed the least likely to be of any value, the blood-sugar curves were carried out only on four non-diabetic patients. Two received ten mg. and two received twenty mg. riboflavin intravenously.

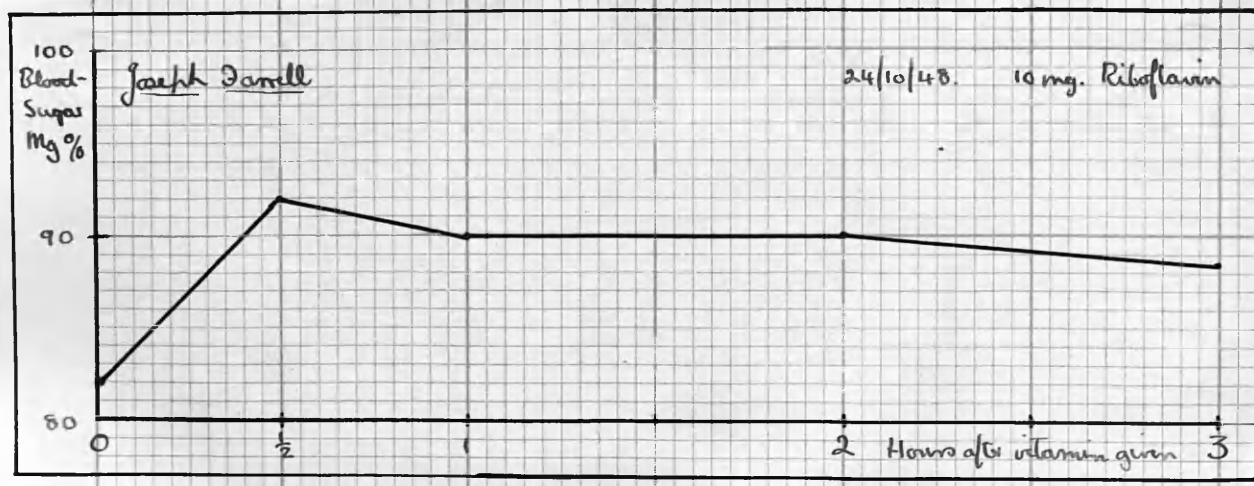
The results given in Table VII indicate that riboflavin has no significant effect on the blood-sugar levels of non-diabetic patients. Graphs of the blood-sugar curves follow the table.

Table VII

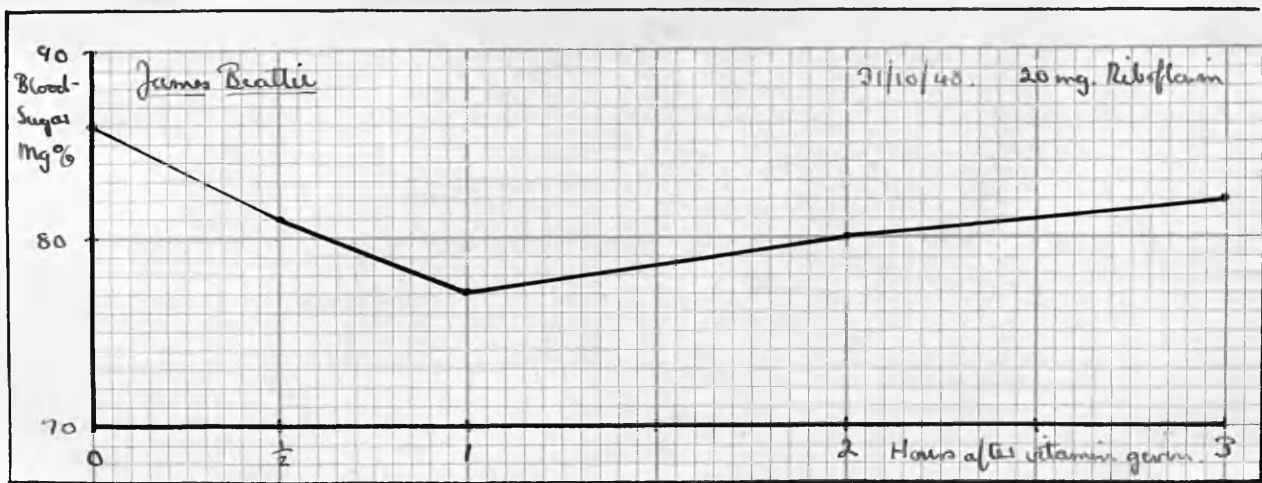
Patient's Initials.	Blood-Sugar Concentration Mg. %					Mean	Standard Deviation
	Time in Hours After Investigation/Commenced.						
	0	$\frac{1}{2}$	1	2	3		
N.L.	148	131	138	138	132	137	6.8
J.F.	82	92	90	90	88.5	88	3.9
J.B.	86	81	77	80	82	81	3.3
D.M.	86	83	90	98	96	91	6.4
Average Standard Deviation							5.1



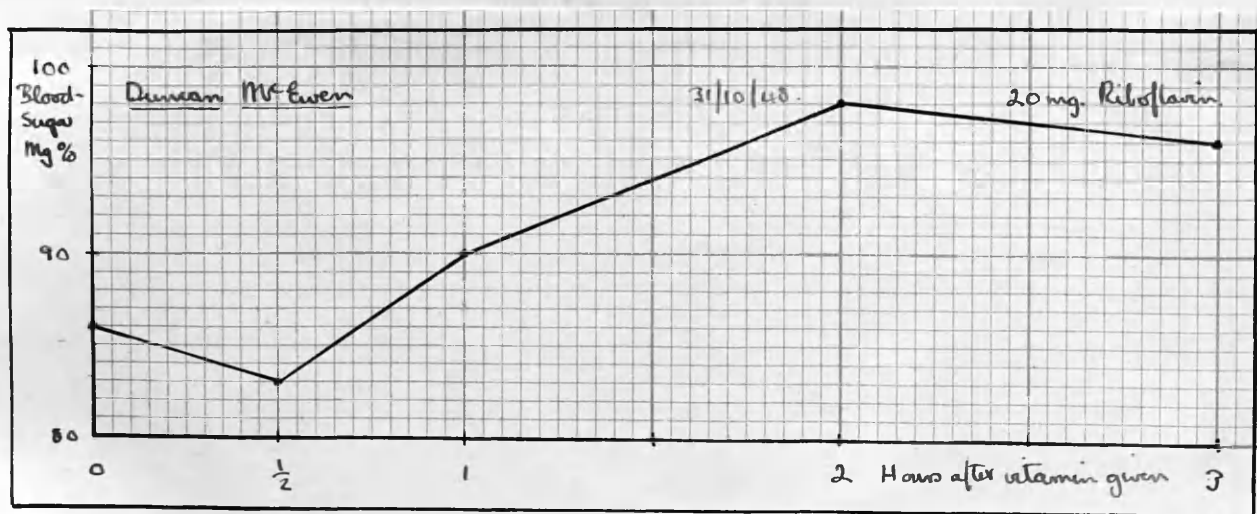
N.L., aged 61, had a cerebral embolism from which he died two days later.



J.F., aged 24, had a large pleural effusion of indefinite causation.



J.B., aged 51, had a large syphilitic aortic aneurysm.



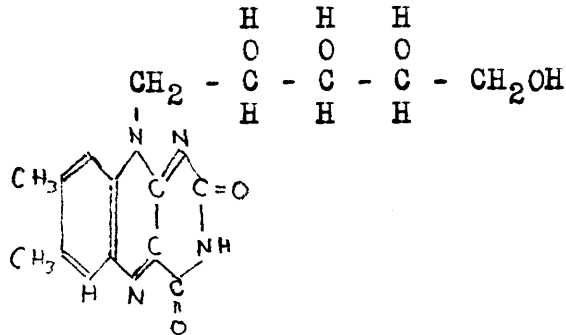
D.M., aged 62, was a case of congestive heart failure secondary to hypertension.

A brief summary of the pharmacology of riboflavin might now suitably be given.

PHARMACOLOGY OF RIBOFLAVIN.

PHARMACOLOGY OF RIBOFLAVIN.

Riboflavin is a fine, orange-yellow crystalline powder which has the structural formula:



It is only slightly soluble in water, and in solution is destroyed rapidly by light.

It is absorbed by phosphorylation from the small intestine. Absorption is impaired with gastro-intestinal lesions such as peptic ulcer or carcinoma, and where there is much vomiting or continued diarrhoea.

Riboflavin is excreted in the urine and sweat, and is destroyed in the large bowel. It is probably also synthesized to some extent in the human intestine.

About 2.5 to 3 mg. daily is a liberal allowance for a normal adult. Its requirement is increased by exercise, pregnancy, lactation, and a high fat diet. Hyperthyroidism, fever and diabetes mellitus are pathological conditions which increase the requirement.

Riboflavin combines with phosphoric acid, a specific protein and ribose to form the "yellow enzyme" as well as at least eight other coenzymes. These riboflavin enzymes

are dehydrogenases, which remove hydrogen from the nicotinic acid enzymes (coenzymes I and II). Using the cytochrome system, the hydrogen ions then combine with molecular oxygen to form water. The riboflavin enzymes thus take part in the carbohydrate metabolism, acting as coenzymes in the transference of hydrogen.

The stages in this process can be briefly stated as follows:

- (1) CARBOHYDRATE SUBSTRATE + NICOTINIC ACID ENZYME oxidation →
OXIDISED SUBSTRATE + REDUCED NICOTINIC ACID ENZYME.
- (2) REDUCED NICOTINIC ACID ENZYME + FLAVOPROTEIN dehydrogenation
(riboflavin enzyme) →
NICOTINIC ACID ENZYME + REDUCED FLAVOPROTEIN.
- (3) REDUCED FLAVOPROTEIN + CYTOCHROME SYSTEM + MOLECULAR
FLAVOPROTEIN + WATER. OXYGEN →

References.

- | | |
|------------------------------------|--|
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| Duncan, G.G. 1943. | Diseases of Metabolism. 1st Ed. |
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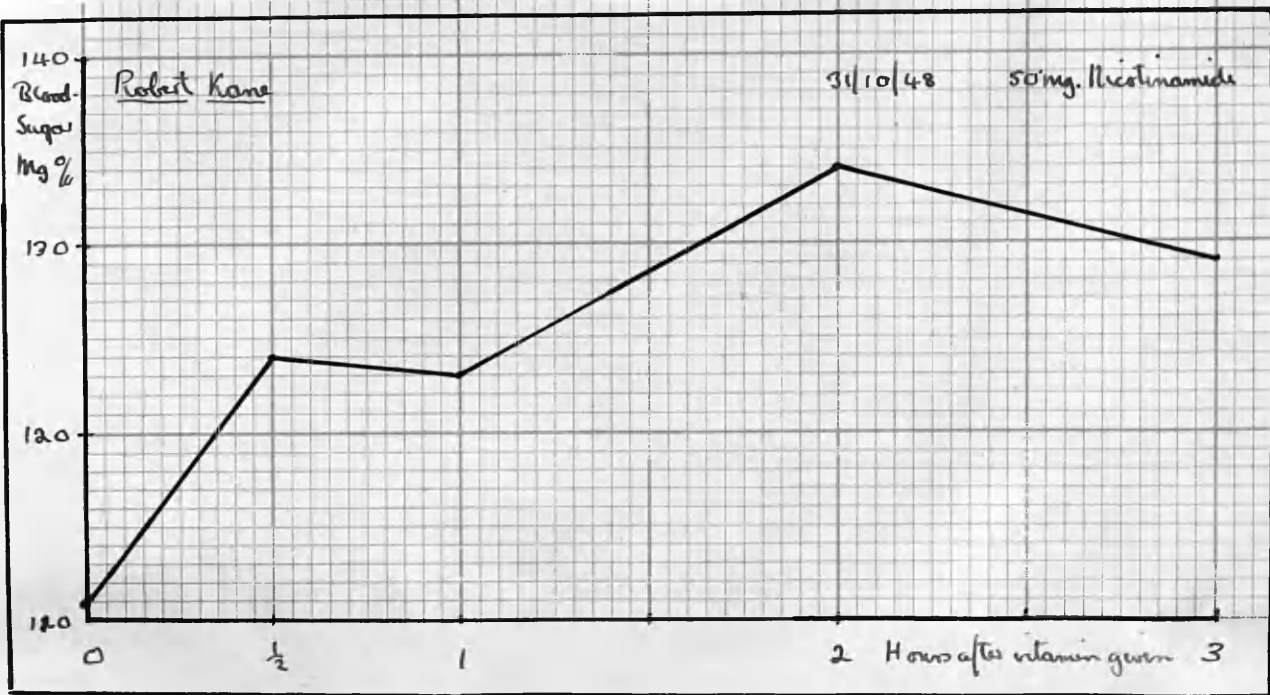
NICOTINAMIDE AND BLOOD-SUGAR LEVELS

NICOTINAMIDE AND BLOOD-SUGAR LEVELS

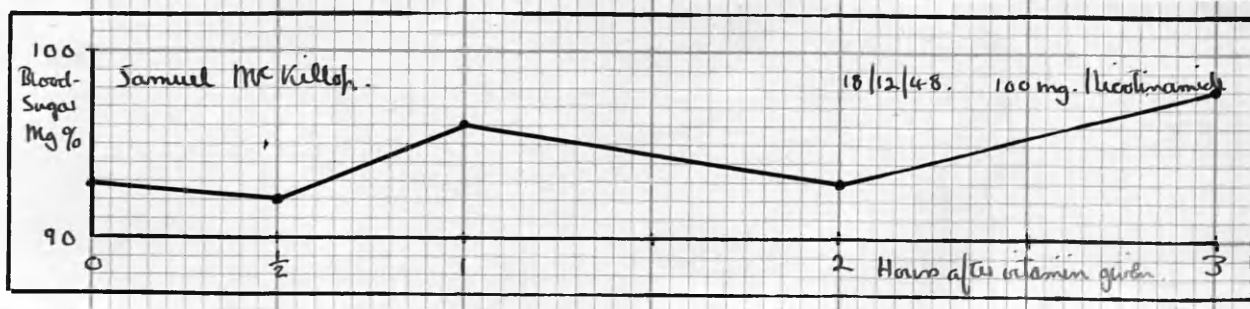
Nicotinamide was given intravenously in doses of fifty to 100 mg. to eighteen non-diabetic and six diabetic patients. The results are shown in Tables VIII and IX respectively. The average standard deviation suggests that nicotinamide has no significant effect on the fasting blood-sugar levels of diabetic and non-diabetic persons. The graphs of these patients follow the respective tables.

Table VIII

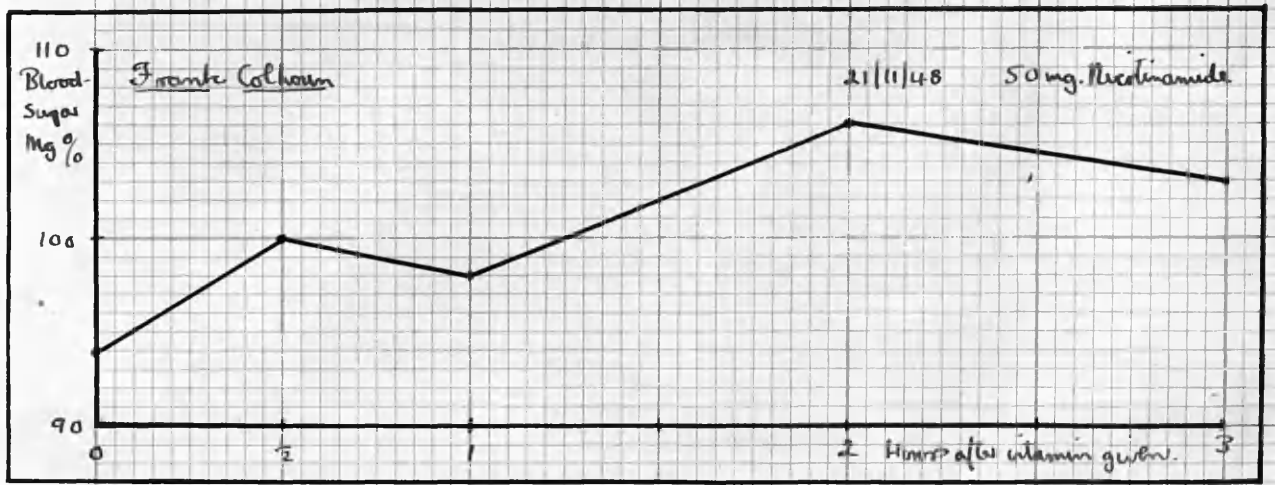
Patient's Initials.	Blood-Sugar Concentration Mg. %					Mean	Standard Deviation
	Time in Hours after Investigation Commenced.						
	0	$\frac{1}{2}$	1	2	3		
R.K.	111	124	123	124	129	124	8.6
S.M.	93	92	96	93	98	94	2.4
F.C.	94	100	98	106	103	101	4.7
G.M.	82	88.5	89.5	102	106	93	10.0
W.T.	102	106	105	98	80	98	10.6
J.D.	92	98	89	95.5	96	94	3.6
A.D.	68	68	60	65.5	68	66	3.5
J.M.	84	90	90	91	88	89	2.8
L.B.	96	101	100	102	106	101	3.6
A.H.	93	97	100	105	100	99	4.4
J.D.	101	119	118	109	119	113	8.0
N.L.	112	104	112	112	116	111	4.4
A.L.	96	92	100	93	104	97	3.8
H.A.	84	82	81	86	88	84	2.9
P.C.	96	100	104	102	100	100	3
D.L.	93	80	82	89	94	88	6.4
W.C.	109	110	105	106	105	105	3.2
A.M.	96	100	101	102	100	100	2.3
Average Standard Deviation						4.9	



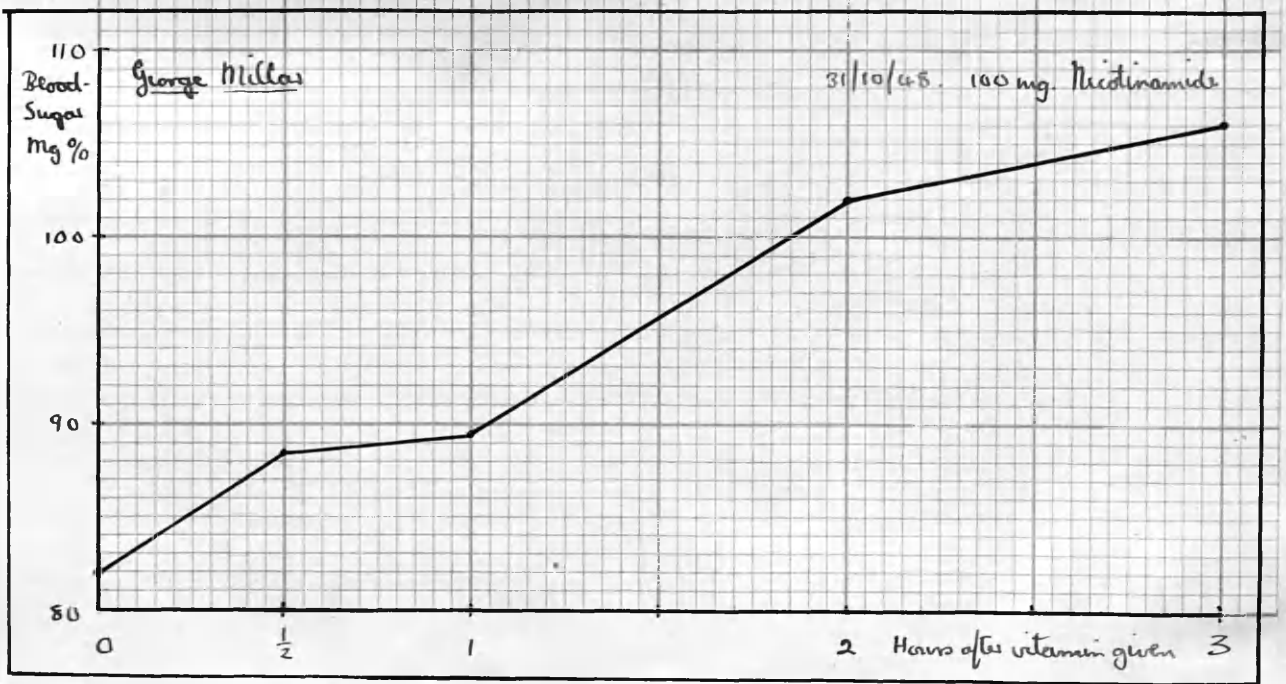
R.K., aged 31, had symptoms of a duodenal ulcer for six years.



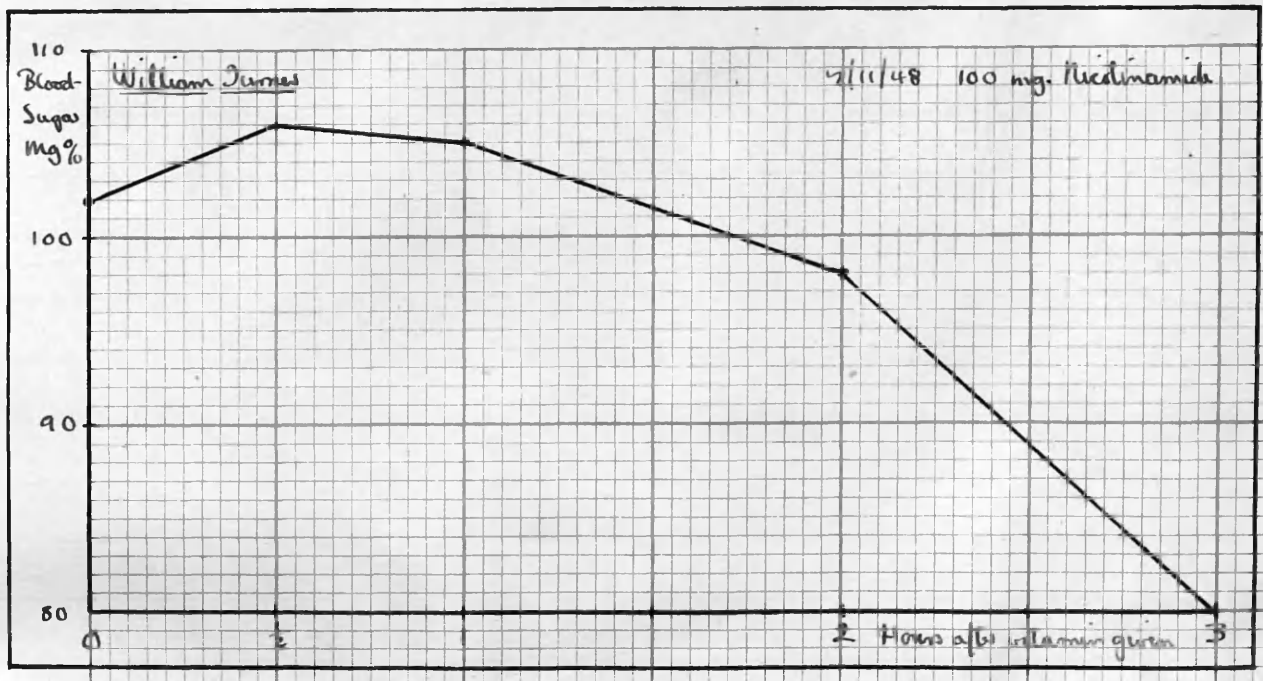
S.M., aged 41, had a mild acute nephritis for one month.



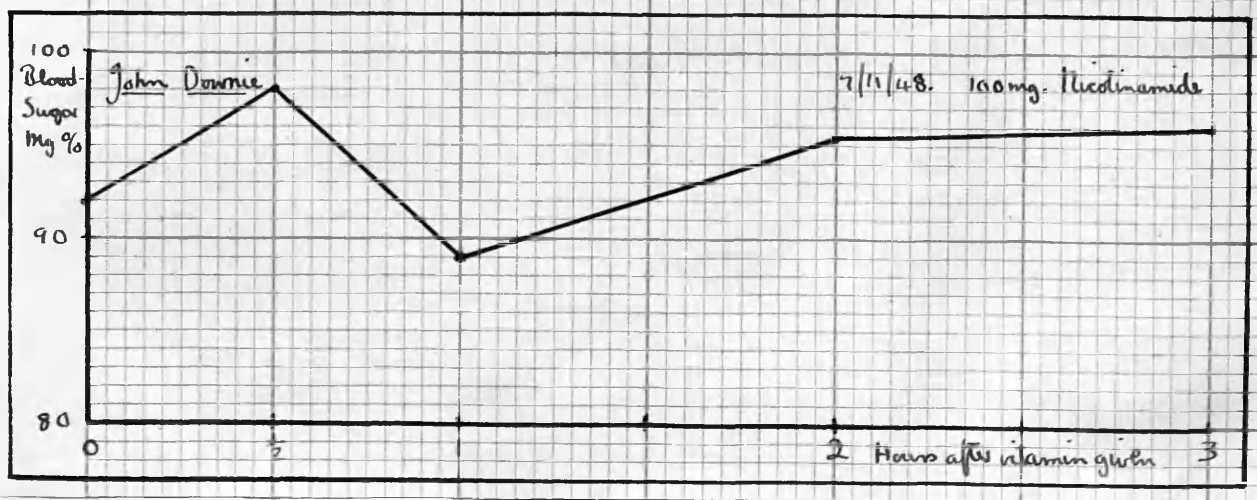
F.C., aged 38, had an acute rheumatism of three weeks' duration.



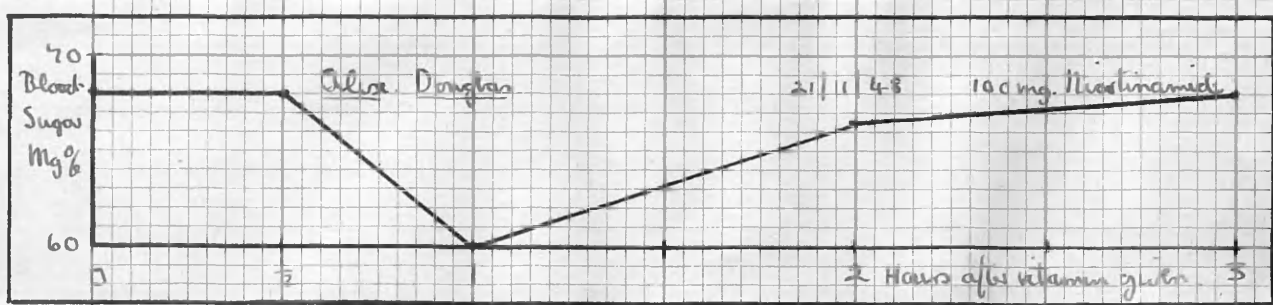
G.M., aged 51, had symptoms of a mild coronary thrombosis.



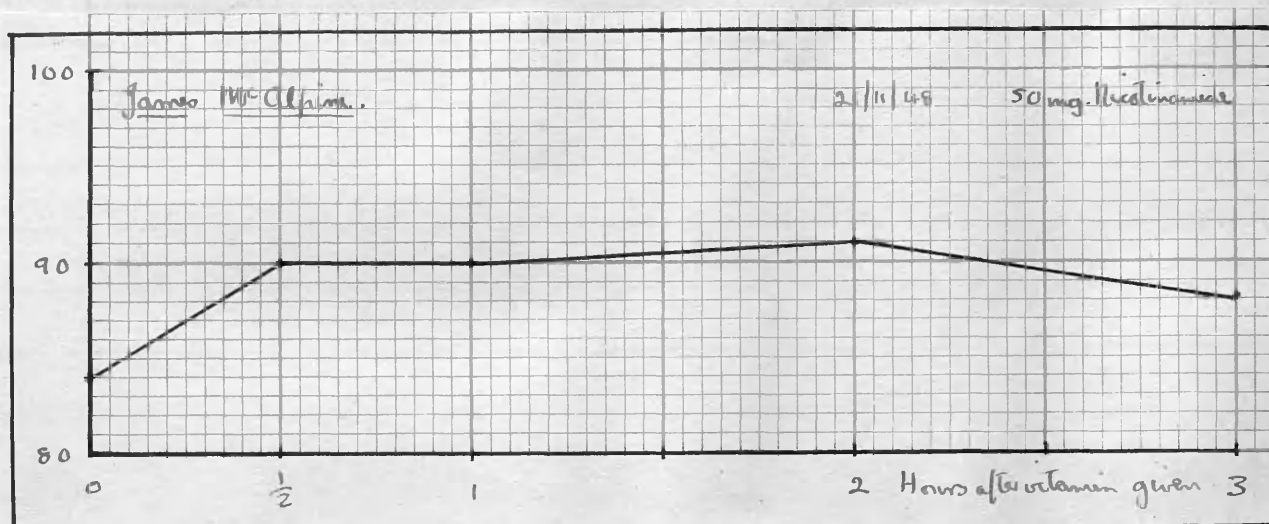
W.T., aged 45, was a mild encephalitis case of unknown etiology.



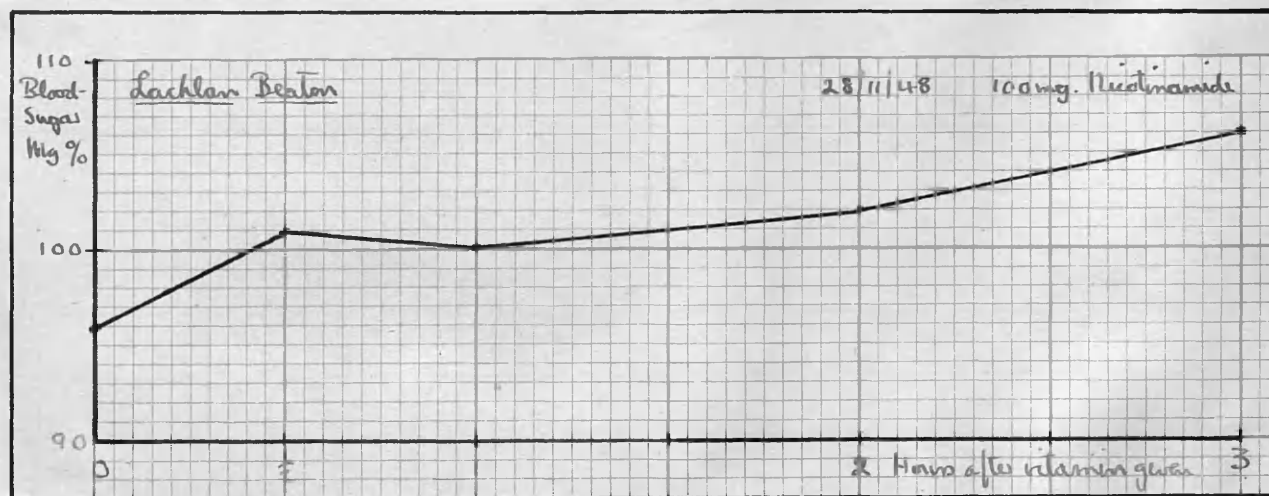
J.D., aged 34, had a right idiopathic sciatica for nine weeks.



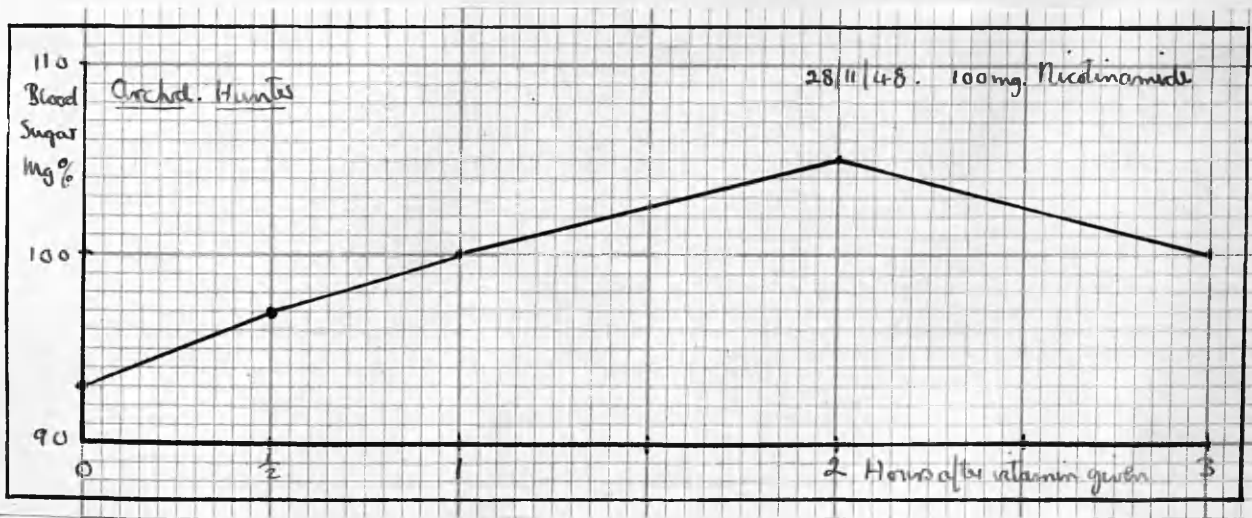
A.D., aged 50, had a mild steatorrhoea following a partial gastrectomy.



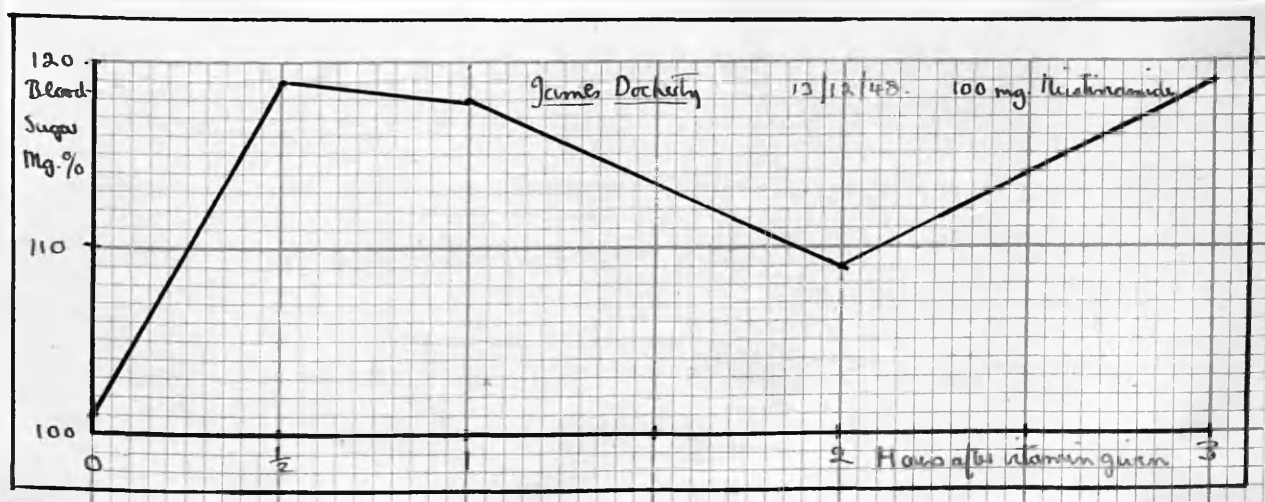
J.M., aged 53, had a rheumatoid arthritis for 2 1/2 years.



L.B., aged 30, had a diarrhoea of uncertain etiology.



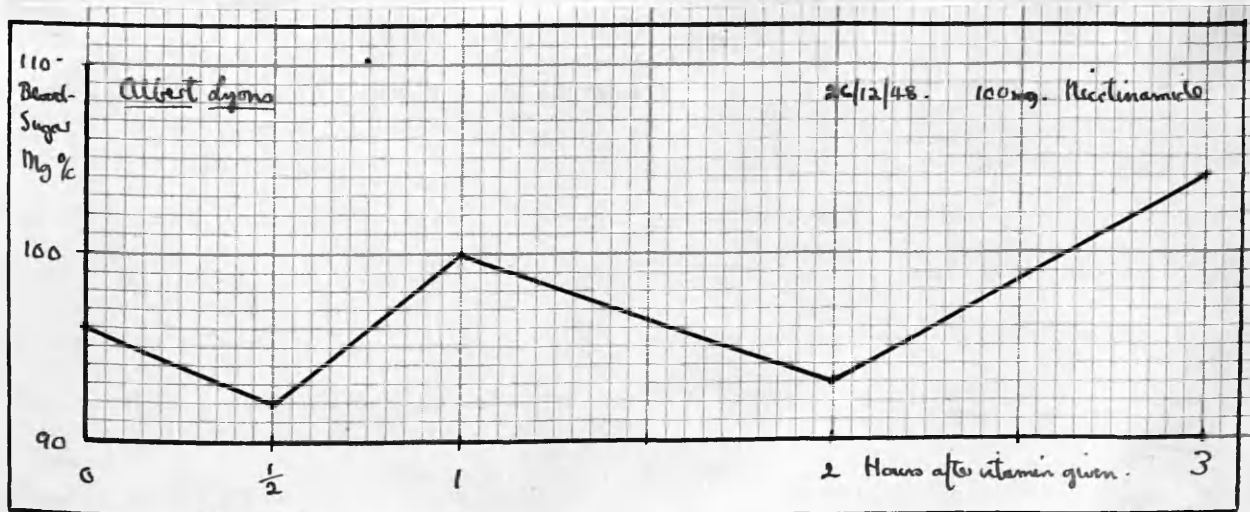
A.H., aged 39, was a case of gastric neurosis.



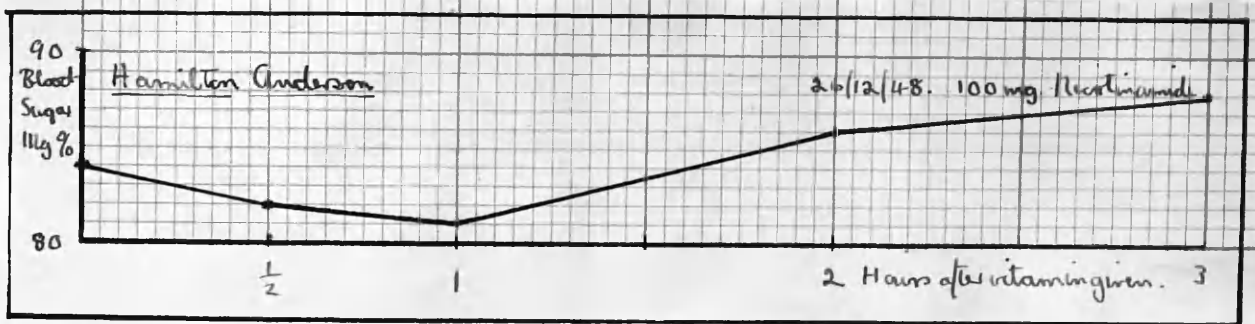
J.D., aged 25, had a duodenal ulcer.



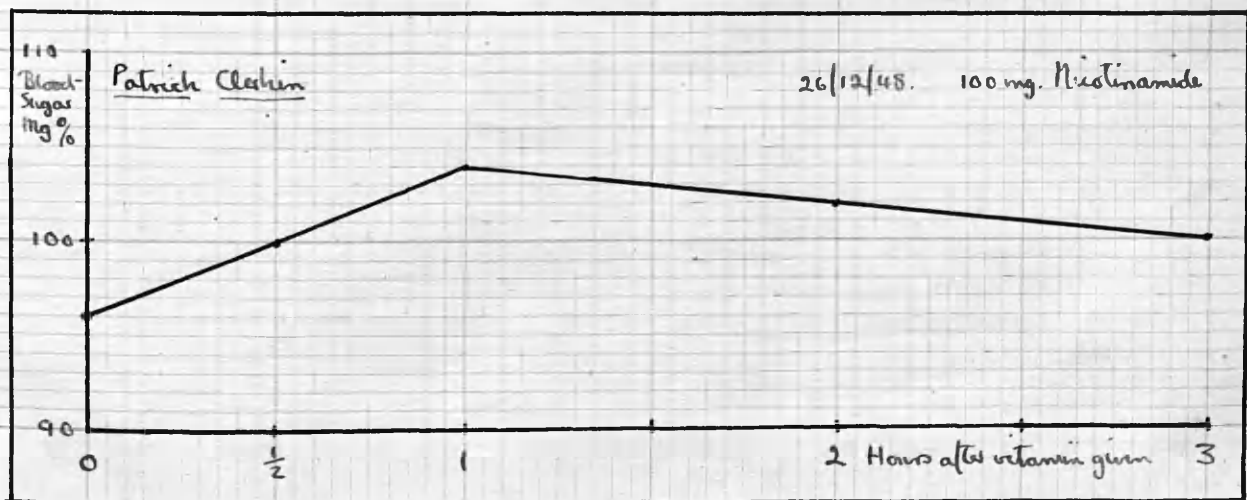
N.L., aged 64, was a case of myocardial degeneration.



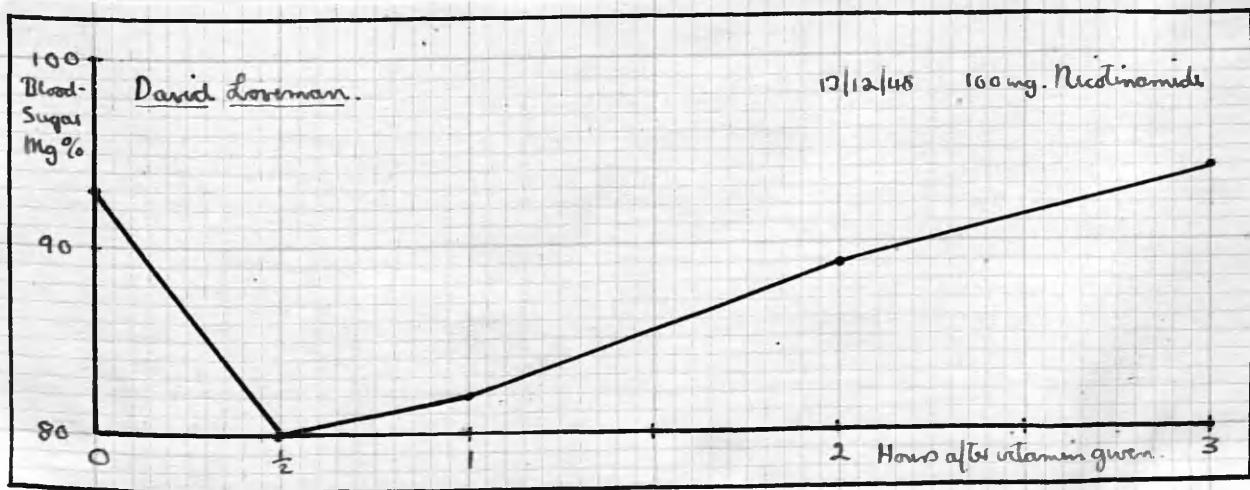
A.L., aged 26, had a benign lymphocytic meningitis.



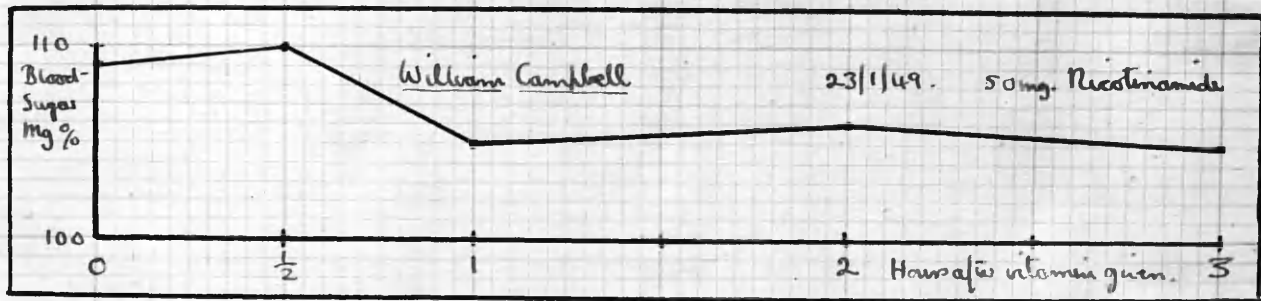
H.A., aged 28, had a duodenal ulcer and haematemesis.



P.C., aged 33, was quite normal.



D.L., aged 48, had a deep gastric ulcer.



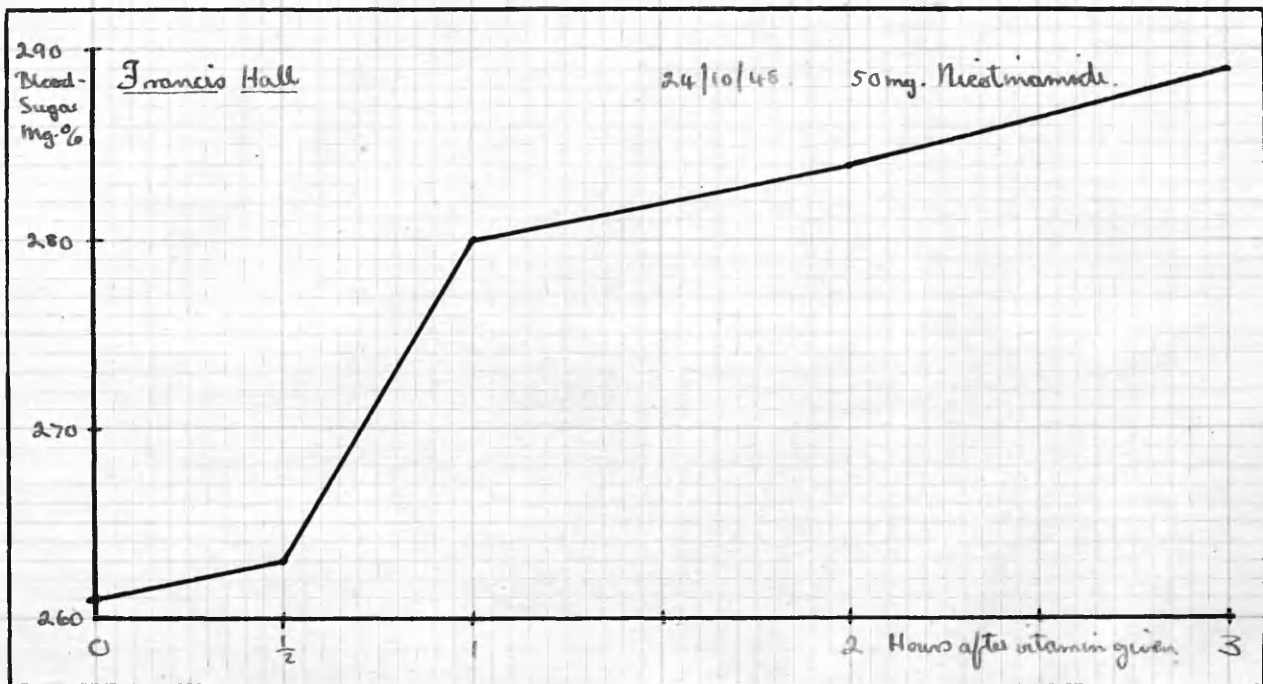
W.C., aged 35, had a large pleural effusion.



A.M., aged 50, had a paroxysmal tachycardia .

Table IX.

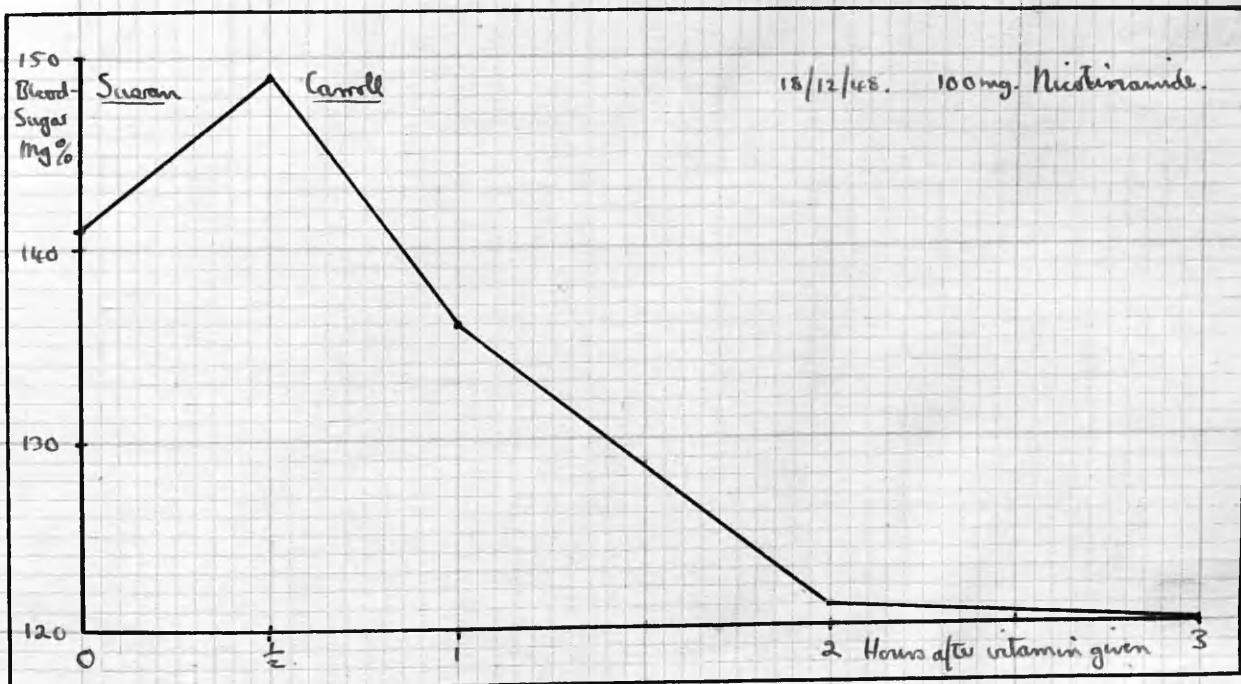
Patient's Initials.	Blood-Sugar Concentration Mg. %					Mean	Standard Deviation
	Time in Hours After Investigation Commenced.						
	0	1/2	1	2	3		
F.H.	261	263	280	284	289	275	12.7
C.W.	232	238	258	245	240	243	9.8
S.C.	141	149	136	121	120	133	12.7
M.B.	192	200	197	196	210	199	6.9
C.B.	140	148	155	144	152	148	6.0
K.W.	300	299	296	286	272	291	12.0
Average Standard Deviation						10.0	



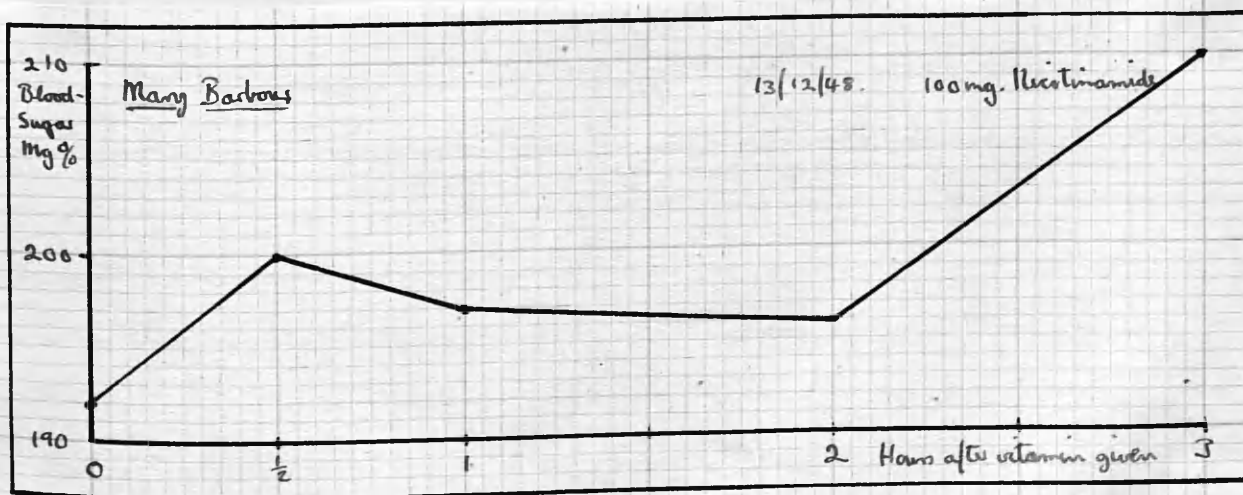
F.H., aged 35, was taking 30 units S.I. and 15 units P.Z.I. daily for his diabetes of five years' duration.



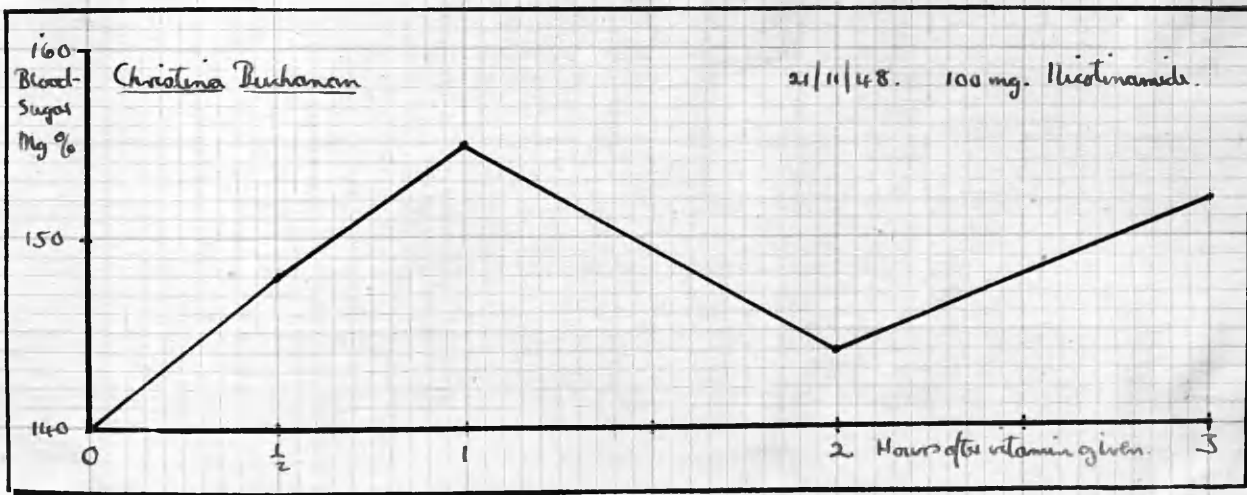
C.W., aged 67, had not yet been started on insulin for her glycosuria of nine weeks' duration.



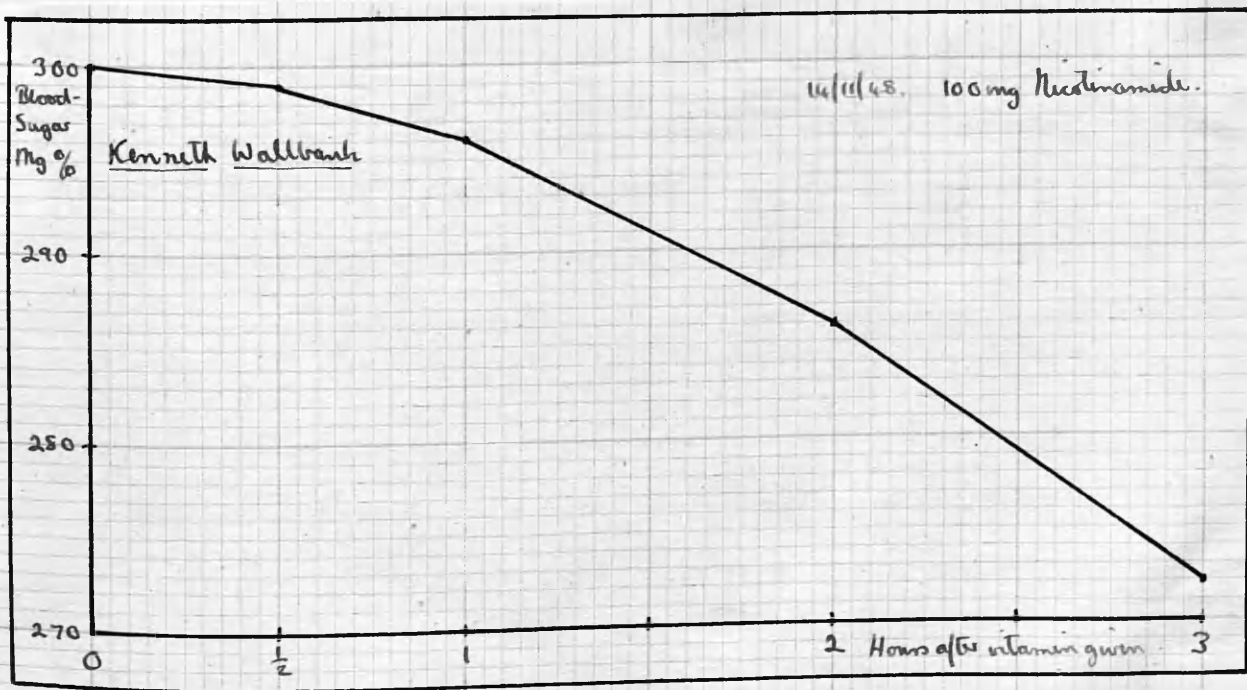
S.C., aged 66, shows an interesting but not statistically significant fall in her blood-sugar level.



M.B., aged 71, was treated by diet for her glycosuria of sixteen years' duration.



C.B., aged 50, was a newly-discovered diabetic.



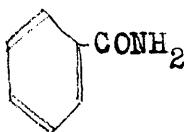
K.W., aged 25, shows an interesting fall in his blood-sugar level, confirmed by repeating the estimations. He had been a diabetic for four years, fairly well controlled on a sixteen line diet with 30 units S.I. and 15 units P.Z.I. daily.

PHARMACOLOGY OF NICOTINAMIDE.

PHARMACOLOGY OF NICOTINAMIDE.

A short summary of the pharmacology of nicotinamide will now be given.

Nicotinamide, also called nicotinic acid amide and niacin, is a stable white substance with the structural formula:



It is probably synthesized to some extent in the human intestine. It is excreted in the urine and sweat.

Nicotinamide combines with adenine, ribose and phosphoric acid to form two coenzymes named coenzyme I (also called codehydrogenase I or cozymase) with two phosphoric acid molecules, and coenzyme II (also named codehydrogenase II) with three phosphoric acid molecules.

These coenzymes catalyse the dehydrogenation of various carbohydrate substrates by absorbing two atoms of hydrogen. The hydrogen atoms are handed on to the riboflavin enzymes, which combine the hydrogen with oxygen to form water. The coenzymes are also involved in phosphorylation and pyruvic acid oxidation.

The present beliefs about the action of nicotinamide may therefore be summarised as follows. Coenzyme I or

diphosphopyridine nucleotide, and coenzyme II or triphosphopyridine nucleotide both contain nicotinamide. Both of these coenzymes act with a large number of apoenzymes, which include the riboflavin enzymes described previously. Each apoenzyme acts on a specific carbohydrate substrate, and each substrate has its own dehydrogenase.

Reduction or hydrogenation of the coenzymes occurs when they accept two atoms of hydrogen from the carbohydrate substrate. Dehydrogenation then follows, when the hydrogen atoms are passed on to other hydrogen acceptors, which may be the riboflavin enzymes or other metabolites. The coenzymes, therefore, simply act as intermediaries in the transference of hydrogen from one compound to another.

The processes in this stage of carbohydrate metabolism can be even more briefly shown as follows:

- (1) SUBSTRATE + COENZYME \longrightarrow OXIDISED SUBSTRATE +
REDUCED COENZYME.
- (2) REDUCED COENZYME + FLAVOPROTEIN \longrightarrow
COENZYME + REDUCED FLAVOPROTEIN.
- (3) REDUCED FLAVOPROTEIN + CYTOCHROME SYSTEM + MOLECULAR
OXYGEN \longrightarrow
FLAVOPROTEIN + WATER.

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NICOTINAMIDE AND THE BLOOD-SUGAR LEVELS OF ANIMALS.

NICOTINAMIDE AND THE BLOOD-SUGAR LEVELS OF ANIMALS

Greco injected nicotinic acid intravenously into fasting dogs. Small doses increased the blood-sugar level, but the rise was less marked with large doses.

A mild hypoglycaemic effect of nicotinic acid on various animals was reported by Boldyreff, the hypoglycaemic action being most marked in turtles.

Burke and McIntyre found that nicotinic acid decreased markedly the duration of hypoglycaemia in rats following the injection of a standard dose of insulin.

That the intravenous injection of nicotinic acid prevented the diabetogenic action of alloxan in five rabbits and six rats, was reported by Banerjee. He thought it possible that nicotinic acid might play some part in the prevention of diabetes. This was based on the suggestion of Dunn et al. that possible defects in the metabolism of purines or of alloxan in man might play some role in the etiology of diabetes. Sufficient nicotinic acid in the diet might prevent the action of alloxan.

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| Banerjee, S. 1947. | Science <u>106</u> , 129. |
| Boldyreff, E.B. 1944. | J. A. M. A. <u>124</u> , 257. |
| Burke, J.C. and
McIntyre, A.R. 1939. | J. Pharmacol. and
Exp. Ther. <u>67</u> , 142. |
| 1938. | Ibid. <u>64</u> , 465. |

(Contd.)

Dunn, J.S. et al. 1943.

J.Path.Bact. 55, 245.

Greco, D. 1939.

Boll.Soc.ital.Biol.sper. 14,403.

NICOTINAMIDE IN NORMAL AND DIABETIC PERSONS.

NICOTINAMIDE IN NORMAL AND DIABETIC PERSONS.

Once again the results of the different investigators are confusing.

Crino and Lenzi found that injections of nicotinamide temporarily increased the blood-sugar in normal people and diabetics.

Subcutaneous insulin had a more pronounced and prolonged effect in pellagrins than in normal subjects (Mainzer). The administration of glucose to pellagrins produced blood-sugar values similar to those produced in normal subjects.

The papers of Sydenstricker et al., and of Vilter et al. indicate that nicotinamide deficiency is often present in diabetics with ketosis or other complications.

The results of Neuwahl published in 1943 are startlingly different from those of many other reliable investigators. The intramuscular and intravenous injection of nicotinamide caused a marked fall in the fasting blood-sugar of nine healthy adults. The venous blood-sugar fell much more than the arterial blood-sugar. He considered that this indicated that the activity of endogenous insulin had been increased by the nicotinamide. The vitamin greatly increased the response of three non-diabetic patients to two units of insulin. Larger intravenous doses of nicotinamide caused intense hyperglycaemia without glycosuria in three fasting healthy subjects. The carbohydrate tolerance of twelve elderly

diabetics improved with nicotinamide therapy. He describes three of these cases in whom the improvement was remarkable.

Further communications by Neuwahl in 1947 are less enthusiastic. The theories which he puts forward on the subject are not impressive. One does not feel that the results of this investigator can be taken too seriously.

W.Gordon reported enthusiastically on one mild diabetic who improved considerably on large oral doses of nicotinamide. He believed that the nicotinamide increased the activity of those islets of Langerhans which were still functioning, but made the rather ambiguous statement that the greater insulin production may not affect the glucose tolerance curve.

L.Gordon described the beneficial effect of nicotinamide on one diabetic and a case of renal glycosuria.

In a paper describing the treatment of thirty diabetics with oral nicotinamide in large doses, Talast agreed with W.Gordon that the vitamin could replace insulin in the treatment of mild elderly diabetics. Nicotinamide enabled a reduction in insulin dosage to be made in more severe cases.

Wade reported no improvement in six mild diabetics who were given large oral doses of nicotinamide for a fortnight. He concluded that nicotinamide alone does not influence the sugar tolerance or improve the diabetic condition. This conclusion could have been given more weight if the number of subjects had been larger and the time of investigation longer.

A short report by Cumings showed that nicotinamide had no effect on the fasting blood-sugar level or blood ceenzyme content of three normal subjects. The opinion is thus becoming more generalised that nicotinamide can have no beneficial effect on most diabetics.

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\emptyset Not consulted in the original.

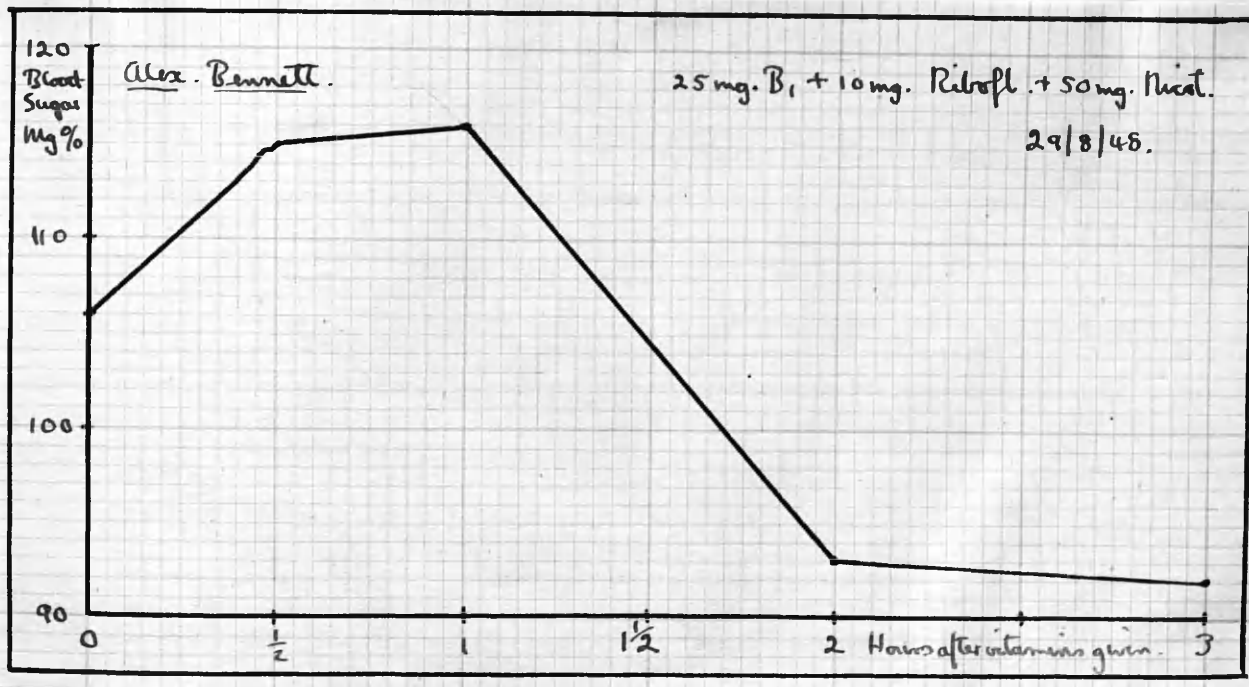
THE SIMULTANEOUS ADMINISTRATION OF
ANEURIN, RIBOFLAVIN, AND NICOTINAMIDE.

THE SIMULTANEOUS ADMINISTRATION OF
ANEURIN, RIBOFLAVIN AND NICOTINAMIDE

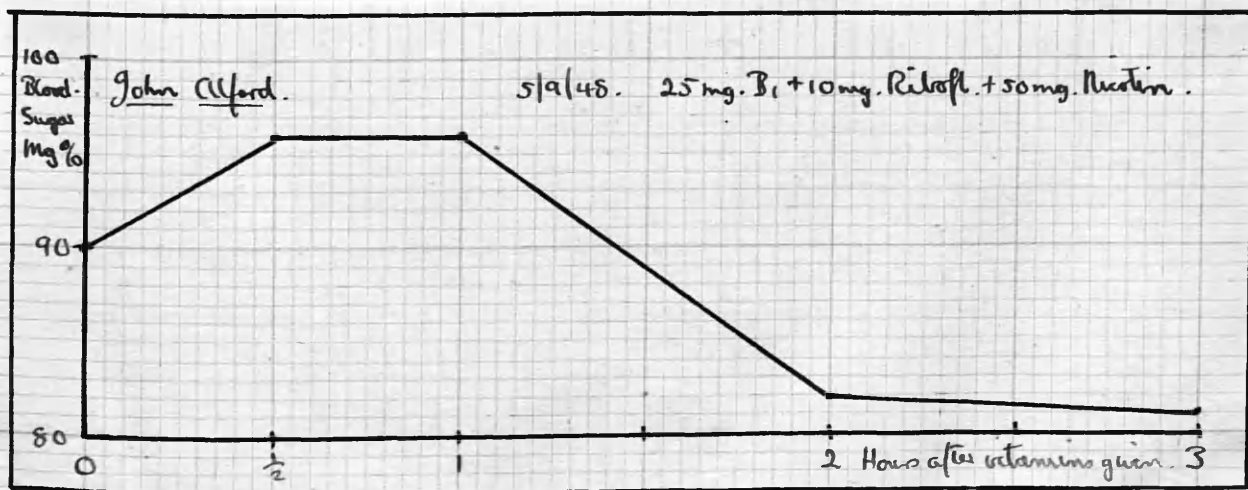
Since the three vitamins separately had been shown to have no definite effect on blood-sugar levels, it remained to be seen whether the three together produced any change. This was carried out on fourteen non-diabetic patients and three diabetics, who were each given 25 mg. aneurin, ten mg. riboflavin and 50 mg. nicotinamide intravenously. The results are given in Tables X and XI respectively. These indicate that aneurin, riboflavin and nicotinamide administered simultaneously have no significant effect on the fasting blood-sugar levels of diabetic and non-diabetic persons.

Table X

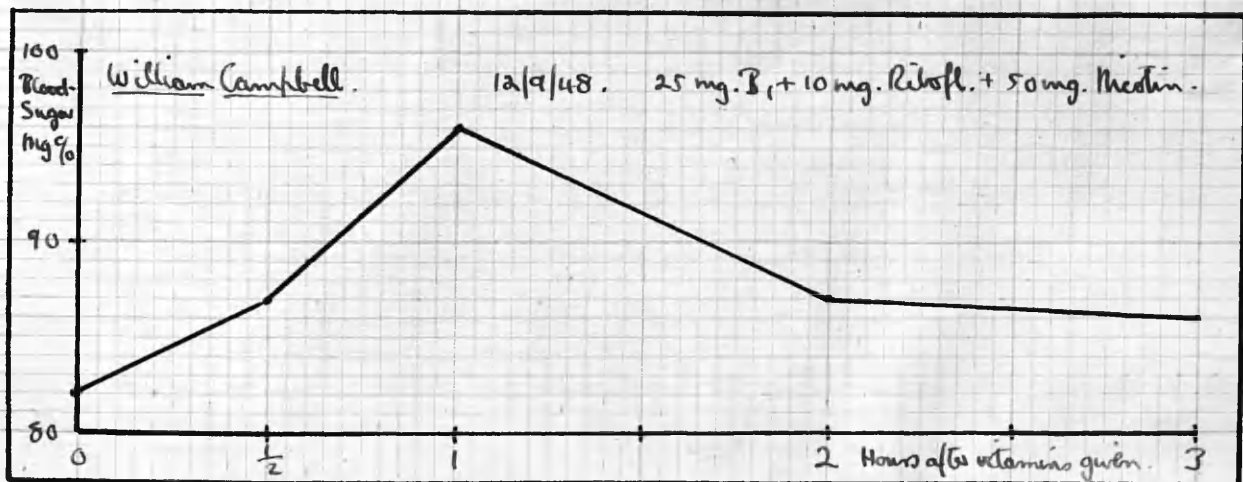
Patient's Initials	Blood-Sugar Concentration Mg.%					Mean	Standard Deviation
	Time in Hours after Investigation Commenced.						
	0	$\frac{1}{2}$	1	2	3		
A.M.	118	119	104	101	114	111	8.2
A.B.	106	115	116	93	92	104	11.6
J.A.	90	96	96	82	81	89	7.3
W.C.	82	87	96	87	86	88	5.0
R.M.	81	86	92	82	83	85	4.4
G.H.	82	87	104	100	106	96	10.7
H.M.	58	60	66	60	63	61	3.2
E.F.	70	62	61	78	83	71	9.7
J.M.	81	84	94	99	95	91	7.7
G.A.	100	96	88	80	79	89	9.4
D.B.	129	136	124	128	121	128	5.7
J.F.	96	87	86	90	88	89	4.0
E.C.	75	89	73	71	72	76	7.4
A.C.	97	104	108	98	91	100	6.6
Average Standard Deviation						7.2	



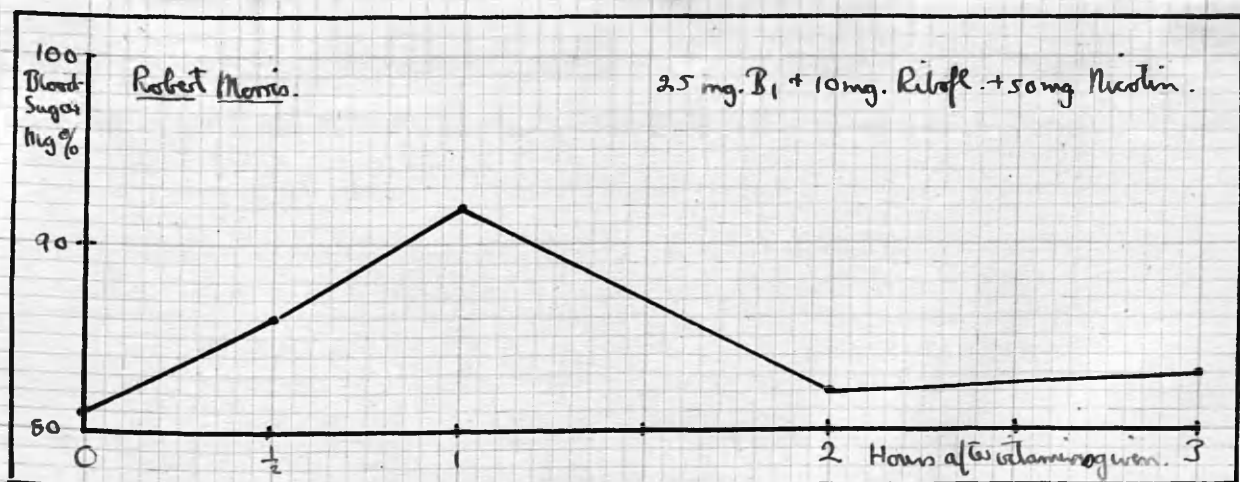
A.B., aged 62, had a cerebral thrombosis and right hemiplegia.



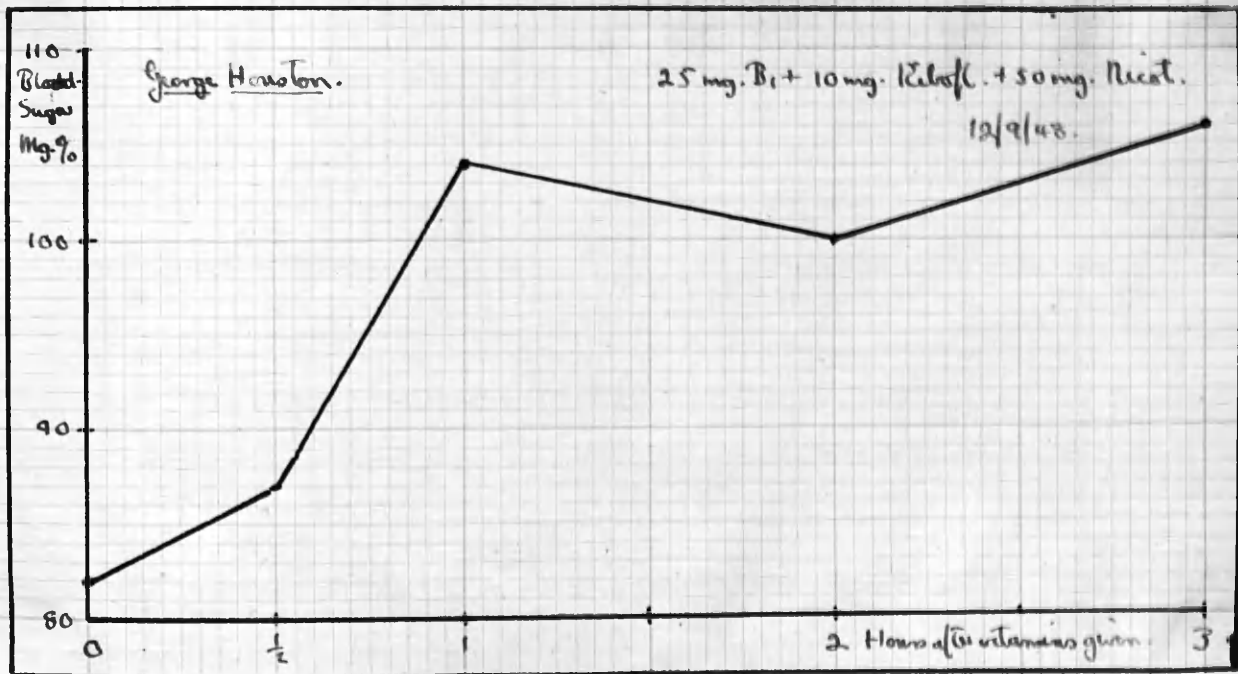
J.A., aged 49, had a tuberculous spine.



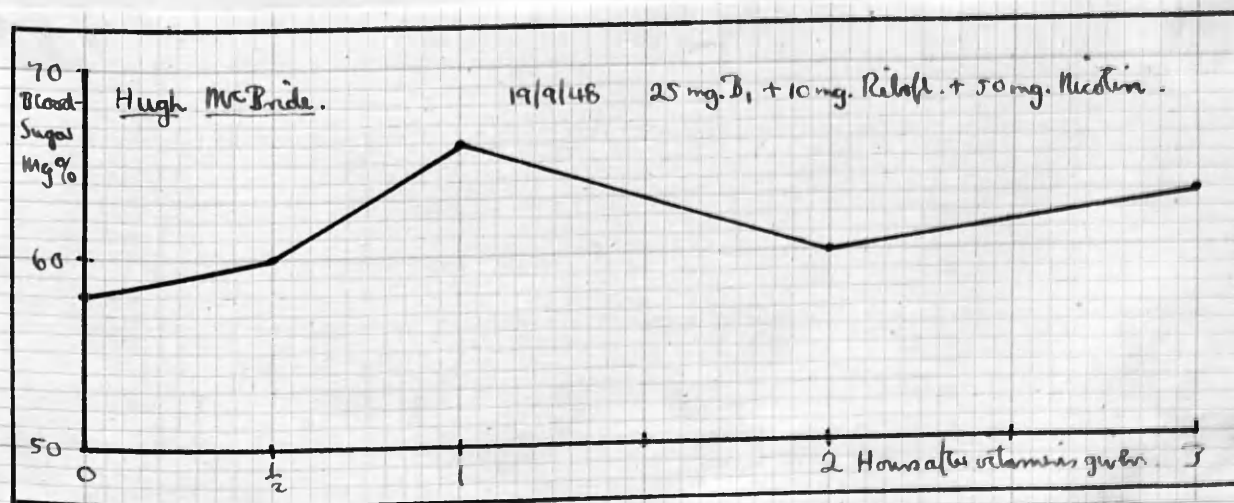
W.C., aged 46, had a bronchogenic carcinoma with spread to the cervical glands.



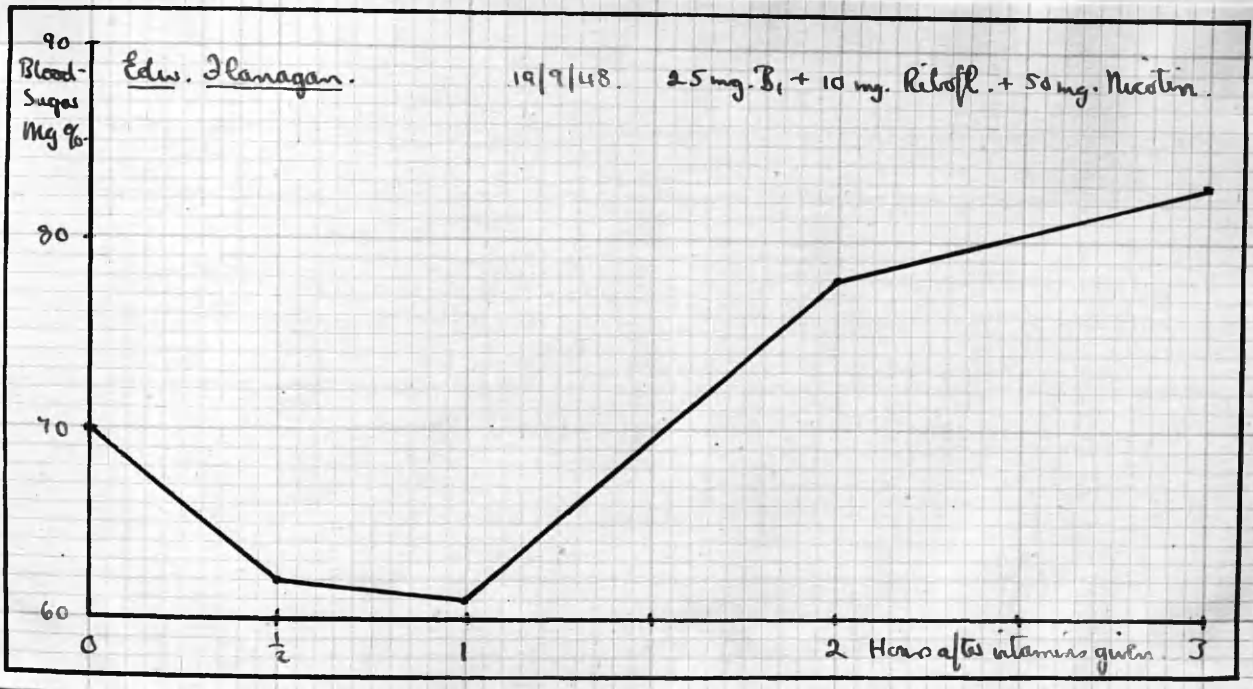
R.M., aged 58, was a case of aspirin poisoning.



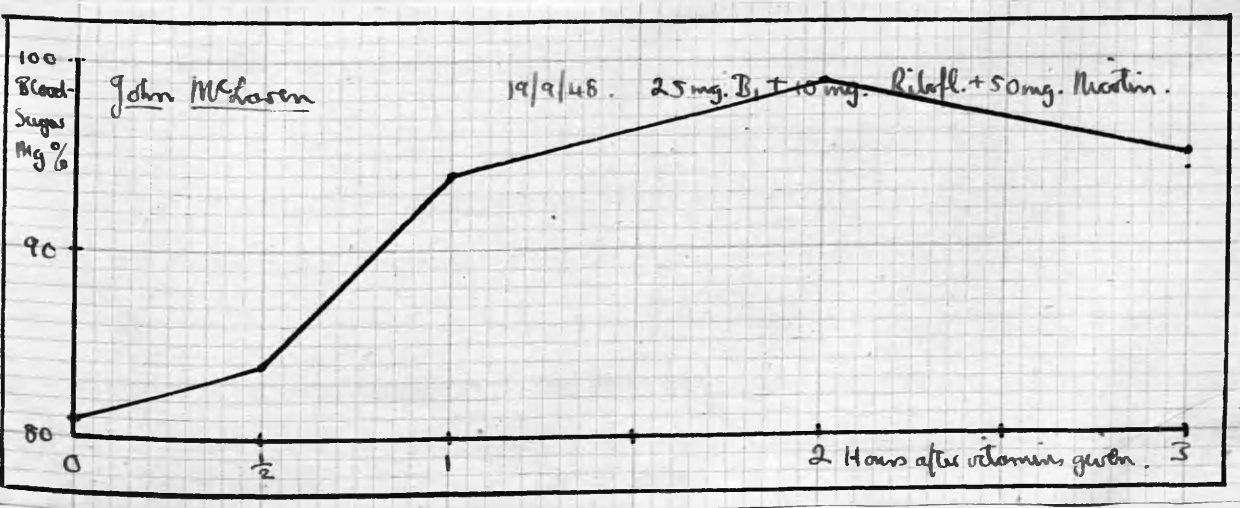
G.H., aged 57, had a severe haematemesis from a peptic ulcer.



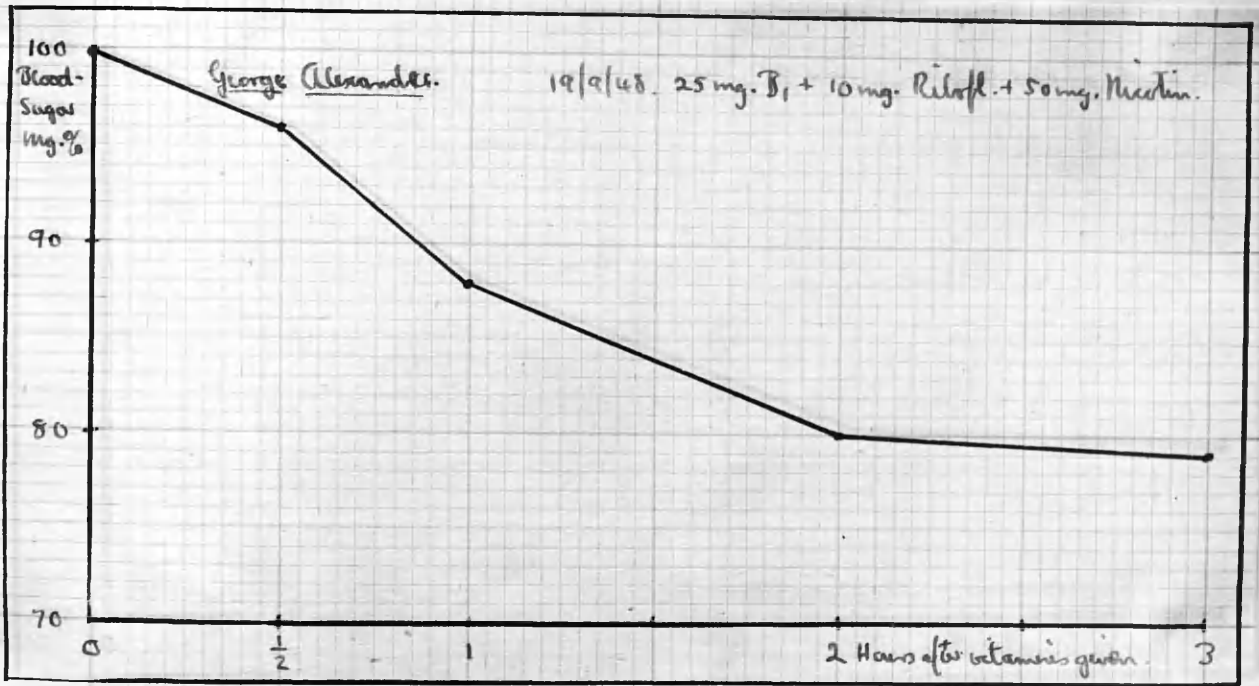
H.M., aged 49, was recovering from a subarachnoid haemorrhage.



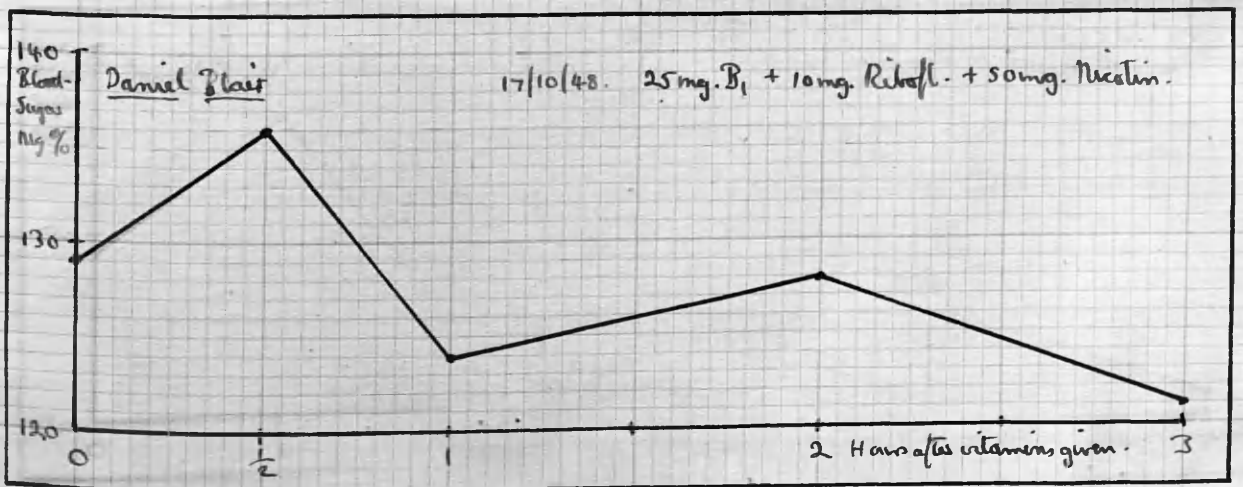
E.F., aged 47, had a severe congestive heart failure due to hypertension.



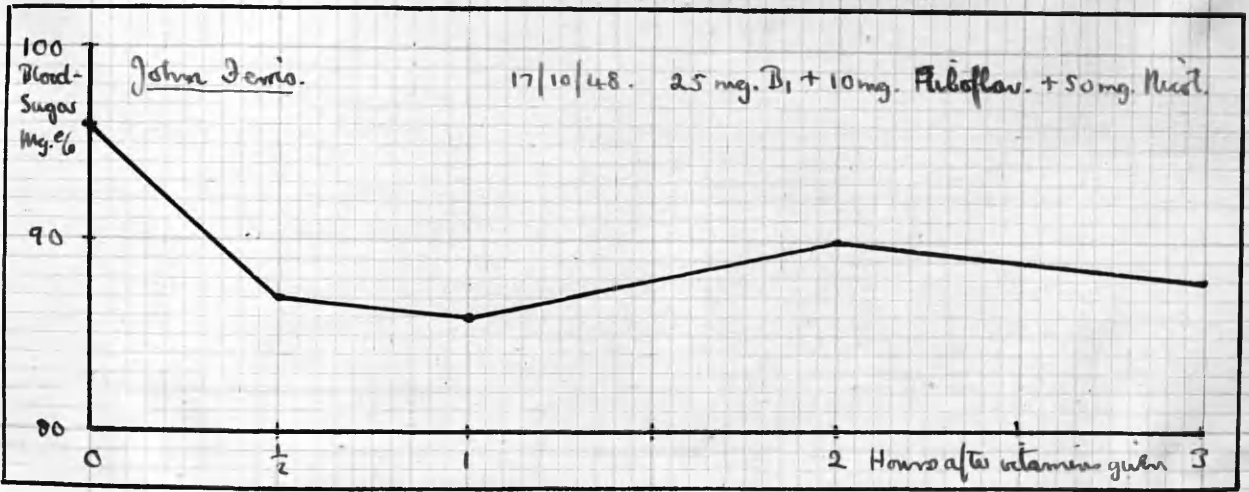
J.M., aged 51, had a chronic bronchitis.



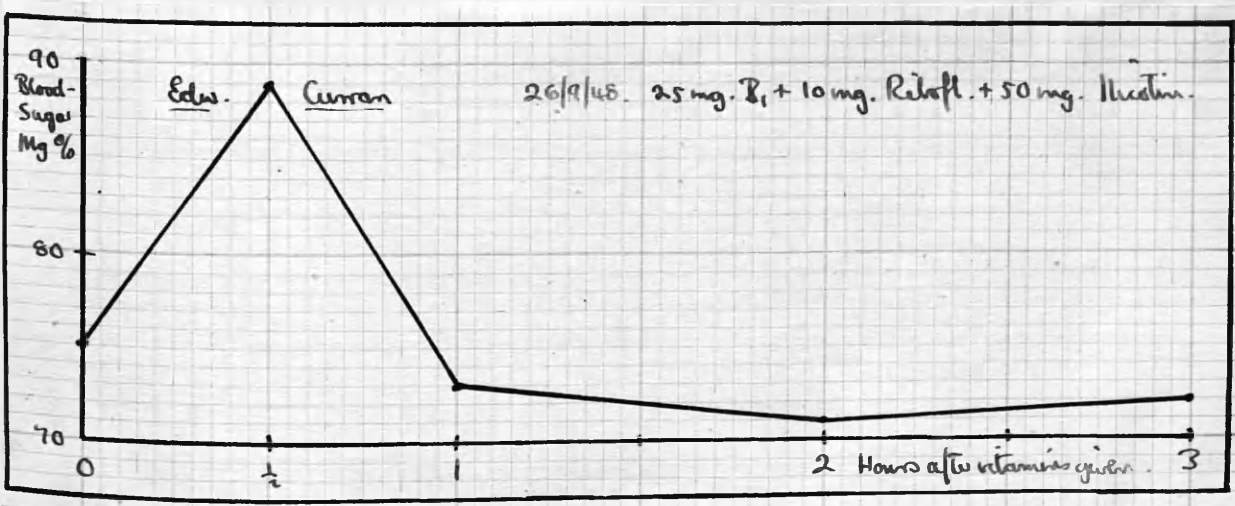
G.A., aged 36, had a pulmonary abscess.



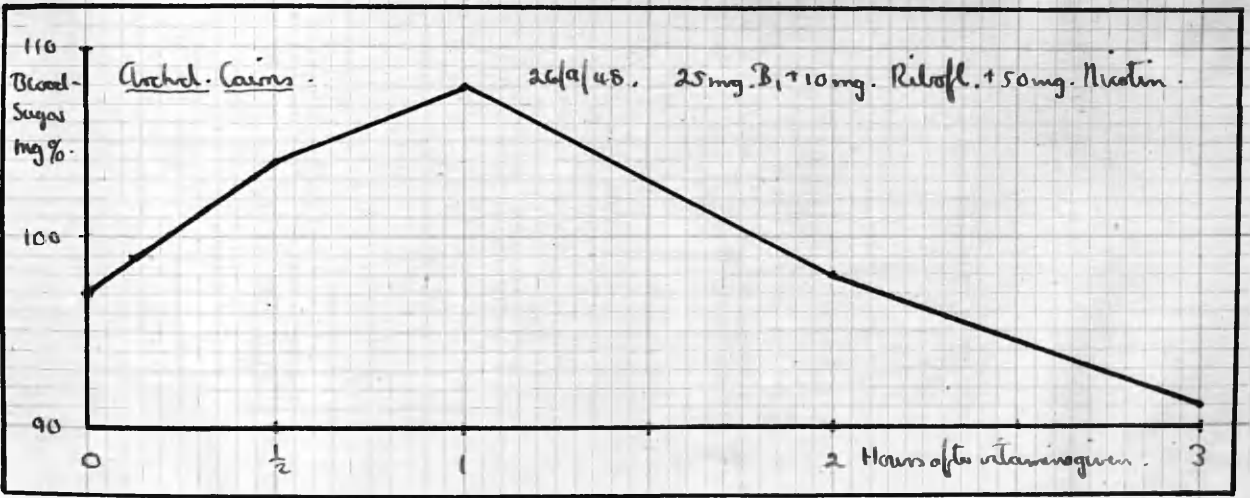
D.B., aged 46, had a pneumonia with neurasthenia.



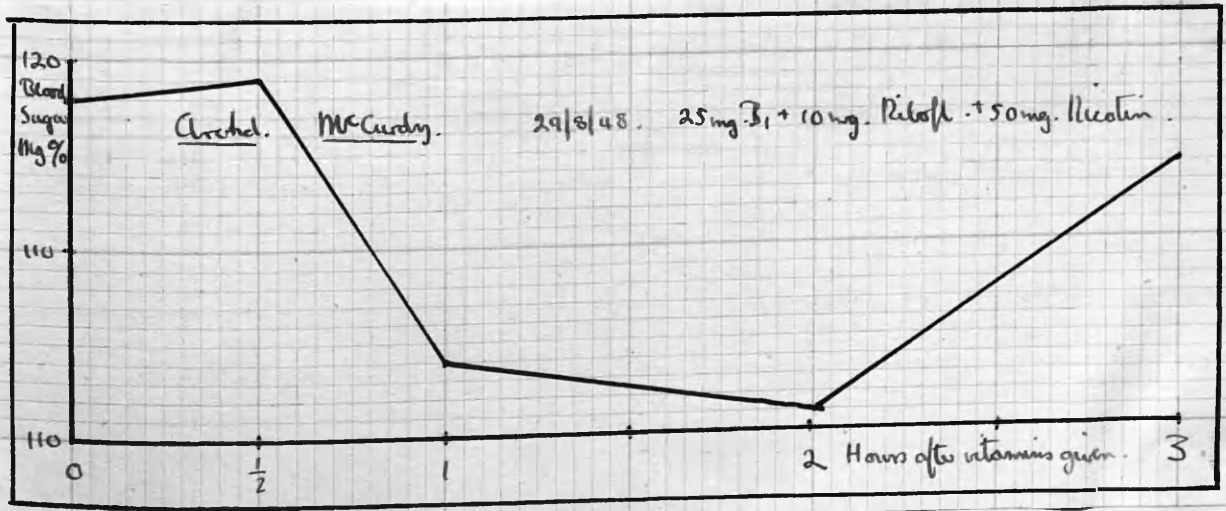
J.F., aged 58, had a tabes dorsalis.



E.C., aged 49, had a pulmonary tuberculosis.



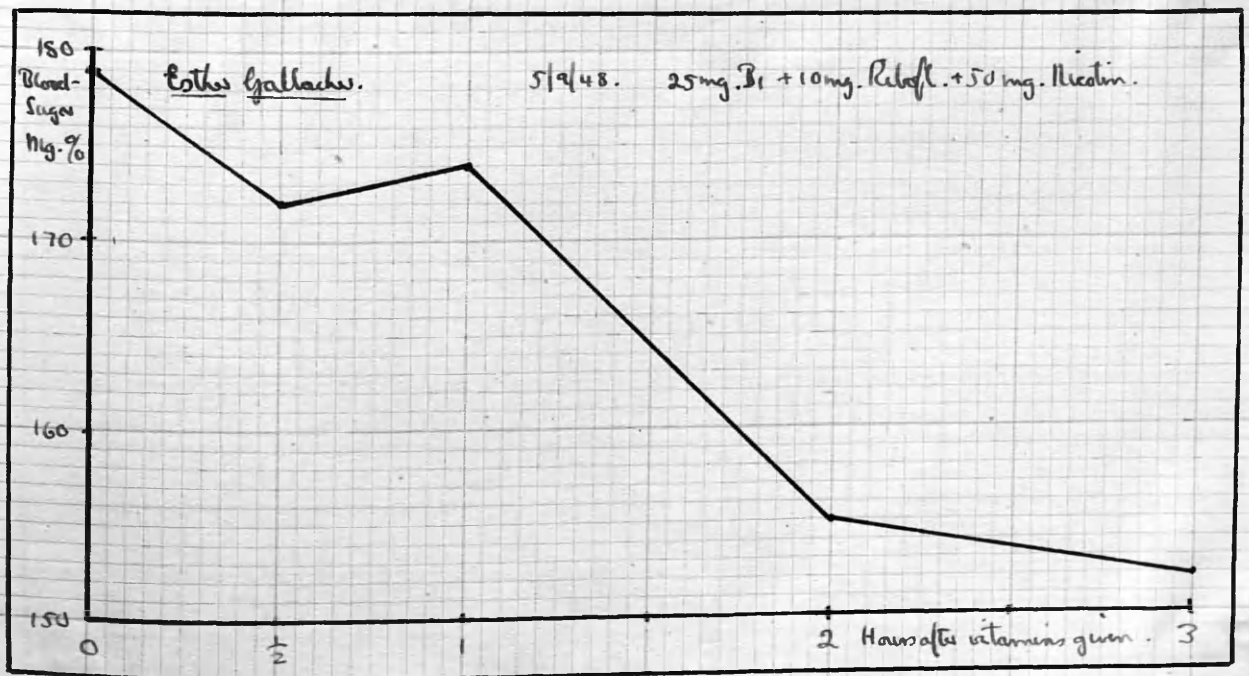
A.C., aged 59, had a deep gastric ulcer.



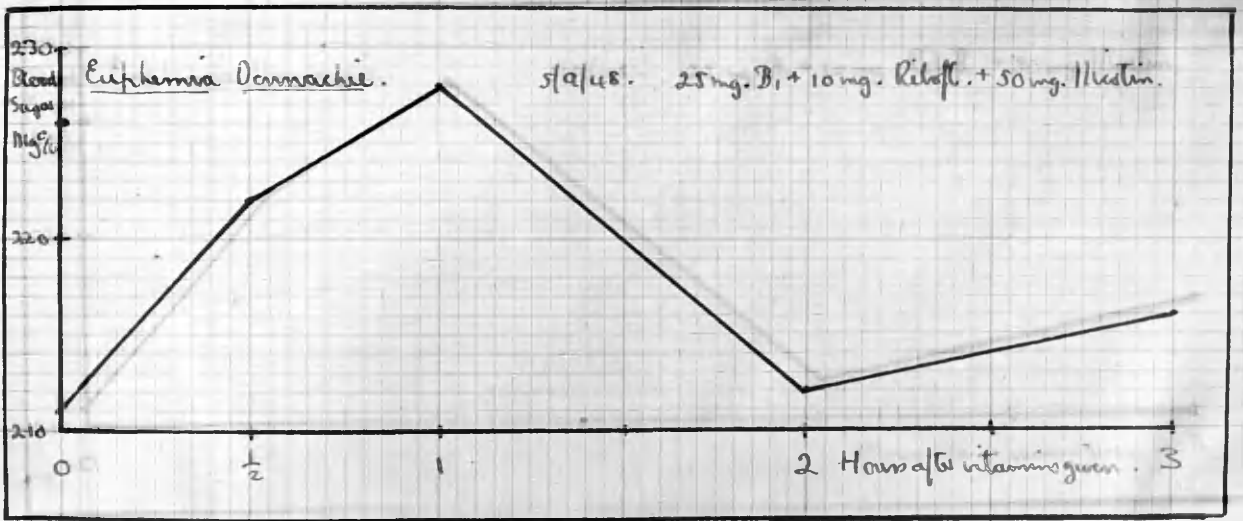
A.M., aged 62, had a carcinoma of lung with cerebral secondaries.

Table XI

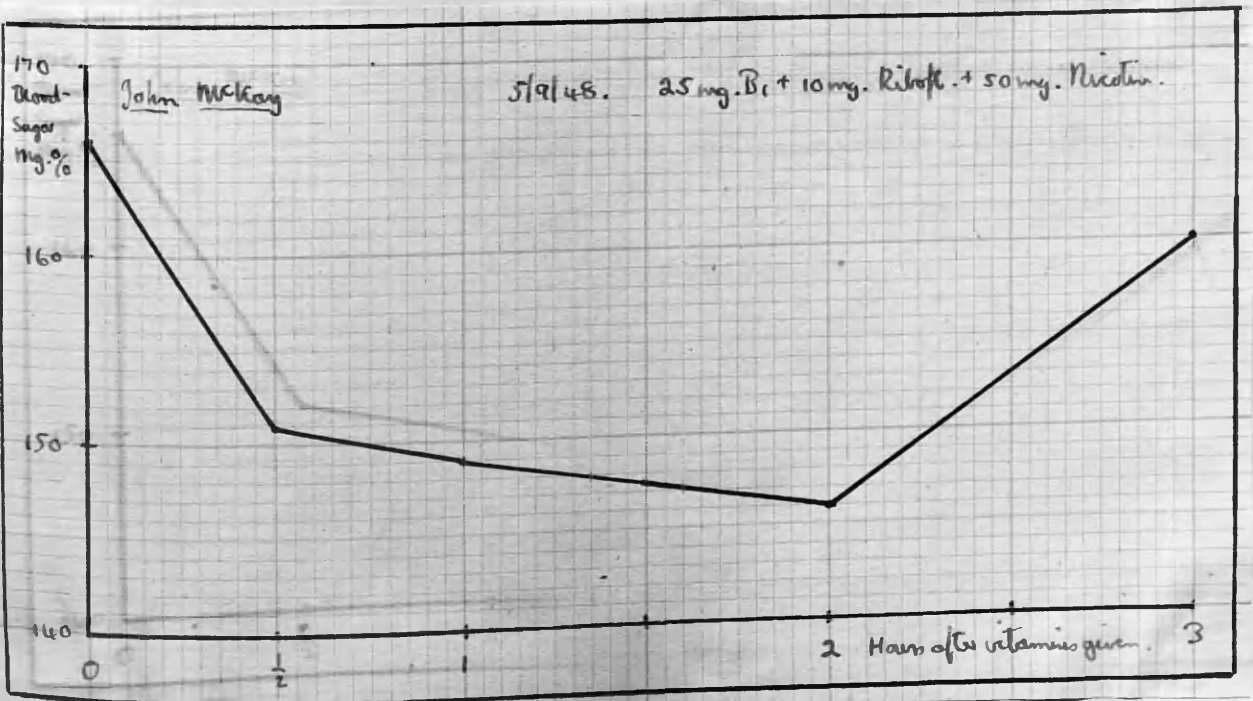
Patient's Initials	Blood-Sugar Concentration Mg. %					Mean	Standard Deviation
	Time in Hours After Investigation Commenced						
	0	$\frac{1}{2}$	1	2	3		
E.D.	211	222	228	212	216	218	7.2
J.M.	166	151	149	146	160	155	9.1
E.G.	179	172	174	155	152	166	12.1
Average Standard Deviation						9.5	



E.G., aged 59, was an obese woman who had not been on insulin for her glycosuria.



E.D., aged 66, had had glycosuria for two years, but had not been on insulin.



J.M., aged 46, did not require insulin for his mild glycosuria.

THE VITAMIN B COMPLEX AND ANIMALS.

THE VITAMIN B COMPLEX AND ANIMALS.

Collip (quoted by Gaebler), in 1925 postulated the existence in plants of an insulin-like hormone, which he called glucokenin. This lowered the blood-sugar level of normal and of depancreatized dogs.

Martin administered insulin to depancreatized dogs on diets free from vitamin B₁ and riboflavin. The animals still suffered from hyperglycaemia and glycosuria. The administration of aneurin alone produced no improvement. When given with riboflavin, however, the action of the insulin was so increased that hypoglycaemic shock was produced. He noted that choline was of no great anti-diabetic efficacy. The action of insulin, he concluded, apparently depended on the presence of factors comprising the vitamin B complex.

Gaebler and Ciszewski withdrew the yeast from the diet of three depancreatized dogs whose glycosuria was adequately controlled with a constant amount of food and insulin. The glycosuria returned in two of the animals. They then tried to produce the beneficial effects of yeast with known vitamins. Inositol, they found, appeared to be one of the active constituents which prevented the glycosuria. The administration of seven of the known constituents of yeast produced the same beneficial effects. These constituents were aneurin, riboflavin, nicotinic acid, inositol, pyridoxin, pantothenic acid and para-aminobenzoic acid. One of the three

dogs did not show any relationship between the vitamin B intake and its insulin requirement. The glycosuria of another of the animals could be controlled by increasing the dose of insulin by 50%. This suggested that the yeast had enabled the insulin dosage to be decreased by one-third.

Further experiments were carried out by Gaebler and Mathies on the same depancreatized dogs made deficient of the water-soluble vitamins. When the food intake and insulin dosage remained constant, the control of the glycosuria was regained when aneurin, riboflavin, nicotinic acid, pyridoxin and pantothenic acid were added to the diet. Pyridoxin and pantothenic acid, separately and together, diminished the glycosuria in experiments in which they were the only variables. Once again the same depancreatized dog showed no response when the vitamins were added or withdrawn.

These reports all tended to support the view that the vitamin B complex might have a beneficial effect in diabetes mellitus.

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- | | |
|---|--|
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THE VITAMIN B COMPLEX AND DIABETES MELLITUS

THE VITAMIN B COMPLEX AND DIABETES MELLITUS.

THE VITAMIN B COMPLEX AND DIABETES MELLITUS.

Once again the mixture of favourable and unfavourable reports makes the issue far from clear.

In 1923, Desgrez stated that the addition of vitamin B to the diet of diabetic patients prolonged and increased the effect of insulin. Owens et al., however, administered large amounts of aneurin and riboflavin to well-controlled diabetics for many weeks. They failed to observe any reduction in the insulin requirement or any alteration in the severity of the disease. Many of the claims of benefit from vitamin therapy, they believed, were based on investigations carried out before the disease had been brought under proper control. They did find, however, that aneurin therapy caused rapid improvement in diabetic neuritis.

The reports of Jackson and Barth, and of Robson et al. were also unfavourable, the former working on diabetic children and the latter on adults. The vitamin B complex had no effect on the insulin dosage or the severity of the diabetes.

Rudy and Hoffmann believed that many of the skin complications of diabetics were manifestations of vitamin B complex deficiency, especially of nicotinamide. While describing the successful clearing up of these lesions with vitamin therapy, they made no mention of any improvement in the diabetic condition.

Biskind and Schreirer, on the other hand, studied 94

diabetics, who they claimed all showed signs and symptoms of deficiency of factors of the B complex. Intensive and persistent therapy with the vitamin B complex improved their general health and often reduced and even eliminated the insulin dosage. They suggested that protracted vitamin B complex deficiency caused impaired hepatic response to endogenous insulin, which they believed was the condition present in the vast majority of diabetics.

Also more optimistic was the report of Parr and Shipton on the beneficial effects of yeast in diabetes mellitus. Brief, though not altogether convincing reports were given on five of their cases which they believed showed considerable functional recovery in some of the β cells of the islets of Langerhans. (The authors suggested, incidentally, that an increased incidence of diabetes mellitus may result from a deficiency of the vitamin B complex in the modern civilised diet).

Trasoff and Bordin found that the carbohydrate tolerance of five out of 15 diabetics on vitamin B therapy was improved. Careful analysis failed to show that the improvement was due to the vitamin therapy. They suggested that the favourable reports of others may be due only to the treatment of unrecognised, subclinical avitaminoses, or to the removal of infection or increase in the carbohydrate ratio.

Before concluding, it would not be entirely irrelevant

to summarise shortly reports on the aneurin therapy of diabetic neuritis.

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VITAMIN B₁ IN DIABETIC NEURITIS.

VITAMIN B₁ AND DIABETIC NEURITIS.

The peripheral neuropathy of diabetic patients was first described by Marchal de Calvi in 1864. Wohl in 1926 first suggested that vitamin B deficiency might be an etiological factor, due to the results of treatment with yeast and yeast concentrates. His article gave a fairly full clinical and pathological description of a fatal case of diabetes with neuritis and other signs of multiple vitamin deficiencies. Dietetic, vitamin and insulin therapy had produced slow but steady improvement, until the patient's mother stopped the insulin and death resulted.

The next few years saw favourable reports by Angle, Minot, Wechsler, and Root and Rogers on the beneficial effects on the neuropathy of a high vitamin intake. Vorhaus et al., and Sciclounoff and Broccard soon suggested on therapeutic grounds that vitamin B₁ deficiency was the main causal factor in diabetic neuritis.

A letter from Lawrence and Oakley described their experience of the administration of large doses of aneurin to diabetics. While the neuritis was often benefited, there was no change in the carbohydrate tolerance or insulin requirement.

Needles found that the aneurin intake of three diabetics with peripheral neuritis was quite adequate. He therefore believed it unlikely that vitamin B deficiency was the cause

of the neuritis. The absorption, utilisation and excretion of the vitamin would have had to be studied in the diabetics, however, before any definite conclusion could be drawn.

In a careful and well tabulated investigation, Fein et al. state that the type of diabetic neuritis due to vitamin B₁ deficiency is a "symmetrical peripheral neuropathy beginning first in, and involving primarily, the lower extremities." The daily administration of ten mg. aneurin hydrochloride by mouth to nine such patients, without any other change in the regimen, resulted in the cure of eight subjects and objective improvement in the ninth. The other types of neuritis in diabetes, involving single nerves or producing vague aches and pains, showed no definite improvement on aneurin therapy.

A further paper by Needles in 1943 quite contradicted these findings. Seven cases of diabetic neuritis failed to show any objective improvement on aneurin therapy; indeed, two of the cases became worse during the treatment.

Root and Bailey commented in 1945: "Though immediate improvement with thiamine is rarely observed in cases of diabetic neuritis, the majority of such cases under such therapy show gradual improvement over a period of several months, provided the cases are brought under good diabetic control."

An unfavourable report came from Broch and Klonstad in 1947. Sixty diabetics with polyneuritis were given vitamin

B₁ and 36.5% were cured or distinctly improved. 16% of the 28 patients receiving no therapy showed similar improvement. In those who benefited, they suggest, improvement was not so immediate as it would be if an aneurin deficiency existed. They concluded, therefore, that their investigations furnished no support for the belief that B₁ deficiency caused diabetic polyneuritis. They believed that a circulatory disturbance was the more likely cause.

In an extensive review of the literature with a report of 125 cases, Rundles also agreed that aneurin deficiency was an unlikely cause, and considered that treatment with the vitamin was unsatisfactory.

Opinions are therefore now veering round to the view that the neurological complications of diabetes are not the result of vitamin deficiency, and will not respond well to vitamin therapy.

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SUMMARY AND CONCLUSIONS

SUMMARY AND CONCLUSIONS.

In the writer's own investigations, aneurin, riboflavin and nicotinamide were administered separately and together to diabetic and non-diabetic patients. No significant changes occurred in the blood-sugar levels during the three hours following administration.

Many of the previous, more favourable reports were based on inadequately controlled experiments with too small numbers of cases. In some reports, the accuracy of the biochemical work was questionable.

The main drawback of the present investigations is that the number of diabetics tested is still too small. Precautions were taken to verify any marked changes in the blood-sugar levels, to exclude the possibility that they were due to inaccuracies in the biochemical estimations.

It is now becoming fairly clear that while various factors in the vitamin B complex play important parts in the metabolism of carbohydrates, it is not likely that any of them could take the place of, or increase the effect of insulin. There is also no definite evidence that an increased need of the vitamins exists in uncomplicated diabetes. Vitamin B therapy is therefore not necessary in the routine treatment of diabetes.

But it is also now becoming more generally recognised

that vitamin B supplements are useful in many complications of diabetes, such as infections, parenteral feeding and old age. Opinions are now more prevalent that very few, if any, cases of diabetic neuritis are due to aneurin deficiency. In the absence of any other definite cause, however, it seems that intensive and prolonged aneurin therapy is still worthy of trial in diabetic neuritis.

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