DIABETOGENIC AND ANTI-DIABETOGENIC SUBSTANCES

A long term study of their influence on Carbohydrate Tolerance in Diabetes Mellitus (including a Study of Carbohydrate Tolerance in Gout)

T H E S I S

presented for the degree of
DOCTOR OF MEDICINE

by Joseph B. Herman
B.Sc., M.B., Ch.B.

University of Cape Town
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To my wife.

C O N T E N T S

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I.

I N T R O D U C T I O N

The discovery of insulin by Banting and Best in 1921 was the climax of years of painstaking research in diabetes and introduced a great era in diabetic treatment.

This discovery resulted largely from animal experiments. It was found that pancreatectomy in animals produced diabetes (von Mering and Minkowski 1889) and that insulin corrected the physiological abnormality thus produced. It thus became widely assumed that diabetes mellitus was due to a pancreatic islet abnormality with defective formation (or production) of insulin.

As we began to understand more about diabetes however, it became evident that the diabetes of pancreatectomy did not represent the whole spectrum of diabetes in man; that in man, the larger group of diabetics or the maturity-onset type, as they are called, had insulin available in their plasma (Bornstein and Lawrence 1951).

Consequently, treatment by means other than insulin in this maturity-onset group seemed logical and the outcome was the advent of the sulphonylurea

and similar drugs of the last decade. This, in turn, has led to a resurgence of interest in research on the metabolic lesion in diabetes.

My own interest in the oral treatment of diabetes commenced in 1947 (when I was attached to the diabetic clinic of Groote Schuur Hospital) before the introduction of the oral anti-diabetogenic agents now in current use.

The majority of diabetics attending the clinic seemed to fall into the two well-recognised groups - the growth-onset (or juvenile type) and the maturity-onset type. In spite of the fact that the two groups were clinically distinct there was the anomaly that both were being treated with insulin. It was noteworthy, too, that insulin failed to influence the high incidence of complications in this maturity-onset group.

To the clinical observer it was evident that insulin had not solved the problem of treatment in the maturity-onset type of diabetes. Perhaps another physiological agent might prove helpful in casting further light on the aetiology of diabetes in man and give a new approach to treatment in the maturity-onset group.

Towards this end, I decided to investigate the effect of a physiologically occurring agent, nicotinamide, on the course of diabetes.

Nicotinamide is the most active constituent of the coenzymes which occur in all living cells of the body. These coenzymes are of vital importance in carbohydrate metabolism, and it has been suggested that nicotinamide is the most vulnerable portion of the coenzyme moiety.

Was this, then, the point where the metabolic lesion in diabetes occurred ?

My studies on the effect of nicotinamide in diabetes led to an investigation of the new pharmacological anti-diabetogenic agents which came into vogue about this time.

My patients had already been observed over a long period and they could now act as their own controls in further investigations on the comparative effects of various hypoglycaemic agents.

In this thesis then, the substances chosen for special study are nicotinamide and the recognised oral

hypoglycaemic agents.

The relationship of these anti-diabetogenic substances to the well-recognised diabetogenic agent, cortisone, is also investigated.

A hitherto poorly recognised phenomenon became evident in this study: several of the patients under observation showed a remission in diabetes. Could we get more information about these patients in remission by noting the effect of cortisone ? Fajans and Conn (1954) opened up an interesting new field by using cortisone for enhancement of the glucose tolerance test. What would be the influence of cortisone on the carbohydrate tolerance in these cases who showed spontaneous or induced remissions ?

The study has been extended to include an investigation of carbohydrate tolerance in gout because of the bearing this disturbance may have on naturally occurring diabetogenic agents.

It has been suggested by Dunn et al (1943) in their studies on the diabetogenic effect of alloxan that there may be a naturally occurring diabetogenic agent in

man, either in the diet or as a result of a disturbance of internal metabolism.

Alloxan resembles the pyrimidine part of uric acid and it has been shown that under certain conditions an injection of uric acid can produce diabetes in animals (Griffiths 1948 and 1950).

Would a study of carbohydrate tolerance in gout give some clue as to whether there is such a factor operative in man ?

Aspects of literature relevant to the thesis have been reviewed with emphasis on the possible correlation of the various agents discussed and the possible light they might throw on the metabolic lesion in diabetes.

This thesis represents the work of a long term study. It deals with fluctuations and remissions in the diabetic state, unusual and rarely recorded.

II.

MATERIALS AND METHODS

MATERIALS AND METHODS:

THE CASES STUDIED:

168 patients were investigated during the course of this long term study at Groote Schuur Hospital.

I. 46 diabetic patients who formed the nucleus of this study at the Diabetic Clinic, of the Hospital received nicotinamide.

As the investigation proceeded, new patients were seen by me at the clinic and the following were singled out for further special study:

(a) Patients who could act as controls of the nicotinamide treated patients,

(b) Patients who would demonstrate the comparative effect of various hypoglycaemic agents,

(c) Patients who might be latent or potential diabetics,

(d) Patients who showed interesting remissions.

II. 86 gouty patients were investigated.

82 patients formed part of the investigation of carbohydrate tolerance in gout and 4 additional patients who showed the association of gout and diabetes were included. 27 non-gouty arthritic patients (not included in the total 168) acted as controls in this section.

All the diabetic patients in this study were personally supervised by me with regard to their treatment, their tests and all investigations.

METHODS OF INVESTIGATION:

The following tests were done on patients in the various sections of this study:

1. 24 hour urine glucose estimations in patients admitted to hospital

2. Fasting blood glucose tests

3. Glucose tolerance tests

4. Cortisone/Glucose tolerance tests.

1. The 24 hour quantitative urine glucose estimation: This is a very valuable method of assessing progress of a case of diabetes. Fluctuations in the quantity of glucose excreted in the urine reveal improvement or otherwise.

This is a relatively simple procedure but careful supervision of the patient and constancy of diet are nevertheless required. These estimations were done by me. Benedict's method was used for the quantitative urine glucose estimations.

2. Fasting blood glucose tests:

For the sake of uniformity all patients (except a few on insulin) were asked to report to the Diabetic Clinic after fasting for at least 12 hours. This simplified the assessment of progress on some form of treatment and acted as a preliminary guide to necessity for a more detailed investigation by glucose tolerance test.

3. <u>GLUCOSE TOLERANCE TESTS</u>:

<u>Preparation for glucose tolerance test</u>: Two points require special mention at this stage:

(i) Diet: Conn (1940) has shown that the patient should be on an adequate carbohydrate diet before the glucose tolerance test is done.

Himsworth (1935) also showed that a severely restricted diet could impair glucose tolerance.

In a panel discussion Duncan (1955) pointed out that a diet containing 300 G. carbohydrate daily for 3 days is an adequate preparation for the glucose tolerance test. Ricketts stated that a normal curve was obtained if the daily intake was above 125 G.

Irving and Wang (1954) have concluded from their observations on carbohydrate intake that the normal diet of an adequately nourished patient need not be augmented before a glucose tolerance test is carried out.

In my study the patients were allowed a diet containing 300 G. carbohydrate for a week prior to the glucose tolerance test.

(ii) Activity: It has been shown by Blotner (1945) that prolonged confinement to bed is responsible for an abnormal carbohydrate tolerance and that resumption

of activity causes a reversion to normal.

In my study, the blood glucose tests were made on ambulant out-patients in practically all cases. Studies were conducted on a few in-patients as well as e.g. those in whom the quantitative urine glucose estimations were done. These patients were not confined to bed.

Choice of Glucose Tolerance Test:

Of the tests, the 'Standard' one-dose (50 G. glucose) oral test appears to be the most valid, being most specific and sensitive (Moyer et al 1950).

Attention was paid to the following conditions in performing the glucose tolerance tests in this study:

(a) For a week prior to the glucose tolerance test the patients were allowed a diet containing 300 G. carbohydrate.

(b) There was a minimum fasting interval of 12 hours before the test was performed.

(c) Capillary blood obtained by the finger prick

method was used throughout. Blood was taken fasting, generally at half-hourly intervals for 2 hours afterwards. (Departures from this are clearly indicated in the results).

(d) The Hagedorn - Jensen method of estimating glucose was used throughout in all the sections of the study (Hagedorn et al 1923).

(e) The same technician/s were as a rule responsible for doing the test in any particular section.

To a very large extent this applied also in the long term follow-up which proceeded throughout the investigation. From the inception of this study in 1947 for approximately 10 years the same technician in the Department of Chemical Pathology was specially associated with the estimations of the fasting blood glucose and glucose tolerance tests. This helped to add uniformity to the tests. Glucose tolerance tests and 24 hour urine glucose tests were done by the author personally in the first year of the investigation (1947).

The glucose tolerance test is unnecessary for diagnosis when definitely abnormal blood glucose levels have been found but in this investigation the glucose

tolerance test was used as a means of assessing the fluctuations produced by various agents. A normal fasting blood glucose test does not necessarily mean a normal glucose tolerance test and the glucose tolerance test was therefore a more sensitive method of establishing whether there were fluctuations in carbohydrate tolerance; it gave information which a fasting glucose test could not possibly give.

It acted as a natural bridge to the next test - enhancement of the glucose tolerance test by cortisone in patients who showed remissions in their diabetes, i.e. the cortisone tolerance tests.

Cortisone/glucose tolerance tests were carried out in:

(i) Patients who showed spontaneous remissions,

(ii) Patients who showed remissions while on hypoglycaemic agents,

(iii) Patients who might be latent or potential diabetics,

(iv) Selected gouty patients.

The Cortisone/glucose tolerance test is discussed in greater detail in the section dealing with Adrenal Cortical Steroids.

Interpretation of Glucose Tolerance Tests:

The generally accepted figures for the upper limit of normality in the glucose tolerance test by the Hagedorn - Jensen method (using capillary blood) are (Rosenthal et al 1950; Lawrence 1947):

Fasting Blood glucose	120 mg.
1 hour level	200 mg.
2 hour level	120 mg.

Moyer et al (1950) (using the Folin-Wu method) consider a 2 hour level between 125 - 140 mg. as presumptively abnormal. 140 mg. and over is definitely abnormal or diabetic.

By our present day criteria, the diagnosis of diabetes would be untenable in the presence of a normal glucose tolerance test, i.e. where the fasting and 2 hour levels are below 120 mg.

These figures are accepted as the upper levels for a normal glucose tolerance test in this investigation.

The border line between normal and abnormal blood glucose levels varies within a narrow range from one authority to another.

In this study when a patient is stated to have a diabetic glucose tolerance test, more rigid criteria for abnormality (than those generally accepted) are used: Both the fasting and the 2 hour levels had to be abnormal. The following figures would therefore be considered abnormal by all standards:

Fasting blood glucose	:	Greater than 150 mg.
2 hour level	:	Greater than 150 mg.
1 hour level	:	Greater than 230 mg.

(The fasting and 2 hour levels are the figures emphasised by most authorities).

There are various factors which influence the glucose tolerance test.

In this study small fluctuations in blood glucose

levels are not relied on for the assessment of progress of diabetes. Factors like emotion or preceding exercise, would not appreciably influence the assessment of glucose tolerance test. Patients with sepsis or infection were excluded from the investigation. Where an unpredictable factor (like coronary thrombosis) occurred during the course of the study this was noted.

The age, sex and weight of the patients were recorded in the results and these factors need not be discussed here.

Special attention was paid to activity and previous diet. Many of the inconsistencies in earlier reports on glucose tolerance tests may be due to the fact that the influence of these were not clearly understood before their importance was pointed out by Conn (1940) and Blotner (1945) e.g. there is a much quoted article on a study of glucose tolerance tests in an old age home when the importance of both these factors was not yet fully realised and taken into account.

In the long term study, each patient was observed over a control period - generally for some

months - and again during the trial periods with various agents which again might last for months or years. Thus the pattern of blood glucose fluctuations for each patient was known and <u>each patient could act as his own control</u>, but attention had to be paid to effects of change of body weight.

III.

THE ROLE OF NICOTINAMIDE IN CARBOHYDRATE METABOLISM

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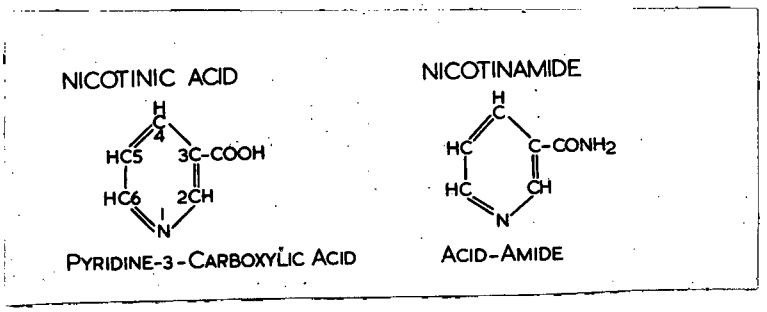


Fig.I.

Nicotinic acid or nicotinamide occurs in all living cells, mainly as constituents of certain coenzymes (Warburg et al 1935 (a) and (b); v. Euler et al 1935), the liver containing more than any other organ. So far as is known, nicotinic acid has no metabolic function other than that exerted through the coenzymes of which it is part (Sebrell et al 1952) (Fig.I).

The coenzyme derivatives of nicotinamide are diphosphopyridine nucleotide (DPN, cozymase, codehydrogenase I, coenzyme I or Co I) (Fig.II) and triphosphopyridine nucleotide (TPN, Warburg's coferment, codehydrogenase II, Coenzyme II) (Warburg et al 1935 (a) and (b)).

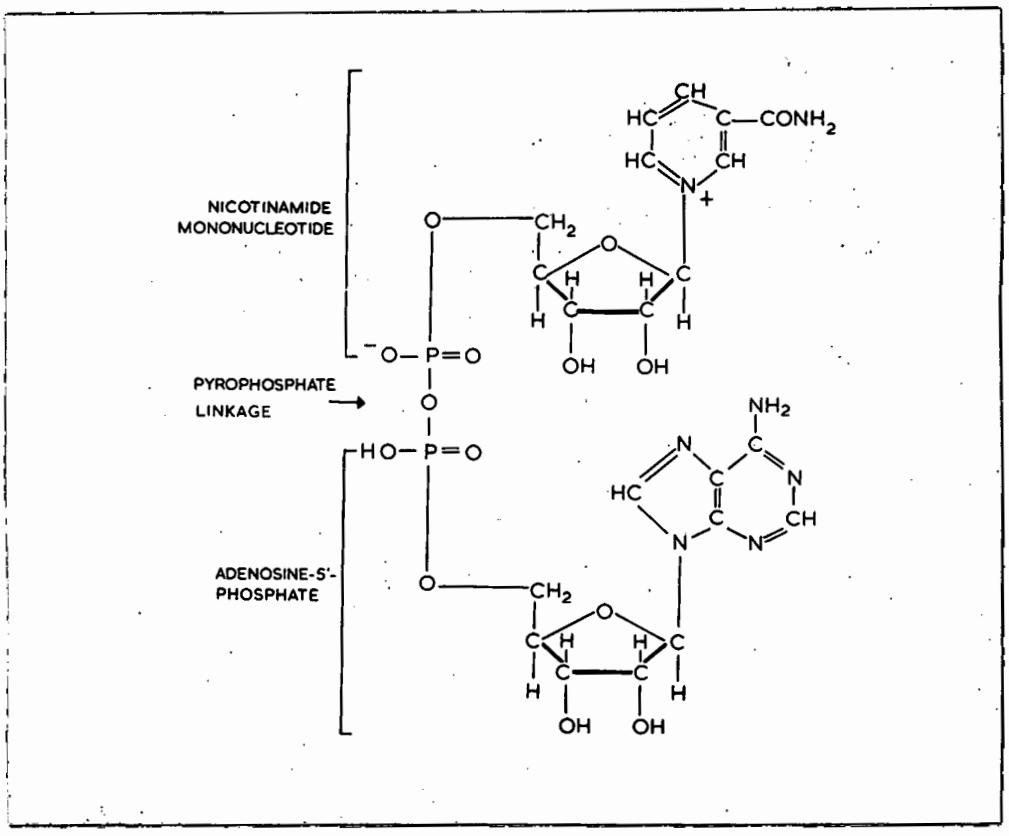


Fig.II.

Formula of Diphosphopyridine nucleotide (DPN), a key substance of biological oxidations.

The coenzymes together with an apoenzyme are the components of an enzyme system which catalyse certain important metabolic reactions. The apoenzyme is a specific protein, which combines with and activates substrate and coenzyme.

The nucleotide acts as a hydrogen acceptor, i.e. it is reduced by the substrate and is then reoxidised indirectly by molecular oxygen. This cycle of oxidation and reduction occurs in the pyridine ring, i.e. in the nicotinamide portion (Warburg et al 1935 (a) and (b)) (Fig.III).

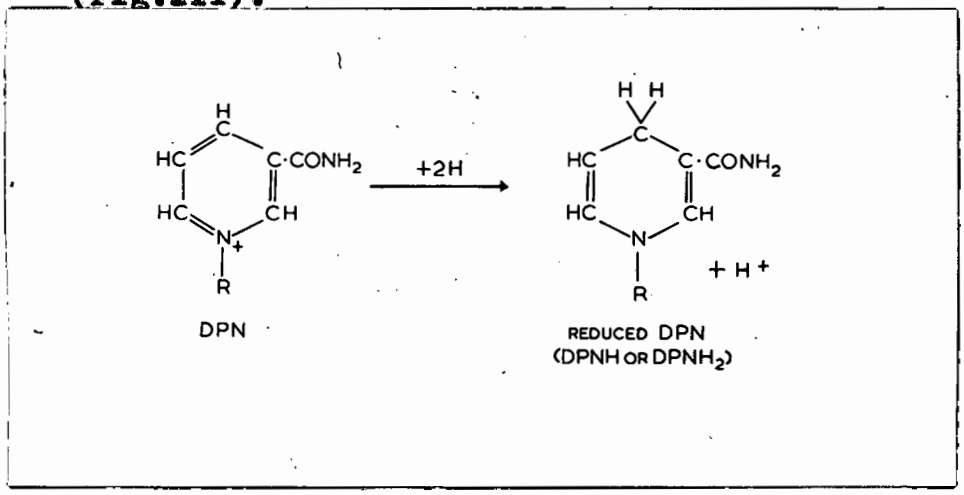


Fig.III.

The nicotinamide portion is thus <u>the most active part</u> of the enzyme system, in so far as it is the nicotinamide portion which is involved in H. transfer

In this discussion it will be shown that the reduced pyridine nucleotide formed by this transfer may be looked upon as the fundamental fuel of biological oxidations.

BIOSYNTHESIS OF DPN

Nicotinamide mononucleotide (Nicotinamide-ribose-phosphate) can be synthesised by red blood cells incubated with nicotinamide and glucose (Leder et al 1951).

DPN can be formed biologically by a reaction between nicotinic amide mononucleotide and ATP, which is the pyrophosphate of adenine mononucleotide, thus :

Nicotinic amide mononucleotide + ATP $\longrightarrow$ DPN + inorganic pyrophosphate.

TPN can be enzymatically formed by phosphate transfer to DPN from ATP :

DPN + ATP $\longrightarrow$ TPN + ADP (Baldwin 1957).

DIETARY NICOTINAMIDE AND ITS RELATION TO TISSUE COENZYMES

There is a direct correlation between the tissue nicotinic acid and the DPN content of muscle and liver and the nicotinic acid intake in the diet (Anderson et al 1944).

Animals with a deficiency of nicotinic acid show a marked decrease in the coenzyme content of liver and muscle (Axelrod et al 1939).

The DPN level in the red cells of rats decreased

with restriction of nicotinamide and increased with nicotinamide addition to diet (Burch et al 1955).

When rats are fed a non-protein, nicotinamide-free ration, the addition of increasing amounts of tryptophan or nicotinic acid to the ration, causes an increase in liver pyridine nucleotide concentration (Feigelson 1951).

In man, too, the concentration of DPN and TPN can be increased by the ingestion of large amounts of nicotinic acid (Axelrod et al 1940, Kohn et al 1939, Handler et al 1943).

As the rate of any enzyme catalysed process depends, other things being equal, upon the concentrations of the enzyme and its substrate (Baldwin 1957), it is likely that nicotinamide by increasing the concentration of coenzyme will accelerate its metabolic functions; that is, if nicotinamide deficiency is the rate determining factor.

NICOTINAMIDE, COENZYMES AND CARBOHYDRATE METABOLISM.

Insulin has been shown to facilitate the entry of glucose into the cells. However, once glucose has entered the cell insulin is believed to have little or no further action on its intracellular metabolism (Levine et al 1950; Park et al 1955 (a) and (b), 1956 (a) and (b)), which is

facilitated or activated by enzyme systems.

These enzyme systems facilitate the complex processes involved in the conversion of glucose for storage as glycogen, or its conversion to protein or fat, or breakdown to provide energy.

This discussion will concern some of the processes of intracellular metabolism of carbohydrate dependent on the functional integrity of those enzyme systems of which nicotinamide is an essential component. It will become clear that as carbohydrates, fats and proteins all contribute to a common metabolic pool, the intermediary metabolism of all these substances is interrelated. A disturbance of metabolism affecting one of these groups will affect the others also.

The nicotinamide-containing coenzymes are of importance in the energy-producing reactions of metabolism.

BIOLOGICAL ENERGY TRANSFORMATIONS OF THE PYRIDINE NUCLEOTIDES.

All living cells require energy. This energy is obtained from the degradation of foodstuffs. It is in the tissues where the energy transformation proper takes place.

Krebs (1954) points out that the striking feature of the picture of energy production in living matter is the relative simplicity of the basic principles.

The first group of reactions comprises those in which the available material is incompletely burned, the end-products being, apart from carbon dioxide and water, one of three substances: Acetic acid ($CH_3.COOH$) in the form of acetyl coenzyme A, alpha-ketoglutaric acid ($COOH.CH_2.CH_2.CO.COOH$) or Oxalo-acetic acid ($COOH.CH_2CO.COOH$). The first of these three contributes the greater amount: two-thirds of the carbon of carbohydrate, all carbon atoms of the common fatty acids and approximately half the carbon of amino acids yield acetyl coenzyme A. Alpha-Ketoglutaric acid arises from several amino acids (e.g. glutamic acid), oxaloacetic acid from aspartic acid (etc.).

These three products are metabolically closely interrelated. They take part in the tricarboxylic acid cycle, which represents the <u>common terminal pathway of oxidation of all foodstuffs</u> (See Fig. IV for Citric Acid Cycle).

The figure shows that one of the results of this cycle is the supply of pairs of hydrogen atoms from the organic molecules.

The hydrogen is transferred to molecular oxygen in a special way, the first step being the transfer of hydrogen to diphosphopyridine nucleotide (See Fig. IV for Citric Acid Cycle).

The reduced pyridine nucleotide formed by this transfer may be looked upon as the fundamental fuel of biological oxidations. It is the further transfer of hydrogen atoms from this substance to molecular oxygen which causes a release of energy. Therefore, the main effect of the metabolic reactions of foodstuffs, as far as they serve to supply energy, is to reduce pyridine nucleotide.

Green et al (1955) conclude from the evidence now available that the pyridine nucleotide coenzymes are indeed 'the work-horses of biological oxidations'. They list amongst some of the reactions mediated by one or other pyridine nucleotide: Four of the five oxidative steps in the tricarboxylic (or citric acid) cycle, the two oxidative steps in glycolysis or fermentation, one of the two oxidative steps in fatty acid oxidation, a key oxidative reaction in the pyrimidine synthesis (Lieberman et al 1953), all the

oxydative steps in the glucose to tetrose sequence of reactions (Racker 1954).

By virtue of their function in the tricarboxylic acid cycle, it has been pointed out (Singer et al 1954), that pyridine-nucleotides participate in the complete oxidation, interconversion and biosynthesis of carbohydrates, fats and amino acids. The fact that all known major routes of acetyl Co A formation ultimately involve pyridino-protein catalysis is a prime example of their importance in metabolism.

Fig. IV shows at which points in the energy-producing reactions of metabolism the nicotinamide containing coenzymes DPN and TPN operate.

GLYCOLYTIC PATHWAYS AND THEIR RELATION TO THE SYNTHESIS OF FATTY ACID AND CHOLESTEROL:

The addition of either DPN or TPN stimulates the oxidation of labeled glucose to CO_2.

It has been shown that DPN is actively involved in the Embden-Meyerhof pathways, while TPN influences the hexosemonophosphate shunt (Siperstein 1958).

CARBOHYDRATE METABOLISM and FATTY ACID SYNTHESIS:

The importance of TPN in fatty acid synthesis:

The HMP shunt is the only route which can yield reduced TPNH.

The TPN - TPNH system is known to be required for fatty acid synthesis (Langdon 1955, 1957).

The feeding of excess glucose to normal animals is known to produce a marked stimulatory effect on the synthesis of fatty acids (Chernick et al 1950; Tepperman et al 1957). On the other hand, it is pointed out that deprivation of glucose oxidation as seen in diabetes or in the fasting state results in a depression of fatty acid synthesis (Chernick et al 1950;, Masoro et al 1950).

The impaired synthesis of fatty acid which is characteristic of diabetes is ascribed primarily to the deficiency in this disease of glycolysis via the HMP shunt, leading to a lack of reduced TPN normally produced by this pathway.

Re-establishment of glucose breakdown in either the diabetic or the fasted animal restores to normal the ability to synthesise both fatty acids and cholesterol and ketosis is abolished (Siperstein 1958).

It is assumed, from this and other evidence, that in these metabolic states the defects in lipid synthesis are secondary to lack of glycolysis.

Acetyl Co A occupies a central position in the metabolism of carbohydrate and fat, not only as a common oxidation intermediate but also as an intermediate in the synthesis of fatty acids from carbohydrate (Ochoa 1954).

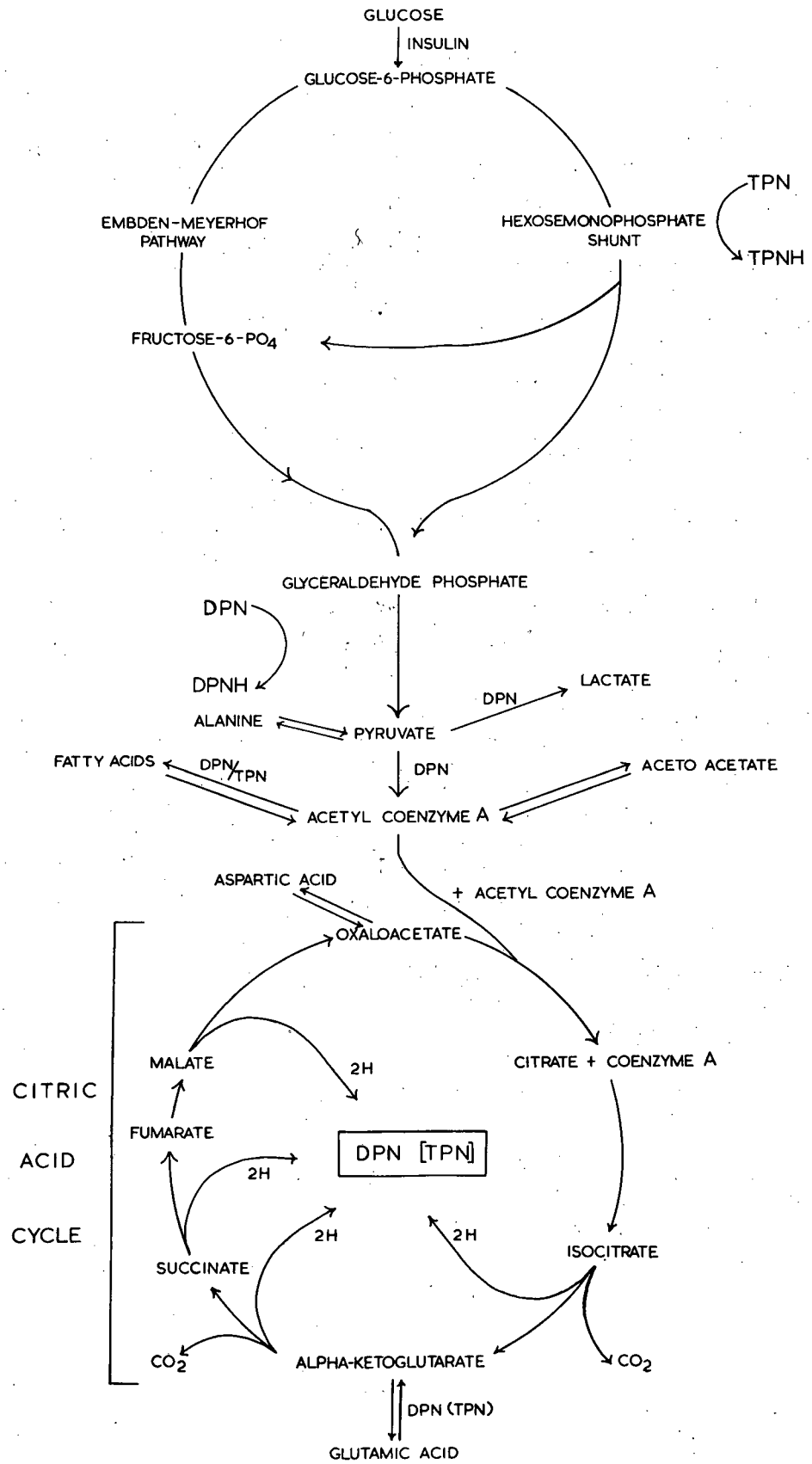
The following reaction also deserves special mention:

$$\text{Alpha ketoglutarate} + NH_3 + \text{DPNH} + H^+ \rightleftharpoons \text{L - glutamate} + \text{DPN}^+.$$

This reaction may be of great biological significance since it provides a link in the synthesis of an animo-acid from a substance which can be derived from carbohydrate or conversely, it demonstrates how energy may be derived from protein by converting the protein to a glycogenic fragment.

Fig. IV

DIAGRAM SHOWING THE IMPORTANCE OF THE
THE NICOTINAMIDE-CONTAINING COENZYMES: DPN AND TPN
IN INTERMEDIARY METABOLISM.



From the diagram (Fig.IV), it may appear that only the coenzymes DPN and TPN are operative at the various points indicated with the enzymes of which they form the enzyme system.

The diagram does not represent the complete picture but it serves to show the universality of action of the nicotinamide-containing coenzymes.

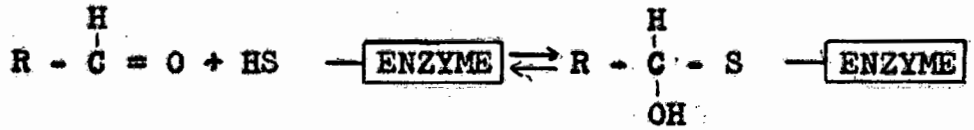
Thus the reaction which may be shown in its simplest form as follows :

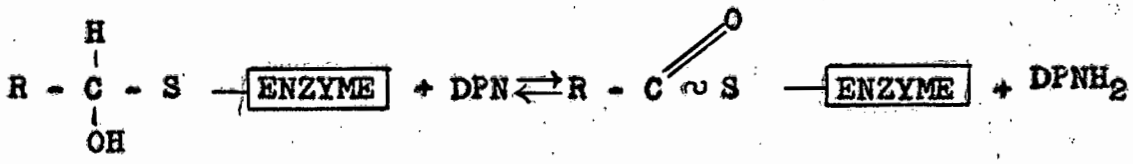
Pyruvic acid + H_2O $\xrightarrow{DPN}$ Acetic Acid + CO_2 + 2H

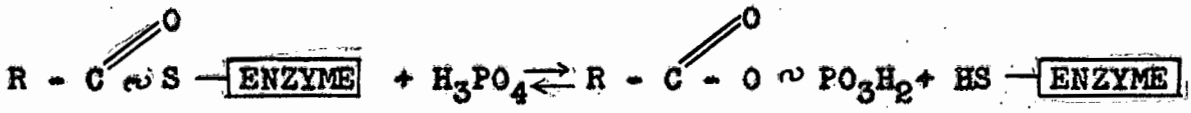
appears to be quite complex . The pyruvate oxidation system involves not only the participation of at least two enzymes, Co-A and DPN, but also that of diphosphothiamine, magnesium ions and alpha-lipoic acid (Ochoa 1954).

Further amplification is required at another point in glycolysis as this may have an important bearing on the problem to be discussed in this thesis.

It now appears that the triosephosphate dehydrogenase itself has glutathione as a prosthetic group through the -SH group of which it unites with its substrate.







The aldehyde group of glyceraldehyde - 3 - phosphate first condenses with the sulphydryl group of the enzyme bound glutathione. The condensation product is then dehydrogenated to an acyl mercaptide or thioester type of compound, the pair of hydrogen atoms being accepted by DPN.

THE INACTIVATION OF DPN AND ITS PREVENTION BY NICOTINAMIDE.

The enzymatic inactivation of DPN has been known from the early studies of von Euler et al (1937).

It was noted that nicotinamide prevented the inactivation of DPN in brain preparations (Mann et al 1941).

Other workers also demonstrated in animal tissues a splitting of the DPN molecule at the nicotinamide ribose linkage and that this splitting was inhibited by nicotinamide (Handler et al 1942).

The ability of the diphosphopyridine nucleotidinase (DPN ase) of beef spleen to catalyse an exchange reaction between the nicotinamide moiety of DPN and added nicotinamide has been reported (Zatman et al 1953) and it has been suggested that this phenomenon serves to explain the well known inhibitory effect of nicotinamide on animal DPN ases.

It seems that nicotinamide can increase the concentration of DPN in the animal and also prevent inactivation.

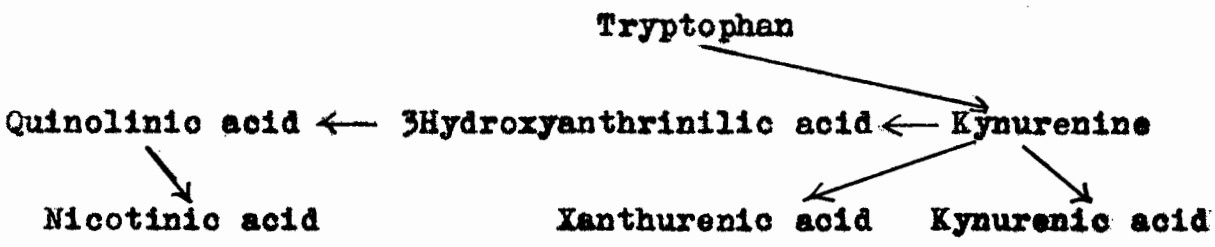
NICOTINAMIDE IN ALLOXAN INDUCED DIABETES.

Alloxan has been reported to compete with DPN in a yeast apozymase enzyme system (Kensler et al 1942). Lazarow et al (1950) decided to test the components of DPN for their protective effect against alloxan-induced diabetes. Thus they found that rats were protected against alloxan diabetes by prior injection of nicotinamide. Banerjee (1947) reported that nicotinamide had the same protective effect against alloxan diabetes in rabbits.

McDaniel et al (1955) reported that conversion of tryptophan to nicotinamide appears to be disturbed in alloxan diabetic rats, but alloxan treated animals which failed to become diabetic converted tryptophan to nicotinic acid as did normals.

TRYPTOPHAN AND NICOTINAMIDE.

In man, nicotinamide can be formed from tryptophan. It is therefore important to consider the metabolism of tryptophan (Garfield Duncan 1959). Likely pathways are:



In pyridoxine deficiency xanthurenic acid is formed as an end product instead of nicotenic acid.

ANTI-METABOLITES OF NICOTINAMIDE

DPN consists of a combination of one nicotinamide group with one adenine, two pentose and two phosphoric acid groups (See Fig. II). TPN contains an additional phosphoric acid group (Warburg et al 1935).

Substances similar in structure (but not in their physiological effect) can replace nicotinamide in the molecule DPN.

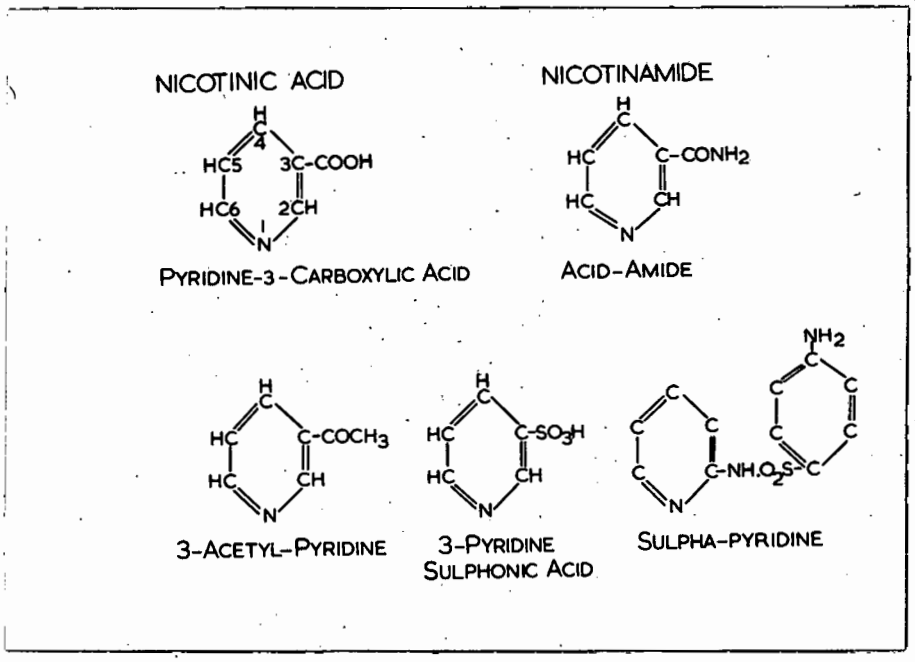
Thus it has been reported (Kaplan et al 1954) that animal tissue DPN ases can catalyse an exchange reaction between the nicotinamide moiety of DPN and compounds related to nicotinamide according to the equation :

$$NRPPRA + X \longrightarrow XRPPRA + N$$

(N is nicotinamide, R is ribose, P is phosphate, A is adenine, X is pyridine compound related to nicotinamide).

The pyridine compounds that have been found to undergo exchange with nicotinamide are isonicotinamide, INH, 3-acetyl pyridine (Woolley 1945) and ethyl nicotinate; the resulting DPN analogues have now all been isolated.

The structural formulae of some of the nicotinic acid antagonists are here compared with those of nicotinic acid and nicotinamide (See Fig. V).



The nicotinamide portion of coenzymes, apart from its importance in carbohydrate metabolism, is probably then the most vulnerable portion of the coenzyme moiety - a disturbance at this point may cause a widespread disruption of cellular metabolism.

NICOTINAMIDE AND CARBOHYDRATE METABOLISM:

To Summarise:

Nicotinamide is the most active part of the coenzymes DPN and TPN. These coenzymes play a vital role in the intermediary metabolism of carbohydrate and fat.

Anti-metabolites have been shown to replace nicotinamide in the molecule of DPN. The nicotinamide portion may be the most vulnerable portion of the coenzyme moiety.

Nicotinamide has been reported to prevent alloxan induced diabetes.

The next section will deal with:

THE ACTION OF NICOTINAMIDE IN DIABETES.

IV.

THE EFFECT OF NICOTINAMIDE ADMINISTRATION IN DIABETES

NICOTINAMIDE IN DIABETES MELLITUS

Pharmacological agents like the sulphonylureas have revolutionised the treatment of diabetes; their impact on research and thinking in diabetes has yet to be completely assessed.

Physiological agents however, may prove to be of even greater significance than the pharmacological agents in throwing light on the aetiology and pathogenesis of diabetes mellitus.

As early as 1914, Funk demonstrated that vitamins in yeast exerted a favourable influence on the carbohydrate metabolism of pigeons (Funk et al 1914). Collip (1923, 1925) and Gaebler and Ciszewski (1945) confirmed this action of yeast on other species. Beckert (1938) reported a favourable influence in diabetes in man in one third of the cases to whom yeast was given.

Although it had not been determined which component of the vitamin B group was responsible for this effect on carbohydrate metabolism, nicotinamide appeared to be the most likely for the following reasons:-

Nicotinamide is an important constituent of

the coenzymes diphosphopyridine nucleotide and triphosphopyridine nucleotide (Warburg et al 1935), which are of vital importance in carbohydrate metabolism (as was pointed out in Section III). In man the concentration of the latter coenzymes can be increased by the ingestion of large amounts of nicotinic acid or nicotinamide (Axelrod et al 1940; Kohn et al 1939; Handler et al 1943). Moreover, nicotinamide has been shown to prevent alloxan induced diabetes (Lazarow et al 1950; Banerjee 1947).

What is the influence of nicotinamide on human diabetes?

The results of investigations of the effect of nicotinamide in diabetes have been inconclusive and conflicting. Some investigators have reported improvement (Göbell 1940; Marche 1943; Neuwahl 1943; Unger 1957), but this improvement has not been confirmed by others (Banerjee 1949; Cumings 1947; Wade 1947; Haller 1957). These investigations were carried out over a short period only.

I have therefore thought it important to repeat

these investigations for longer periods as it seemed useful information might be gained from a prolonged comprehensive study of the effect of nicotinamide administration to diabetics.

MATERIALS AND METHODS:

THE CASES STUDIED:

In this study the patients were limited to those under my PERSONAL SUPERVISION for some length of time at the Diabetic Clinic. They were selected after I had established that there was no precipitating cause for their diabetes, such as infection or injury.

46 patients were given nicotinamide and investigated for a sufficiently long period to enable me to draw conclusions as to its effect.

METHODS OF INVESTIGATION:

Fasting blood sugar estimations and glucose tolerance tests were the chief methods of investigation in the majority of cases.

Prior to the administration of nicotinamide there

was a control period on diet alone during which time fasting blood sugar tests were done. In some patients glucose tolerance tests were done as well.

The fasting blood sugar estimations and glucose tolerance tests were repeated during the period of nicotinamide administration (usually 500 mg. daily in divided doses; in some cases much larger doses were given, e.g. 1000 mg. daily orally plus parenteral nicotinamide as well).

These tests were continued after nicotinamide had been stopped.

Diet remained constant throughout.

An additional method of assessing the value of treatment was by estimating 24 hour quantitative urine sugar excretion in these patients before, during and after nicotinamide.

In patients in whom dietary restriction alone was considered to be the treatment of choice, a Groote Schuur Hospital Step 2 diet was prescribed as the standard commencing diet at the diabetic

clinic. This is a 1150 calorie diet and is calculated to be composed of carbohydrate 97 G., Protein 55 G., and Fat 61 G.

Before starting patients on this trial they were placed on a diet which had been individualised for the patient concerned - depending on the severity of the diabetes and with regard also to the patient's caloric requirements.

Thus to eliminate the influence of diet on carbohydrate tolerance these patients were as a rule allowed a fairly liberal carbohydrate diet of moderate caloric value (carbohydrate 150 G., protein 75 G., and fat 70 G. = approximately 1500 calories).

The preparation for the glucose tolerance tests and the conditions observed are described in the SECTION: MATERIALS AND METHODS.

How This Study Developed.

This study on nicotinamide commenced in 1947. The initial period consisted of an intensive study of patients by frequent glucose tolerance tests. In those who were admitted to hospital, 24 hour urine glucose estimations were done as well. The glucose tolerance tests and 24 hour urine glucose estimations were carried out by me in the first year of this study (1947).

After the initial periods these patients were again seen by me at the diabetic clinic of Groote Schuur Hospital where I was able to continue observations.

At this time tests were also carried out in the Department of Chemical Pathology (Prof. G.C. Linder) which enabled me to have a double check and more frequent tests on changes in blood glucose levels occurring at this important stage in the investigations.

These patients who were placed on nicotinamide constitute the nucleus of the investigations in this thesis.

Thus the patients who were first seen in 1947 were followed up for a variable period and some are still being seen at the time of writing in 1960 (e.g. D.R. case 127, G.S. case 136).

Subsequently more patients were included in this study (e.g. J.F. case 47) and these patients too, are still the subjects of study.

A further long term study was embarked upon particularly in those patients who had shown an interesting response to nicotinamide. The object of this was twofold:

1. To provide a further control period.

2. To assess the subsequent response to hypoglycaemic agents in relation to the response to nicotinamide.

The effect of prior administration of nicotinamide on cortisone enhancement of the glucose tolerance test was also investigated in a few cases, and will be discussed under the section on CORTISONE ENHANCEMENT, page

The Safety of the Procedures used in this study:

Nicotinamide:

Nicotinamide was used in this study because it does not produce the unpleasant side-effects of nicotinic acid. However, the physiological effect of both these substances is identical and therefore in the discussion no distinction will be drawn between them.

In spite of the unpleasant side-effects of large doses of nicotinic acid there are now several reports on the safety of its use in large doses, e.g. 3000 mg. (and more) over long periods in man (Altschul et al 1958; Parsons et al 1956). These doses are much larger than those used in this study.

Can glucose tolerance tests harm the diabetic patient?

The administration of glucose in diabetes: There is no evidence to show that glucose administration as in the glucose tolerance test harms a patient with

maturity-onset type of diabetes. In fact it would be as incorrect as saying that oatmeal harms the diabetic patient, and yet the oatmeal diet was an eminently successful form of treatment of diabetes in the pre-insulin days (von Noorden 1903).

As glucose is handled in the same way as is oatmeal after its digestion and absorption, the administration of glucose for glucose tolerance tests in this type of diabetic is probably harmless. I have seen no single instance of harm in all the cases in whom glucose tolerance tests were done.

This study, however, was on the maturity-onset type of diabetics. In one case where the patient was considered to belong to the juvenile type (or growth-onset type of diabetic) the study was conducted under observation in hospital as a precautionary measure.

RESULTS:

The results in the Nicotinamide study can be classified into 2 groups:

GROUP A: 20 patients who showed improvement after treatment with nicotinamide had been commenced.

GROUP B: 28 patients who showed no improvement after commencing treatment with nicotinamide. (2 of these patients (P.K. 74; W.R. 126) are also included in GROUP A because of their subsequent marked response with the addition of insulin to nicotinamide).

GROUP A. (Total 20 : G.T.T.'s in 17)

The following cases showed improvement in blood glucose estimations after Nicotinamide had been commenced:

Case.	Name.	Age yrs. 1st seen.	Duration D.M. before control period.	G.T.T.	See Graph Page:
3	J. A.	15	3/12	No	61
2	M. A.	68	4/12	Yes	109
31	J. C.	65	11/12	Yes	112
32	N. C.	35	1/12	Yes	106
41	T. E.	32	7 yrs.	No	—
47	J. F.	47	1 yr.	Yes	107, 108
80	M.La.	46	1 yr.	Yes	110
82	M. L.	53	6/12	Yes	65
83	L. L.	58	1/12	Yes	103
86	J. L.	67	2/12	Yes	—
95	C. M.	51	18/12	Yes	111
112	S. N.	55	2 yrs.	Yes	—
127	D. R.	43	4/12	Yes	55, (101), 102
130	K. R.	67	3/12	Yes	64
136	G. S.	53	3/12	Yes	104, 105
161	G. W.	50	1/12	Yes	63, 197, 206
5	J.Al.	50	1 yr.	No	—
81	My.L.	48	3/12	Yes	117
74	P. K.	37	2/12	Yes	113
126	W. R.	51	3/12	Yes	114, 115, 206

The type of response seen in GROUP A can be further classified as follows:-

(i) Improvement to a normal glucose tolerance test or practically normal glucose tolerance test: Total 6.

Case	Name	Comments (Lowest fasting and 2 hr. figures of G.T.T's)	Weight
127	D.R.	Normal G.T.T's after grossly abnormal G.T.T's. (F 87mg.; 2 hr. 111mg.)	Gain: 10 lbs.
161	G.W.	Normal G.T.T. (F 110mg.; 2 hr. 107mg)	Constant
83	L.L.	(F 128mg.; 2 hr. 142 mg. 1½ hr. 121mg.)	Loss 2-4 lbs.
32	N.C.	(F 124 mg.; 2 hr. 147mg.)	Loss 3 lbs.
2	M.A.	Normal G.T.T. (F 118mg.; 2 hr. 120mg.)	± Constant
82	M.L.	(F 119mg.; 2 hr. 142mg.)	Loss 2 lbs.

(ii) Improvement showing trend towards normal glucose tolerance test, but stopping short of complete remission: Total 3.

Case	Initials
136	G.S.
47	J.P.
80	M.La.

(iii) Normal Fasting blood glucose levels after period of established abnormality: Total 6.

Case	Initials	F.B. Glucose	G.T.T.
31	J.C.	Back to normal (Low normals)	F = normal 2 hr. = Near normal
95	C.M.	Low normals	F = normal 2 hr. = abnormal
81	My.L.	Low normals	F = normal 2 hr. = abnormal
112	S.N. (No illus.)	Low normals	F = abnormal 2 hr. = abnormal
86	J.L. (No illus.)	Low normals	F = normal (110 mg.) 2 hr. = abnormal (195 mg.)
130	K.R.		F = normal 2 hr. = abnormal

(iv) Some improvement demonstrated while receiving nicotinamide: Total 3.

Case	Name	Comments
3	J.A.	Juvenile type of diabetic. Reduction in 24 hour urine glucose excretion; reduction in insulin requirement.
5	J.Al.	Reduction in insulin requirement.
41	T.E.	Improvement in insulin control.

(v) Marked improvement with nicotinamide + insulin - necessitating discontinuance of insulin. (These patients showed no initial response to nicotinamide alone and are therefore included in GROUP B as well).

Case	Name	Comments	Weight
74	P.K.	A better G.T.T.	Gain 6 lbs.
126	M.R.	A better G.T.T. Persistence of low fasting levels.	Gain 14 lbs.

DIABETOGENIC AND ANTI-DIABETOGENIC SUBSTANCES.

SUMMARY:

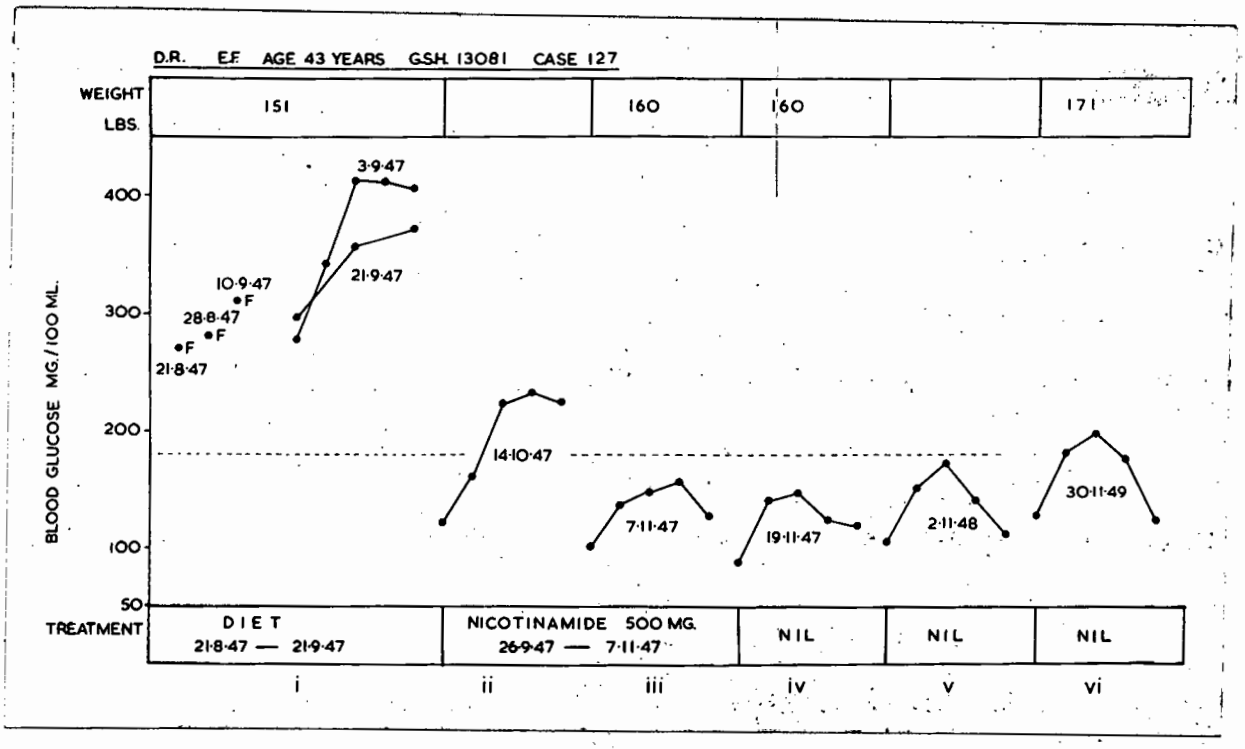
This is a long term study of the influence of various substances, diabetogenic and anti-diabetogenic, on the glucose tolerance of diabetic patients.

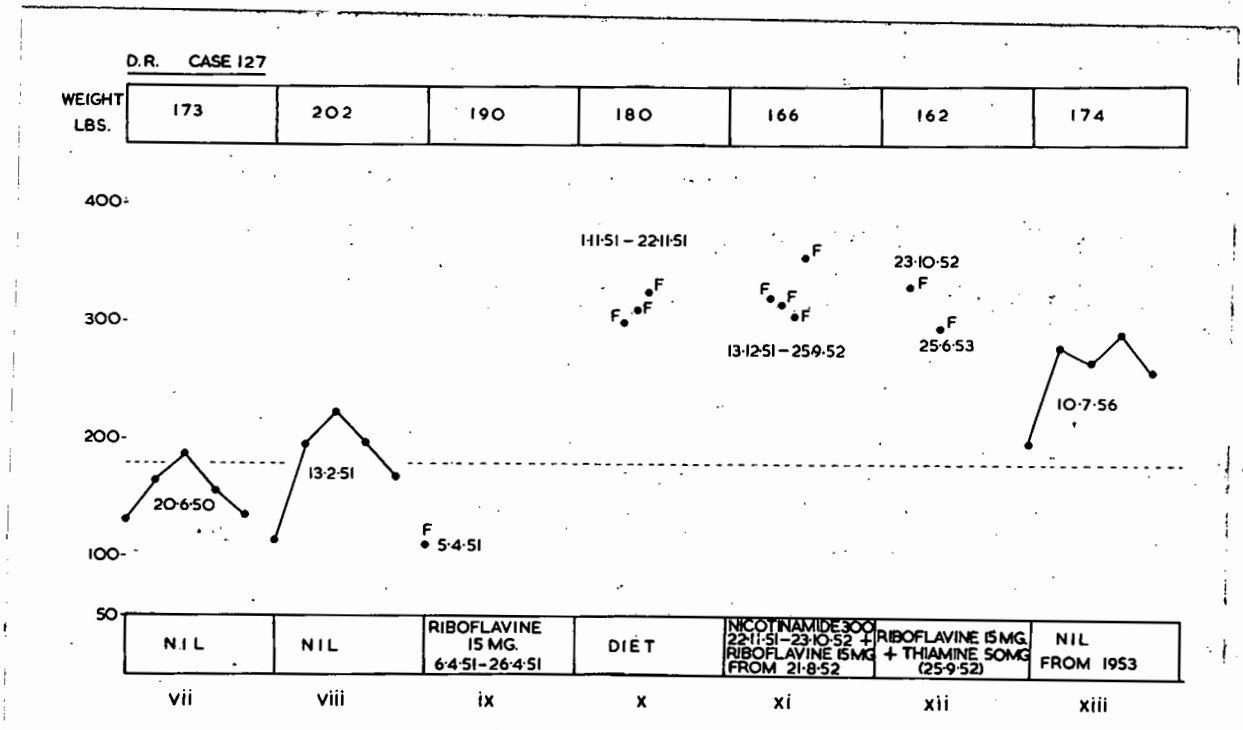
The effect of nicotinamide in diabetic patients is investigated. These patients were studied over a period of years and formed the nucleus of the patients who were further investigated with other agents, i.e. the pharmacological hypoglycaemic agents: the sulphonylureas and the biguanides.

Carbohydrate tolerance was investigated in a group of gouty patients. Gouty patients with a diabetic or abnormal glucose tolerance curve were followed up.

Cortisone/glucose tolerance tests were performed on patients from the various groups studied.

In the discussion of the thesis as a whole, the interrelationship of the various aspects of the study is pointed out.


D.R. E.F. AGE 43 YEARS GSH. 13081 CASE 127
WEIGHT LBS.
151
160
160
171
BLOOD GLUCOSE MG./100 ML.
400
300
200
100
50
3·9·47
21·9·47
10·9·47
F
28·8·47
F
F
21·8·47
14·10·47
7·11·47
19·11·47
2·11·48
30·11·49
TREATMENT
DIET
21·8·47 — 21·9·47
NICOTINAMIDE 500 MG.
26·9·47 — 7·11·47
NIL
NIL
NIL
i
ii
iii
iv
v
vi


D.R. CASE 127
WEIGHT LBS.
173
202
190
180
166
162
174
400
300
200
100
50
1·11·51 – 22·11·51
F
F
F
F
F
F
F
13·12·51 – 25·9·52
23·10·52
F
F
25·6·53
10·7·56
20·6·50
13·2·51
F
5·4·51
NIL
NIL
RIBOFLAVINE 15 MG. 6·4·51 – 26·4·51
DIET
NICOTINAMIDE 300 22·11·51 – 23·10·52 + RIBOFLAVINE 15 MG FROM 21·8·52
RIBOFLAVINE 15 MG. + THIAMINE 50 MG (25·9·52)
NIL FROM 1953
vii
viii
ix
x
xi
xii
xiii

Glucose tolerance test (vii) on 20.6.50 could still be considered within the range of normal in spite of the fact that her weight now was 173 lbs.

A relapse to a diabetic type of glucose tolerance curve has occurred on 13.2.51 (viii). At this time her weight was 202 lbs. Diabetes is frankly manifest in November 1951 (x) with a relapse to the previously high fasting glucose levels seen in (i). This is not influenced by a second course of nicotinamide.

Five more patients were found to show this type of response, viz. L.L., G.W., E.C., M.A., M.L.

A trend towards a normal glucose tolerance curve, but stopping short of a complete remission was seen in G.S., J.F. and M.La.

This was regarded as a significant response, as an improved curve was seen to precede a normal glucose tolerance test in GROUP A (i).

(iii) Four of the 6 cases where low fasting blood glucose levels, (e.g. 90 mg.) were recorded might

have shown response similar to those in (i) or (ii), had sufficient glucose tolerance tests been available.

FOR THE ILLUSTRATIONS OF THE FOLLOWING PATIENTS IN GROUP A, SEE PAGE NUMBERS INDICATED. THESE PATIENTS FORMED PART OF A LONG TERM STUDY AND ARE INCLUDED IN SECTION V. (in some cases)

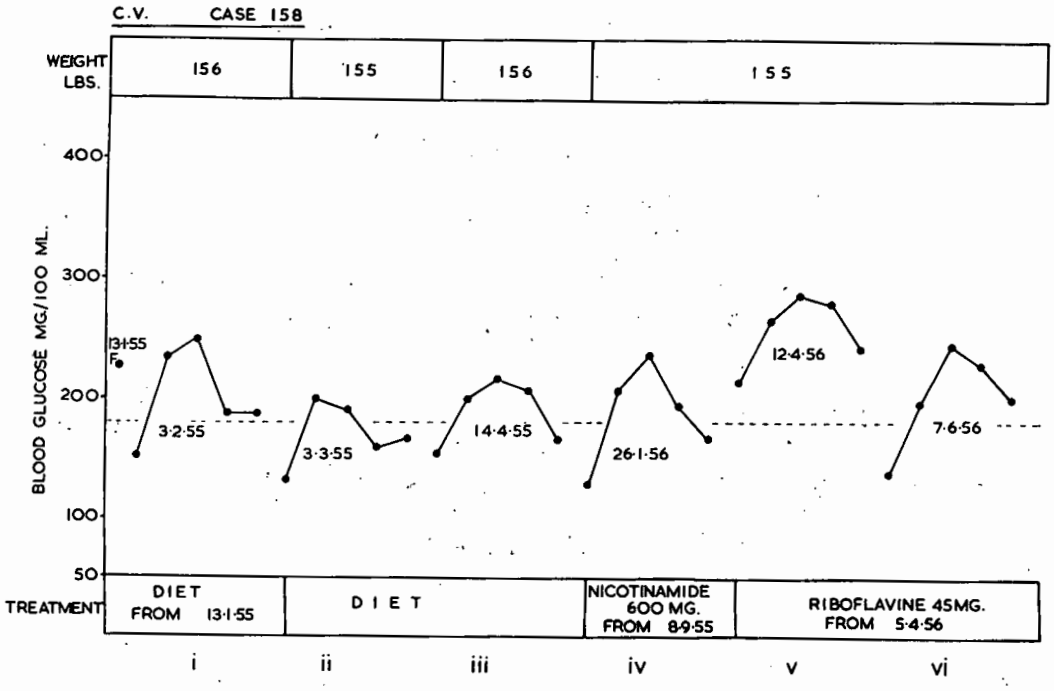
Name	Case	Page
L.L.	83	103
G.W.	161	63, 197, 206
N.C.	32	106
M.A.	2	109
M.L.	82	65
G.S.	136	104, 105
J.F.	47	107, 108
M.La.	80	110
D.R.(Cont'd)	127	55, (101), 102

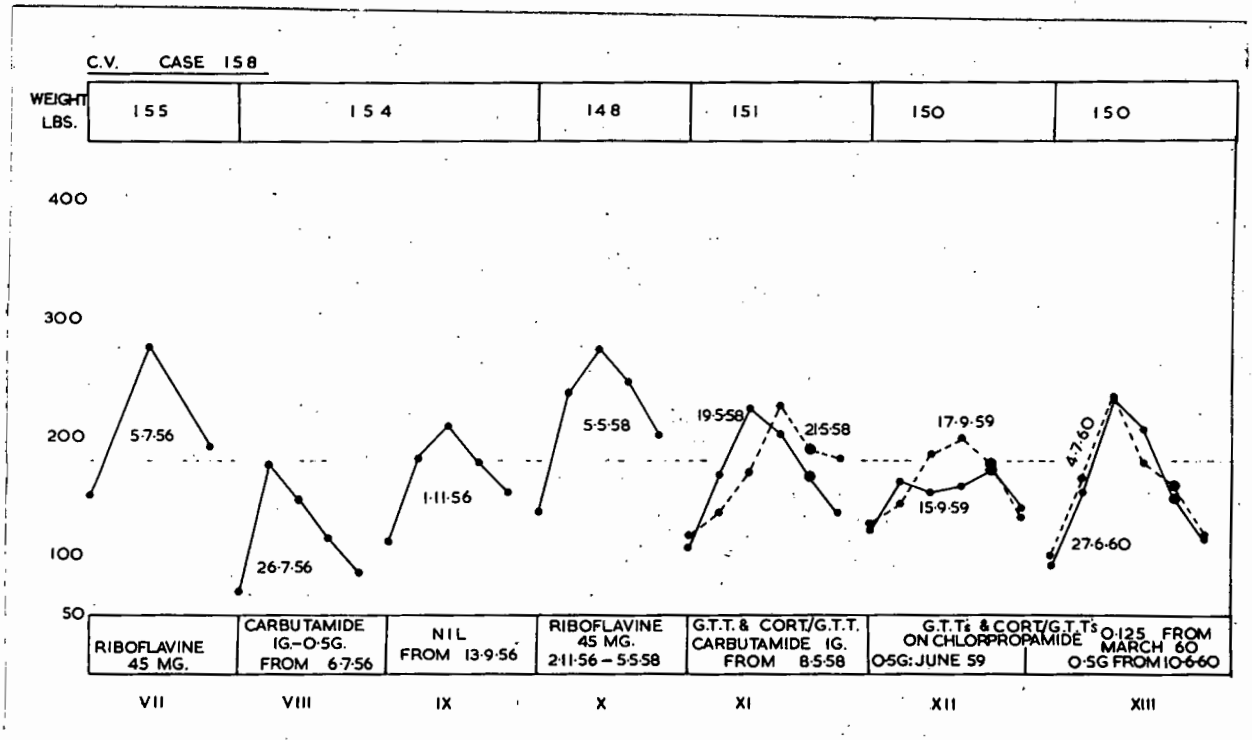
GROUP B. (Total 28 ; G.T.T.'s in 13).

The following patients showed no improvement in blood glucose estimations after Nicotinamide had been commenced:

Case.	Name.	Age yrs. 1st seen.	Duration D.M. before control period.	G.T.T.	See Graph Page (Facing).
4	S.A.	55	3 yrs.	No	—
13	R.B.	51	2 yrs.	No	—
28	L.C.	48	1 yr.	No	—
29	E.C.	55	1 yr.	Yes	119, 120
30	T.C.	57	6 yrs.	Yes	—
39	K.D.	66	18/12	Yes	68
195	E.F.	53	5 yrs.	No	—
67	R.J.	62	4/12	Yes	66
68	A.J.	39	-	No	—
75	I.K.	61	5 yrs.	No	—
78	D.L.	61	15/12	Yes	—
89	M.Li.	44	-	No	—
85	H.L.	54	2 yrs.	No	—
102	P.M.	39	1 yr.	Yes	60
94	S.M.	62	6 yrs.	No	—
97	H.Mr.	35	1/12	Yes	137
101	F.M.B.	50	3/12	No	—
114	W.N.	40	1 yr.	No	—
123	E.Pa.	58	10 yrs.	No	62
119	E.P.	47	5/12	Yes	—
121	A.P.	57	8 yrs.	No	—
131	M.R.	53	3 yrs.	No	—
156	I.U.	67	2/12	Yes	121
158	C.V.	49	1/12	Yes	59, 116
157	S.V.	42	9/12	Yes	67
138	R.S.	60	15 yrs.	No	—
74	P.K.	37	2/12	Yes	113
126	W.R.	51	3/12	Yes	114, 115, 206

P.K.(74) and W.R. (126) also included in GROUP A.


C.V. CASE 158
WEIGHT LBS.
156
155
156
155
400
300
200
100
50
BLOOD GLUCOSE MG/100 ML.
13·1·55 F
3·2·55
3·3·55
14·4·55
26·1·56
12·4·56
7·6·56
TREATMENT
DIET FROM 13·1·55
DIET
NICOTINAMIDE 600 MG. FROM 8·9·55
RIBOFLAVINE 45MG. FROM 5·4·56
i
ii
iii
iv
v
vi


C.V. CASE 158
WEIGHT LBS.
155
154
148
151
150
150
400
300
200
100
50
5·7·56
26·7·56
1·11·56
5·5·58
19·5·58
21·5·58
17·9·59
15·9·59
4·7·60
27·6·60
RIBOFLAVINE 45 MG.
CARBUTAMIDE IG.–0·5G. FROM 6·7·56
NIL FROM 13·9·56
RIBOFLAVINE 45 MG. 2·11·56 – 5·5·58
G.T.T. & CORT/G.T.T. CARBUTAMIDE IG. FROM 8·5·58
G.T.Ts & CORT/G.T.Ts ON CHLORPROPAMIDE 0·5G: JUNE 59
0·125 FROM MARCH 60 0·5G FROM 10·6·60
VII
VIII
IX
X
XI
XII
XIII

GROUP B:

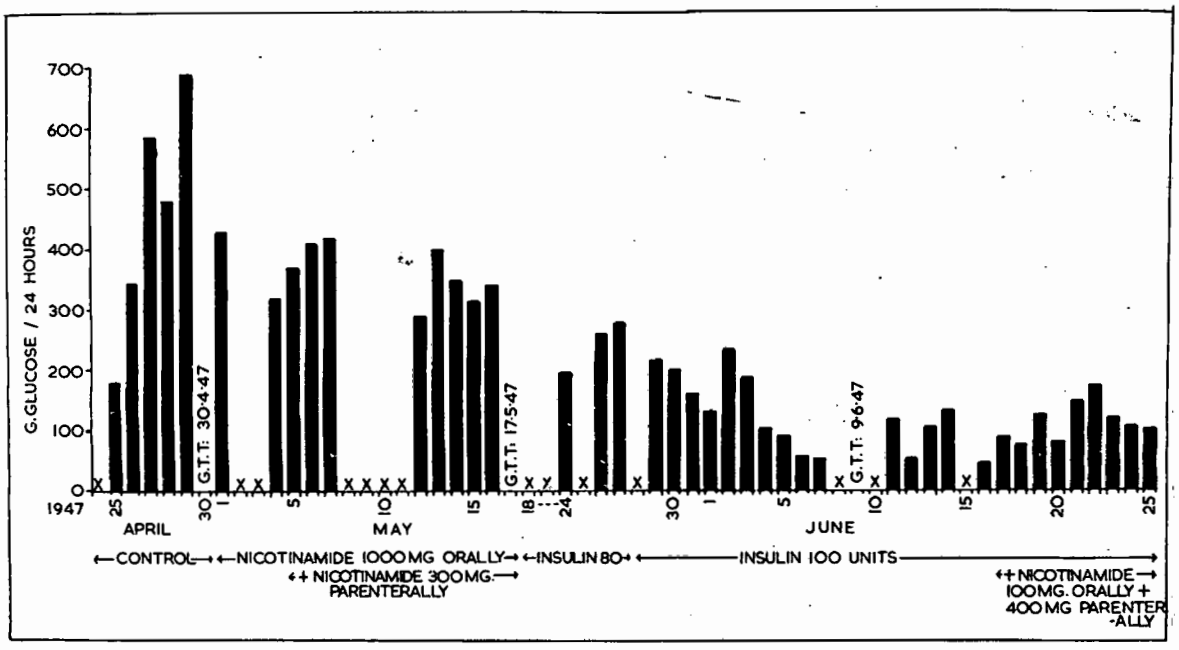
In this group there were sufficient data available on 28 diabetic patients who had received nicotinamide to state that these were not benefited. Where there was improvement in fasting levels this could not be attributed to nicotinamide. The numbers and initials of these patients are listed.

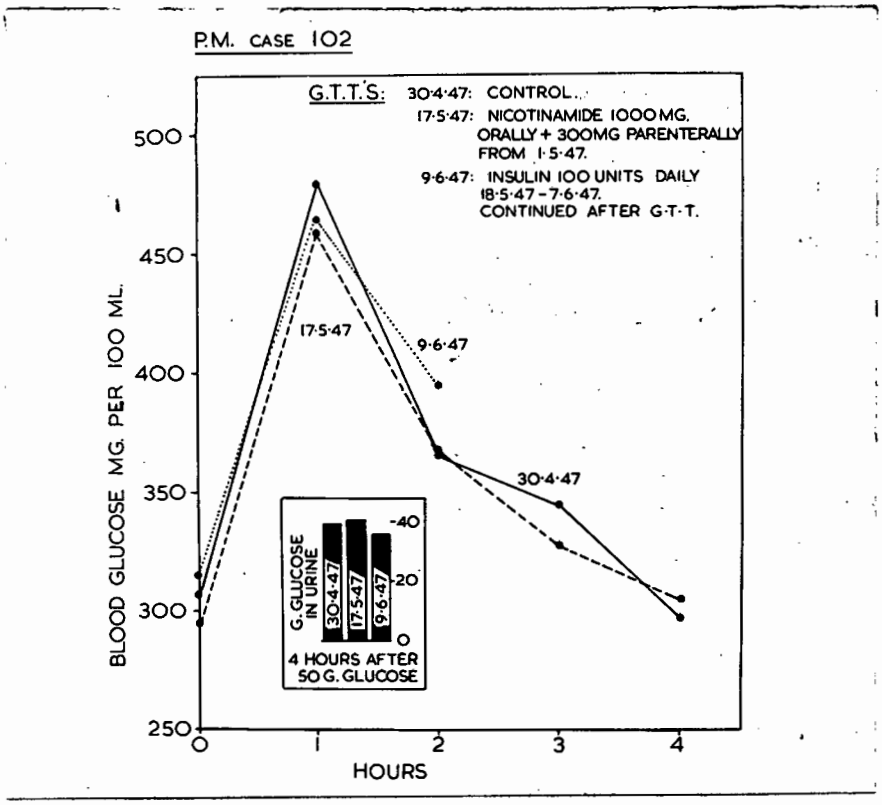
Most of these patients were seen over a period of years. In 13 patients glucose tolerance tests (one or several) were done.

Typical of the method of investigation and response in this group is C.V. (Case 158).

(See facing page).

P.M. CASE 102 24 HOUR QUANTITATIVE URINE GLUCOSE ESTIMATIONS





The case of P.M. (102), a severe diabetic, is also of especial interest. This Coloured man aged 39 years was a case of 'growth-onset' type of diabetes and illustrates complete lack of response to nicotinamide.

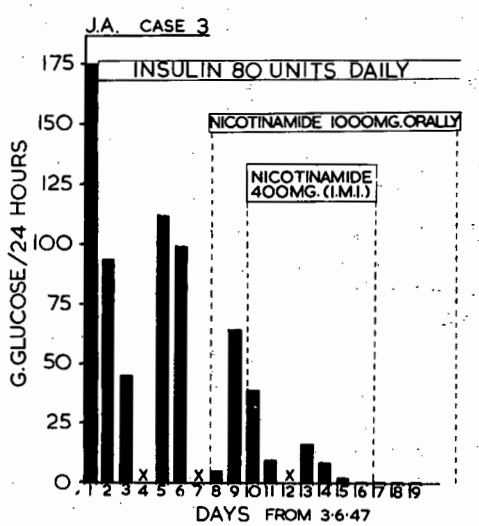
The patient failed to report back to the Diabetic Clinic after his first visit and remained for 4 months on an uncontrolled diet, without treatment. An investigation, under observation in hospital, prior to starting insulin injections, showed that glucose tolerance was not influenced by the administration of nicotinamide; nor was the glucose tolerance test influenced by a course of insulin.

24 hour quantitative urine glucose estimations showed no appreciable difference in the quantity of glucose excreted before or after nicotinamide administration. Similarly, while on insulin, nicotinamide administration orally or parenterally made no appreciable difference to the glucose excretion.

The patients described on pages 61 - 68 apply chiefly to SECTION IV and illustrate the different methods of investigation.

Illustrations of long term cases are included in other Sections of the thesis.

(See index to illustrations)

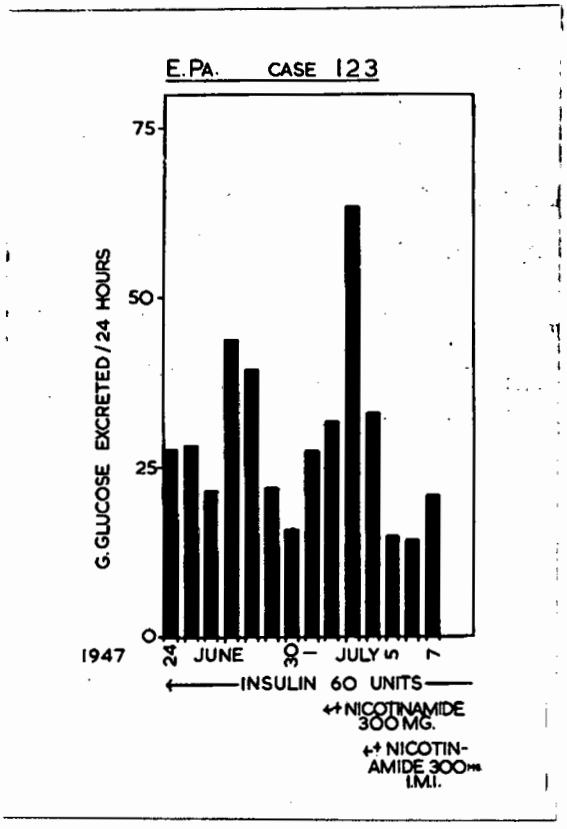

J.A. CASE 3
INSULIN 80 UNITS DAILY
NICOTINAMIDE 1000MG. ORALLY
NICOTINAMIDE 400MG. (I.M.I.)
G. GLUCOSE/24 HOURS
175
150
125
100
75
50
25
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
DAYS FROM 3·6·47

J.A. Case 3, a Coloured boy aged 15 years.

This was a case of severe diabetes in a young boy - an acute onset with Ketosis and blood glucose estimations often over 300 mg. He was admitted to hospital for control.

With the diet and insulin dosage being kept constant, there was a reduction in the amount of glucose excreted daily in the urine - after commencing nicotinamide orally and by intramuscular injection.

His subsequent course continued to be that of the growth-onset type - although his insulin requirement was lower.

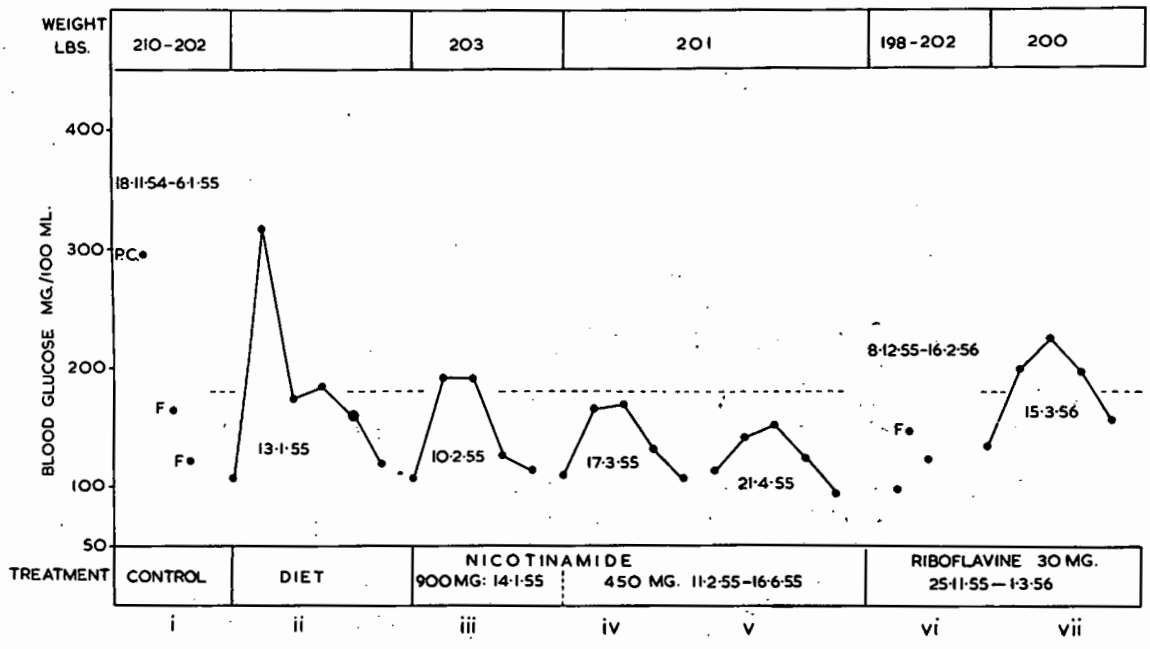

E. PA. CASE 123
75
50
25
0
G. GLUCOSE EXCRETED / 24 HOURS
1947
24
JUNE
30
JULY
5
7
INSULIN 60 UNITS
NICOTINAMIDE 300 MG.
NICOTIN-AMIDE 300 mg. I.M.I.

E.Pa. (Case 123):

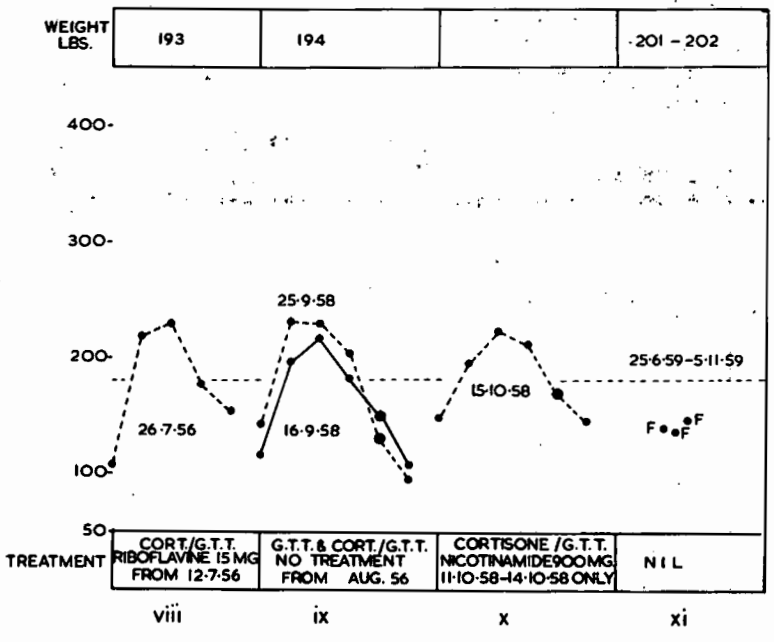
This patient was an elderly European woman.

No significant reduction is shown in 24 hour quantitative glucose excretion in urine after nicotinamide orally and by injection.

G.W. CASE 161



G.W. CASE 161



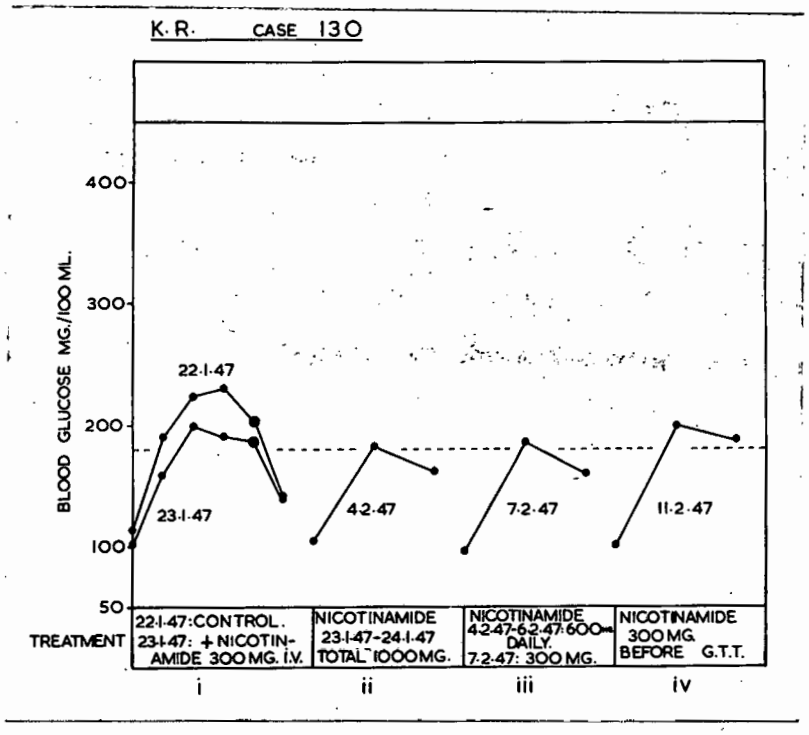
G.W. Case 161, European man aged 50 years.

This patient also had gout. Hyperglycaemic levels were established over a 6 weeks' period.

A glucose tolerance test after being under observation for 2 months was abnormal (ii).

Glucose tolerance tests while on nicotinamide (iii), (iv) and (v) became completely normal.

While taking large doses of riboflavine the fasting glucose levels were elevated (vi) and a glucose tolerance test showed suspiciously high one hour (224 mg.) and 2 hour (156 mg.) levels. A cortisone/glucose tolerance test while on riboflavine (viii) showed no significant change from the glucose tolerance test on 15.3.56 (vii). Glucose tolerance tests performed subsequently (ix) and (x) showed comparable figures although those of 15.10.58 (x) could be considered to be within the diabetic range. A follow up in 1959 showed a tendency towards a rise in fasting glucose levels.


K. R. CASE 130
BLOOD GLUCOSE MG./100 ML.
400
300
200
100
50
22-1-47
23-1-47
4-2-47
7-2-47
11-2-47
TREATMENT
22-1-47: CONTROL.
23-1-47: + NICOTINAMIDE 300 MG. I.V.
NICOTINAMIDE 23-1-47-24-1-47 TOTAL 1000 MG.
NICOTINAMIDE 4-2-47-6-2-47: 600 MG. DAILY. 7-2-47: 300 MG.
NICOTINAMIDE 300 MG. BEFORE G.T.T.
i
ii
iii
iv

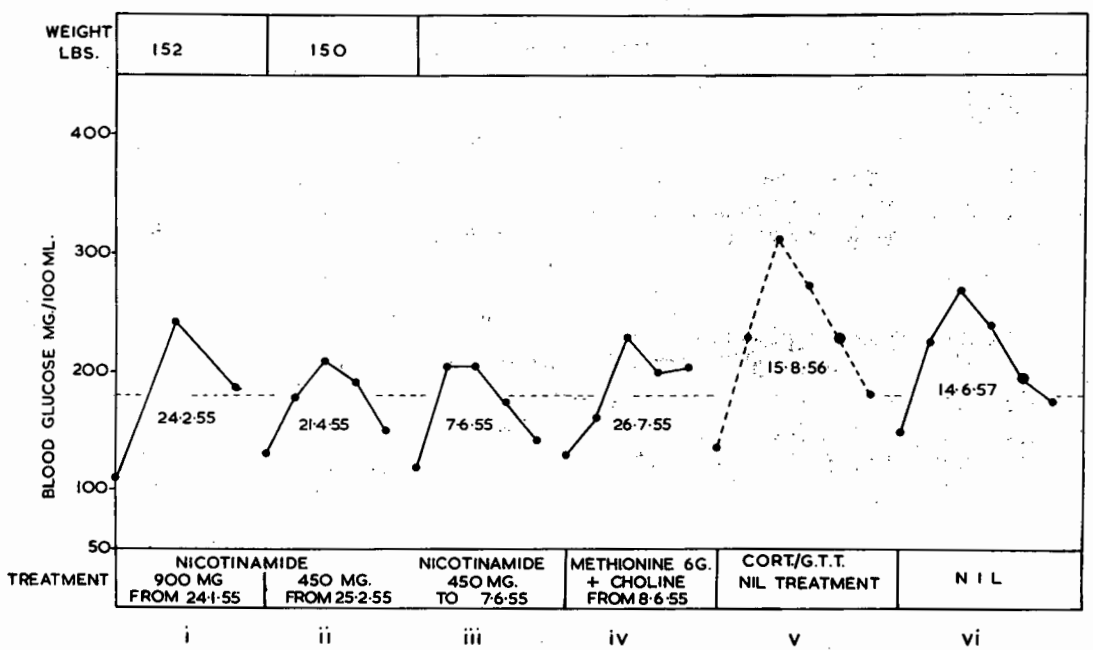
K.R. (Case 130):

This patient was an elderly European woman.

Some reduction in the abnormal levels of the glucose tolerance test is shown after the previous intravenous injection of nicotinamide (i).

No further improvement is shown in glucose tolerance tests (ii) - (iv).

M.L. CASE 82

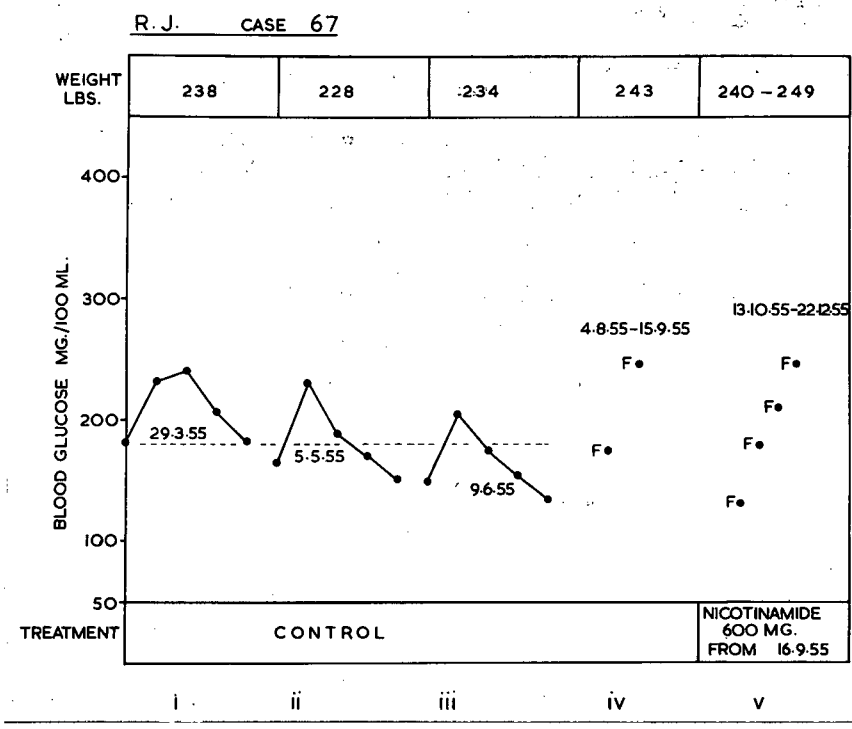

WEIGHT LBS.
152
150
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
24·2·55
21·4·55
7·6·55
26·7·55
15·8·56
14·6·57
TREATMENT
NICOTINAMIDE 900 MG FROM 24·1·55
450 MG. FROM 25·2·55
NICOTINAMIDE 450 MG. TO 7·6·55
METHIONINE 6G. + CHOLINE FROM 8·6·55
CORT./G.T.T. NIL TREATMENT
N I L
i
ii
iii
iv
v
vi

M.L. Case 82, a European man aged 53 years.

This patient was found to have an hepatomegaly and glycosuria. There was a family history of diabetes.

While on nicotinamide his glucose tolerance test evolved from abnormal (i) to a practically normal glucose tolerance test on 21.4.55 (ii) and 7.6.55 (iii).

On lipotropic agents the glucose tolerance test again showed a definitely abnormal 2 hour level and a cortisone enhanced glucose tolerance test showed considerable impairment of tolerance. A glucose tolerance test on 14.6.57 showed a manifest diabetic curve.

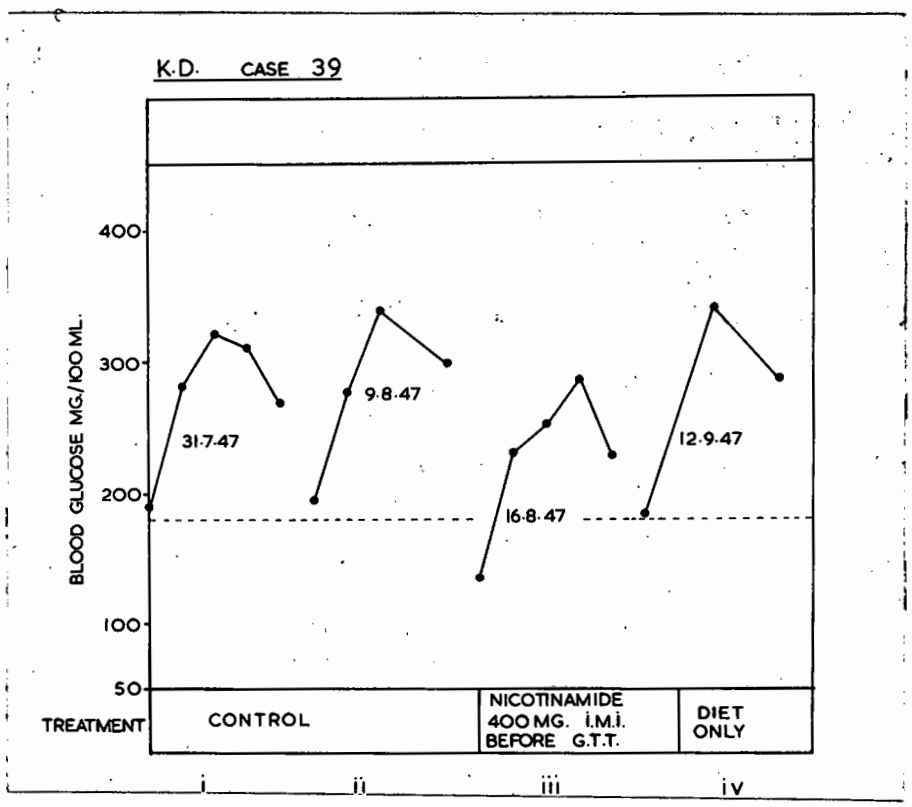

R. J. CASE 67
WEIGHT LBS.
238
228
234
243
240 – 249
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
29.3.55
5.5.55
9.6.55
4.8.55–15.9.55
F
13.10.55–22.12.55
TREATMENT
CONTROL
NICOTINAMIDE 600 MG. FROM 16.9.55
i
ii
iii
iv
v

R.J. (Case 67):

This patient was an elderly European man.

Glucose tolerance tests (i), (ii), (iii), show a tendency towards remission but a relapse to hyperglycaemic levels is shown shortly afterwards (iv).

Fasting levels are not lowered by nicotinamide.


K.D. CASE 39
BLOOD GLUCOSE MG./100 ML.
400
300
200
100
50
31.7.47
9.8.47
16.8.47
12.9.47
TREATMENT
CONTROL
NICOTINAMIDE 400 MG. I.M.I. BEFORE G.T.T.
DIET ONLY
i
ii
iii
iv

S.V. (Case 157):

This patient was a middle-aged Coloured woman.

Her glucose tolerance tests remained completely abnormal.

K.D. (Case 39):

This patient was an elderly European woman with established diabetes.

A slight reduction in the levels of the glucose tolerance test (iii) was shown when a single intramuscular injection of nicotinamide preceded the glucose tolerance test.

The following 2 cases (W.R. 126, and P.K. 74) were included both in GROUP A and GROUP B : remissions occurred after the concurrent administration of insulin and nicotinamide.

Mrs. W.R., aged 51 years, showed an initial deterioration of glucose tolerance test while on nicotinamide. Insulin was given in addition to nicotinamide, and a rapid reduction in insulin requirement occurred. Insulin could be discontinued 4 months later. Glucose tolerance tests done at this time showed improvement over previous glucose tolerance test. A gain in weight was coupled with an improvement in general condition.

After stopping nicotinamide, this patient behaved like a 'maturity-onset' type of diabetic and later responded well to the administration of the new hypoglycaemic agents. (See pages 114, 115).

P.K. (Case 74), a man aged 37 years, failed to respond to diet and nicotinamide. Insulin was given for control and with nicotinamide, a rapid reduction

in insulin was possible, until it could be omitted. Glucose tolerance after insulin had been stopped for 3 weeks showed considerable improvement. His subsequent course was more suggestive of the juvenile-type of diabetes and insulin was required again for control. (See page 113).

DISCUSSION OF THE EFFECT OF NICOTINAMIDE IN DIABETES:

The action of nicotinamide in diabetes has been the subject of past investigations.

Göbell (1940) found that nicotinamide administration caused a reduction in blood sugar in man of 20 - 45 mg.%. An injection of nicotinamide produced a glucose tolerance test with lower blood glucose levels. Marche et al (1943) and Poumeau-Delille et al (1943) confirmed this hypoglycaemic action in normal human adults. Neuwahl (1943) also recorded a fall in blood glucose after administration of nicotinic acid to

non-diabetic subjects and an improvement in carbohydrate tolerance in diabetics. Unger (1957) noted a considerable fall in the blood glucose of diabetics in a 4 hour period after administration of sodium nicotinate; but no effect was demonstrated in normal human adults.

This blood glucose lowering effect, however, was not confirmed by other workers (Banerjee et al 1949; Cumings 1947; Wade 1947; Haller et al 1957).

Banerjee et al (1949) found that the blood glucose of diabetic and normal subjects was practically unaffected by the i.v. injection of 500 mg. nicotinamide. Cumings (1947) showed that nicotinamide is without effect on blood sugar in normal subjects. Wade (1947) found no evidence that 600 mg. nicotinamide t.d.s. for 14 days influenced the glucose tolerance tests in 6 diabetics. More recently, Haller et al (1957) claimed that the fall in blood glucose noted by Unger could be reproduced in his control series when nicotinamide was omitted.

The results of these investigations have been inconclusive and contradictory.

It is to be noted that almost all these observations were made in short-term studies of the action of nicotinamide.

Nicotinamide is a physiological agent of prime importance in the normal physiology of carbohydrate metabolism (See SECTION III). If it has an action on abnormal carbohydrate metabolism, the benefit produced may be expected to be a long lasting one. Short term studies would not demonstrate or give information on this point. A long term study is also more likely to illumine the role of nicotinamide in diabetes by giving information about the subsequent progress of diabetes.

As the study evolved it was realised that the subsequent progress may be of great significance.

Discontinuance of nicotinamide did not imply that the benefit which it might have induced would not persist. Nicotinamide may have corrected some fundamental error of metabolism.

Could we expect to see a correction of the most fundamental disturbance of carbohydrate metabolism viz. the glucose tolerance test reverting to normal ?

DISCUSSION OF RESULTS:

The first and most dramatic response seen in this study on nicotinamide was that of the remission in diabetes to a normal glucose tolerance test in Mrs. D.R. (Case 127).

This case, D.R., was of great interest: an established case of moderately severe diabetes improved to such an extent after starting nicotinamide administration that our most sensitive test for diabetes, viz. glucose tolerance test, failed to show the presence of diabetes. Thus there was an apparent cure of an established case of diabetes. With the improvement in glucose tolerance there was an accompanying improvement in wellbeing and a gain in weight.

3½ years later when she had exceeded her pre-diabetic heaviest weight there was a recurrence of symptoms of diabetes. The diabetes now was not influenced by the administration of nicotinamide, dietary restriction or weight loss.

This trend towards improvement followed by relapse was seen in practically all the cases who had initially remitted and who were followed up over a period of years. D.R. (127), L.L. (83), N.C. (32), M.A. (2), M.L. (82), G.S. (136) J.F. (47).

The most important outcome of this study was the occurrence of remissions to a normal glucose tolerance test in 6 of the cases studied with nicotinamide.

REMISSIONS IN DIABETES:

It became important to assess the part played by nicotinamide in producing the remissions seen. The problem was approached in two ways:

1. Remissions of diabetes in the world literature were reviewed.

2. An attempt was made to find other cases of remissions in our large diabetic clinic (similar to those who went into remission on nicotinamide).

1. In the literature, data on remissions were found to be inadequate, for the following reasons:

(a) The definition of remissions varied: some authors considered a wellmarked improvement in the diabetes as a remission.

(b) Some reports of remissions were based on the previous finding of glycosuria alone; or one abnormal blood glucose test only.

(c) The period of established diabetes was often short, e.g. one week only.

(d) The follow-up was too brief.

(e) Glucose tolerance tests were not done to demonstrate the completeness of the remission.

(f) Where glucose tolerance tests were done these were often still grossly abnormal (Taylor 1960).

Remissions in my study are meant to imply an improvement not only to a normal fasting blood glucose level, but also in the glucose tolerance test to a normal form oe near normal form after a period of established abnormality. These were the criteria applied to the 6 cases in GROUP A of the nicotinamide study.

In a section in the Medical Annual 1959, remissions of diabetes are stated to be very rare - "there are less than 20 cases on record" (The Medical Annual 1959).

In a review of the literature of reported remissions of diabetes there are some remarkable cases (Harwood 1957, Peck et al 1958, Cheng et al 1953, del Greco et al 1953, Johnson 1958). However, in none of these cases was the period of established diabetes a lengthy one (Joslin (1952) stipulates established diabetes of at least one month's duration). The follow-up was usually not long enough. Harwood's case perhaps best fulfils the criteria demanded by Joslin. The period of established diabetes was brief

and the remission had lasted for 23 months at the time of publication.

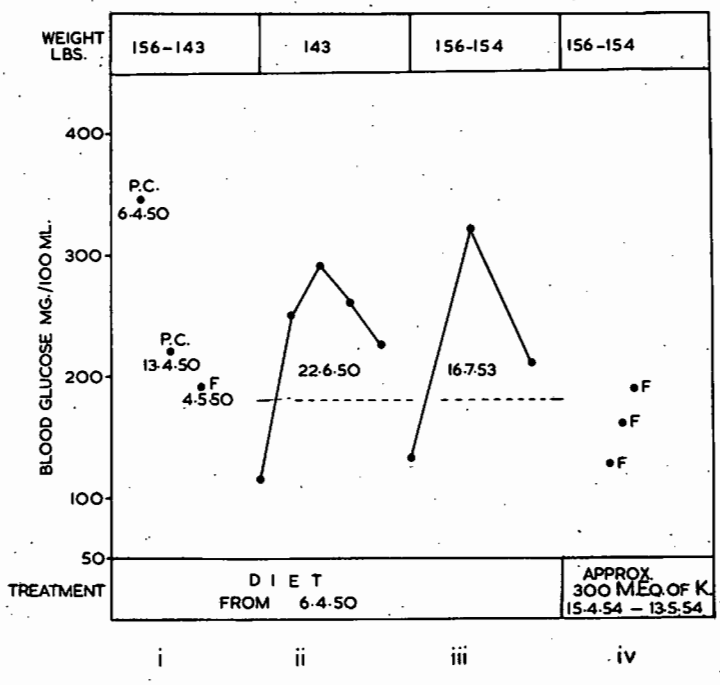
The case of D.R. would thus be almost unique. There is an adequate control period of an unremitting established diabetes followed by a proven remission confirmed not only by normal fasting blood glucose tests, but normal glucose tolerance tests as well in a patient who had gained weight.

Remissions following weight loss are known to occur. Newburgh and Conn (1939) reported that this occurred when the patients had lost a considerable proportion of the excess weight.

Thus 2 of the patients in their series who showed the earliest return of a normal response had lost 35 lbs. and 38 lbs. respectively. Some of these patients later abandoned the diet and again became obese; it was noted that their carbohydrate tolerance was eventually lost and that the diabetic symptoms recurred.

In a subsequent paper, Newburgh (1942) reported that a small percentage of his obese diabetic patients

C.G. CASE 51


WEIGHT LBS.
156–143
143
156–154
156–154
BLOOD GLUCOSE MG./100 ML.
400
300
200
100
50
P.C. 6·4·50
P.C. 13·4·50
F 4·5·50
22·6·50
16·7·53
F
F
F
TREATMENT
DIET FROM 6·4·50
APPROX. 300 M.EQ. OF K. 15·4·54 – 13·5·54
i
ii
iii
iv

who co-operated fully and succeeded in reducing their weight to normal, failed to achieve normal glucose tolerance curves - a finding that cast some doubt on his theory that the diabetes of obesity was a different disease from ordinary diabetes.

2. Would a search at a large diabetic clinic reveal remissions similar to those seen in these patients while on nicotinamide ?

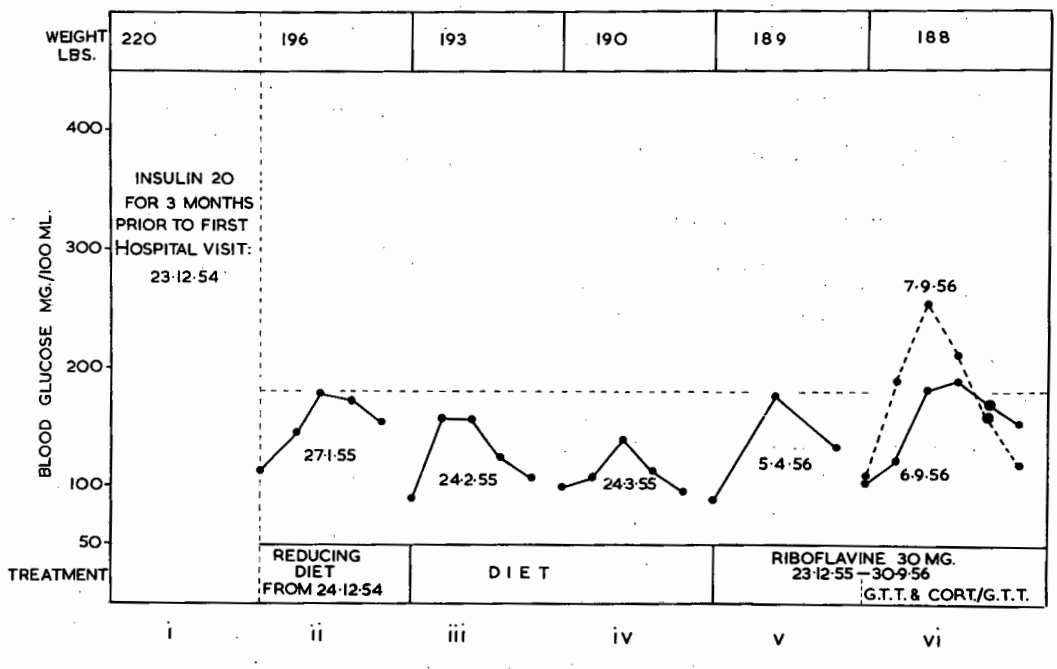
Remissions at our diabetic clinic:

(i) Cases who showed a good hypoglycaemic response judging from fasting glucose tests and treated by diet alone were selected from the diabetic clinic. The object was to see whether I could find responses to match those seen in the cases who had shown a remission with nicotinamide.

In one such case which seemed to fulfil these criteria best (C.G. Case 51), a glucose tolerance test still showed a typical diabetic curve. (See facing page).

(ii) The only 'remission' recorded in 210 patients selected at random from the diabetic clinic for a special

E.S. CASE 135


WEIGHT LBS.
220
196
193
190
189
188
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
INSULIN 20 FOR 3 MONTHS PRIOR TO FIRST HOSPITAL VISIT: 23·12·54
27·1·55
24·2·55
24·3·55
5·4·56
7·9·56
6·9·56
TREATMENT
REDUCING DIET FROM 24·12·54
DIET
RIBOFLAVINE 30 MG. 23·12·55 — 30·9·56
G.T.T. & CORT./G.T.T.
i
ii
iii
iv
v
vi

clinical study (Markman et al 1959), was a patient of mine (P.K. Case 74).

(iii) Remissions accompanied by weight loss: In my series of cases (not treated with nicotinamide), the following was the best example I could find: an obese woman (E.S. Case 135) who had been on insulin showed a remission in diabetes after insulin was stopped. This was accompanied by weight reduction. However, the original glucose tolerance test was not convincingly abnormal and 18 months later there seemed to be a reversion to an abnormal 2 hour figure, in spite of the fact that the patient had maintained her weight loss.

(iv) Acute diabetes arising from curable causes: The following case which was precipitated by trauma showed a remission in diabetes.

M.D. (Case 38), a healthy looking man aged 43 years, was seen by me at the diabetic clinic when he was taking 60 units of Lente insulin. Diabetes had first manifested itself after an accidental rupture of the tendo Achillea. It was possible to reduce insulin and to omit it altogether 2 months later. For 12 months his urine remained sugar free and then hyperglycaemia developed again.

CONCLUSIONS:

1. Nicotinamide was found to have a beneficial effect on the carbohydrate tolerance in 18 patients of the maturity onset type of diabetes of recent onset.

2. The improvement could not be ascribed to weight loss which in many of these cases was negligible. This improvement was usually most manifest while the patient was regaining weight.

3. When there was a relapse of the hyperglycaemia this failed to respond to diet or nicotinamide.

4. In 2 patients of the 'growth-onset' type of diabetes one showed some improvement; the other showed no response.

5. In 2 patients of an intermediate type of diabetes, there was a rapid reduction in insulin requirement when given concurrently with nicotinamide.

FURTHER INVESTIGATIONS ON PHYSIOLOGICAL AGENTS

IN THE CYCLE OF RESEARCH:

(1) RIBOFLAVINE.

While the observations on the action of nicotinamide in diabetes were being made, other incidental points became evident.

Some of the patients who had been taking nicotinamide for prolonged periods developed an angular stomatitis. It was thought that this phenomenon could be due to a vitamin imbalance produced either by the nicotinamide administration or else occurring in diabetes per se.

Riboflavine in large doses (e.g. 15 - 45 mg. daily) was prescribed. In the meantime, observations on the blood glucose levels in these patients were still being recorded.

On examining these results retrospectively, it was found that in some cases there had been a change in blood glucose levels - usually a steady rise - after riboflavine administration had commenced.

It was therefore decided to record observations made on changes in blood glucose levels following riboflavine administration.

11 patients were observed.

RESULTS:

Case	Name.	Comments
127	D.R.	Elevation in fasting blood levels after a course of riboflavine.
162	I.W.	Aggravation of glucose tolerance tests.
95	C.M.	Elevation of fasting blood glucose levels.
126	W.R.	No significant change in glucose tolerance tests.
113	E.N.	Slight elevation in fasting blood glucose levels.
135	E.S.	Abnormal glucose tolerance test developed.
161	O.W.	Elevation of fasting blood glucose levels and development of abnormal glucose tolerance test.
158	C.V.	Glucose tolerance tests (1) Elevation of all levels, (2) Elevation of 1½ and 2 hr. levels only.
29	E.C.	Elevation in fasting blood glucose levels.
31	J.C.	Glucose tolerance tests unchanged.
138	R.S.	Inconclusive.

TOTAL: 11 patients: elevation of blood sugar levels: 8.

no change or inconclusive: 3.

Examination of the results showed that following administration of riboflavine some elevation was shown in fasting blood glucose levels or glucose tolerance test/s or both in 8 of the 11 patients.

DISCUSSION OF THE RESULTS:

The results of this investigation would suggest that riboflavine had a diabetogenic effect in the patients studied. This is a point of great interest.

It has been suggested that since alloxan joins with 1, 2 - dimethyl 4 - amino - 5 (d - 1 ribitylamino) - benzene to form riboflavine the question has been raised as to whether the reverse reaction may occur under certain conditions (Banerjee et al 1945).

The studies of Diengott et al (1959) are also of great interest in this connection. In animal studies they have demonstrated that a dietary lack of pantothenic acid or protein or riboflavine (but not thiamine) leads to a diminished activity of hepatic insulinase.

This study might help to explain the finding of low levels of blood glucose and muscle glycogen in riboflavine deficient animals (Forker et al 1954).

Is it possible that riboflavine in excess may have the reverse effect ?

This has been a subsidiary study and may be a point which should be elucidated in further studies.

CONCLUSIONS:

There is sufficient evidence available from these investigations on riboflavine to make it appear that riboflavine in large doses may have a diabetogenic effect. Further investigation into this aspect is required.

(2) OBSERVATIONS ON THE ACTION OF POTASSIUM IN DIABETES:

It was reported that potassium may have a beneficial effect on carbohydrate metabolism in steroid diabetes (Kinsell et al 1953). It was decided to test the effect of potassium orally in doses of 300 m. Eq. daily on the blood glucose in diabetes. (Potassium acetate and chloride together; or potassium acid phosphate was used).

The following 7 patients received potassium:

E.C. (case 29); R.B. (case 13); C.G. (case 51); L.C.(case 28); J.F. (case 47); G.S. (case 136) and J.He. (case 196).

3 of these patients were on insulin at the time.

Results:

In 6 patients, the only change noticed was a slight rise in blood glucose over a short term study. (See illustration page 78 C.G. Case 51). The nature of response was not influenced by changing to phosphate from the acetate and chloride.

It seemed unjustifiable to continue the administration of potassium. The results are recorded since the rise in blood glucose was fairly uniformly demonstrated.

(3) DIABETON-M.

The commencement of my study in 1947 antedated the introduction of the hypoglycaemic agents in current use.

One of these preparations, Diabeton-M, which was the first to become available was tried in a few patients.

Diabeton-M is a tablet composed of:

5 - Hydroxy - anthranilic acid	0.2 mg.
Vitamin B6	2 mg.
Vitamin C	20 mg.
DL - Methionine	20 mg.
Diabeton (a herbal extract)	200 mg.

As the first 2 ingredients of this tablet are closely related to tryptophan metabolism (and nicotinamide can be derived from tryptophan) it seemed that observations on this may be of interest in relation to a study of nicotinamide in diabetes.

There seems to be no logical basis for the inclusion of the other 3 substances in this tablet as

an anti-diabetogenic compound.

The observations on the results of administration of this tablet are included in this study.

Results:

The results in 4 patients are available:

(i) M.A. (Case 2) showed progressive improvement towards a normal glucose tolerance test.

(ii) M.La. (Case 80) showed improvement in first glucose tolerance test 2 weeks after commencement of Diabeton; but after a further 2 weeks the glucose tolerance test showed some regression again and was abnormal in all respects.

(iii) E.C. (Case 29) showed no improvement in fasting blood glucose levels (Note the insulin doses had been increased).

(iv) D.R. (Case 127) showed a deterioration in glucose tolerance test.

Discussion:

Since one of the components of Diabeton-M, viz. Vitamin B6 (pyridoxine) is involved in the normal

production of nicotinamide from tryptophan, and since another component of the tablet, 5 - Hydroxy - anthrinilic acid is known to be a derivative of tryptophan, it is likely that the mechanism of action of Diabeton-M may be closely related to that of nicotinamide.

At about this time the oral hypoglycaemic agent, carbutamide, became available. Because of its dramatic hypoglycaemic effect further observations on Diabeton were terminated.

V.

THE ACTION OF THE PHARMACOLOGICAL HYPOGLYCAEMIC AGENTS IN DIABETES MELLITUS

THE ACTION OF THE PHARMACOLOGICAL HYPOGLYCAEMIC AGENTS IN DIABETES.

INTRODUCTION:

The search for orally effective hypoglycaemic agents has proceeded for many years.

Prior to the advent of insulin, Watanabe (1918) demonstrated that guanidine lowered blood glucose levels. A guanidine derivative, decamethylene diguanidine, was used in the treatment of diabetes in man (Frank et al 1926), but fell into disuse because of its toxicity, chiefly liver damage (Graham and Linder 1928).

In the meantime the successful use of insulin had become firmly established. It was natural that this great discovery by Banting and Best in 1921 would divert research in the treatment of diabetes towards the new focal point, insulin.

It now seemed that the final answer to diabetic treatment was at hand, but as time went on it became clear that insulin was necessary only in a proportion of diabetics. In the acute-onset diabetes of the

juvenile type, often associated with ketosis, insulin would correct the physiological abnormality. The maturity-onset type of diabetic - who had been shown to have available plasma-insulin (Bornstein and Lawrence 1951 (a) and (b)) - was not fundamentally benefited, as far as we know, by exogenous insulin.

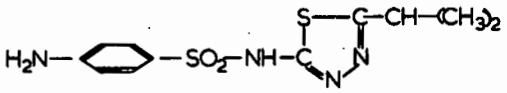
Attempts to correct the hyperglycaemia in diabetes by means other than insulin proved unsuccessful or impracticable until the advent of the sulphonylureas.

This new era in the treatment of diabetes followed on the incidental observation by Janbon et al (1942) (during an investigation on the action of drugs in typhoid) that the sulphonylurea I.P.T.D. had a hypoglycaemic action. Loubatieres published the results of his extensive investigations on I.P.T.D. (1955).

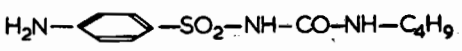
A group of workers (Franke et al 1955, Achelis et al 1955, Bertram et al 1955) reported on the clinical use of another sulphonylurea, carbutamide.

Carbutamide (BZ 55) is now generally believed to be too toxic for routine use. With the replacement

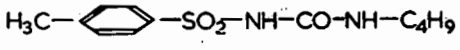
THE SULPHONYLUREAS



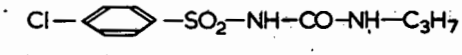
P-AMINOBENZENESULPHONAMIDOISOPROPYLTHIODIAZOLE
[=I.P.T.D.] JANBON (1942)



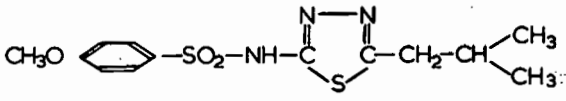
P-AMINO-BENZENESULPHONYL-BUTYL-UREA
[=BZ55, CARBUTAMIDE] (1955)



1-BUTYL-3-P-TOLYLSULPHONYLUREA
[=TOLBUTAMIDE, D860] (1955)



1-PROPYL-3-P-CHLORBENZENESULPHONYLUREA
[=CHLORPROPAMIDE] (1958)



ISOBUZOLE
[=STABINOL FWH 114]

of the NH_2 group by the CH_3 in tolbutamide the toxic effects were greatly diminished, but unfortunately the hypoglycaemic activity was also somewhat decreased.

In chlorpropamide the chlorine radical has replaced the NH_2 or CH_3 group.

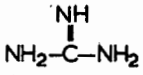
Another hypoglycaemic agent also included in this study is isobuzole which shows an interesting relationship to the first sulphonylurea compound I.P.T.D., which was shown to be a powerful hypoglycaemic agent.

The similarity of the chemical structure of the sulphyonylureas is evident from their formulae (See facing page).

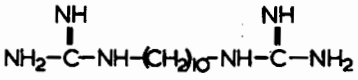
The demonstration of the successful use of the sulphonylureas in the treatment of diabetes created a resurgence of interest in the older compounds which had been abandoned - the guanidine derivatives.

The diguanidines, e.g. synthalin, were too toxic for use in the treatment of diabetes. The diguanides, where 2 guanidine molecules are linked with the elimination of an NH group, still retained the

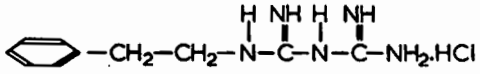
THE GUANIDINE DERIVATIVES



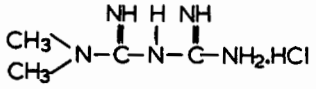
GUANIDINE (1918)



DECAMETHYLENEDIGUANIDINE (SYNTHALIN)
A DIGUANIDINE (1926)



PHENETHYLDIGUANIDE HYDROCHLORIDE [=DBI]
A DIGUANIDE DERIVATIVE



N.N. DIMETHYLDIGUANIDE HYDROCHLORIDE
[=LA 6023, GLUCOPHAGE]
A DIGUANIDE DERIVATIVE

hypoglycaemic effect of synthalin (Slotta et al 1929), but the toxicity had been largely eliminated.

A natural outcome of this latter observation was the re-appraisal of the action in man of diguanide derivatives, the precursors of which had fallen into disrepute after the advent of insulin.

Phenethyl diguanide (DBI) was shown to be an effective hypoglycaemic agent (Ungar 1957), and free of any serious toxic effects. The high incidence of gastro-intestinal side effects, however, has precluded its widespread use in diabetes. Because of the side effects of DBI, another diguanide, dimethyl-diguanide (LA 6023) has also been investigated. (See facing page for the Guanidine Derivatives).

The mechanism of action of both these groups of drugs remains obscure. Several suggestions have been made as to their mode of action (Loubatieres 1946), Mirsky et al 1956), but none has proved entirely satisfactory. Loubatieres suggested that the hypoglycaemic action of the sulphonylureas was due to stimulation of the beta cells of the pancreas to greater

insulin production. Mirsky et al showed that there was inhibition of insulin destruction by the sulphonylureas. Beringer et al (1956) demonstrated an increase of liver glycogen content in starving rabbits receiving carbutamide.

Recent work has shown that the suggested concepts on the mode of action of the sulphonylureas have to be re-evaluated (Weaver et al 1958).

The sulphonylurea drugs and the biguanides may prove to be a stepping stone towards the search for the biochemical lesion in diabetes and its correction. The hypoglycaemic action of these drugs is undisputed but it is problematical whether the other biochemical abnormalities of diabetes mellitus are corrected by these pharmacological agents.

In this age of great therapeutic advances we are witnessing the apparent paradox of pharmacological substances (e.g. the sulphonylurea drugs) being used for the correction of a physiological aberration such as diabetes, on the one hand, and on the other hand of

a physiological agent, cortisone, being used for its pharmacological action in the treatment or 'cure' of a variety of inflammatory and allergic conditions.

There are many puzzling features connected with the clinical applications of these drugs. If we consider the maturity-onset type of diabetes only - why do some patients in this group respond to the sulphonylureas and others not ? A proportion of the diabetics who respond satisfactorily to tolbutamide fail to respond after continued treatment. Why should this secondary failure occur ? Why may patients respond to chlorpropamide when tolbutamide has failed either initially or later ? Is there a difference in their action (or is the apparent difference merely one of absorption and blood level) ?

Why do patients respond to the diguanides when they have failed to respond to all the sulphonylureas or, alternatively respond to a sulphonylurea drug and fail to respond to the diguanides ?

These phenomena that are still obscure and that are poorly understood were singled out for study.

MATERIALS AND METHODS:

THE PATIENTS IN THIS STUDY were as follows:

1. Patients who were seen in the initial study of the action of nicotinamide in diabetes and the associated studies. Special emphasis was placed on this group for the following reasons:

(a) These patients had been observed over a long period of time; the course of the diabetes was already well known.

(b) The blood glucose estimations and the glucose tolerance tests of previous investigations were available.

(c) The response to hypoglycaemic agents could be compared with the previous response to nicotinamide.

2. Patients of the maturity-onset type in whom diet alone failed to control the glycosuria and hyperglycaemia.

3. Some patients on insulin who were probably of

maturity-onset type, and eager to change to treatment with tablets.

4. A few patients of growth-onset type who were (a) either taking large doses of insulin or (b) showing poor control on insulin, were given additional administration of the hypoglycaemic agent to evaluate its effect.

DIET:

(i) Patients from prior studies who found their previous diet adequate were maintained on that diet.

(ii) New patients, or patients who were already on insulin were allowed a fairly liberal calorie diet (depending on their requirements) e.g. 2000 calories or more (and containing 200 G. carbohydrate or more).

(iii) Once the patient was on a trial of the hypoglycaemic agents, no further dietary adjustments were made.

THE METHODS OF INVESTIGATION:

These remained the same as in the preceding study viz. Fasting blood glucose estimations and glucose tolerance tests under the conditions previously stated. A glucose tolerance test was always preceded by a generous 300 G. carbohydrate intake for one week before.

RESULTS:

The results of these investigations are presented graphically in the following pages.

The comments on the illustrations in this section deal chiefly with the influence of the pharmacological agents on the blood glucose levels and glucose tolerance tests.

Other features of the investigation are also shown in the illustrations to give a better profile of the course of the case as a whole.

Cortisone enhancement of the glucose tolerance test is discussed in SECTION VII.

PRESENTATION OF RESULTS:

Points to be noted pertaining to all parts of the presentation:

1) GLUCOSE TOLERANCE TESTS:

(i) Glucose tolerance tests usually show figures plotted at ½ hourly intervals.

(ii) Where only 3 points are plotted, these are Fasting, 1 hour and 2 hour levels.

(iii) Where a glucose tolerance test continues beyond 2 hours, the 2 hour level has been marked by a heavy dot.

(iv) The scale for the glucose tolerance tests remains constant throughout both for the blood glucose level and for the period of time over which it is performed.

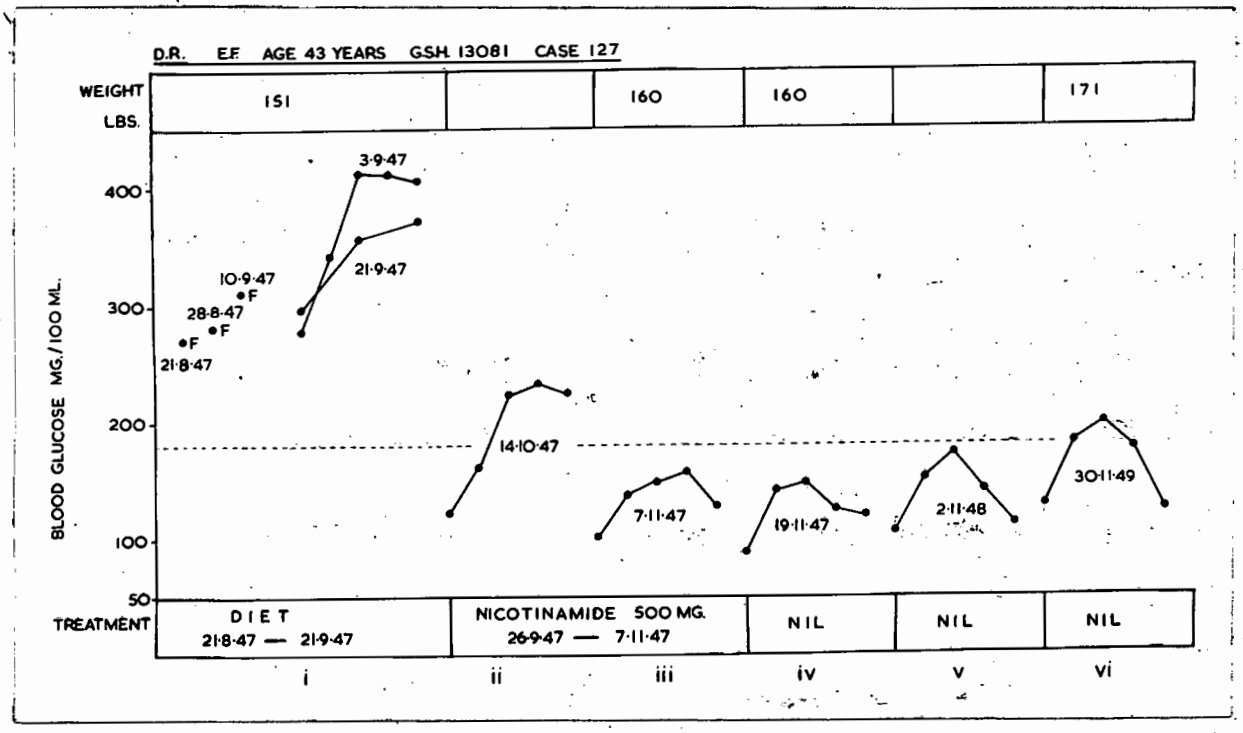
(v) Cortisone/Glucose tolerance tests are distinguished by broken lines.

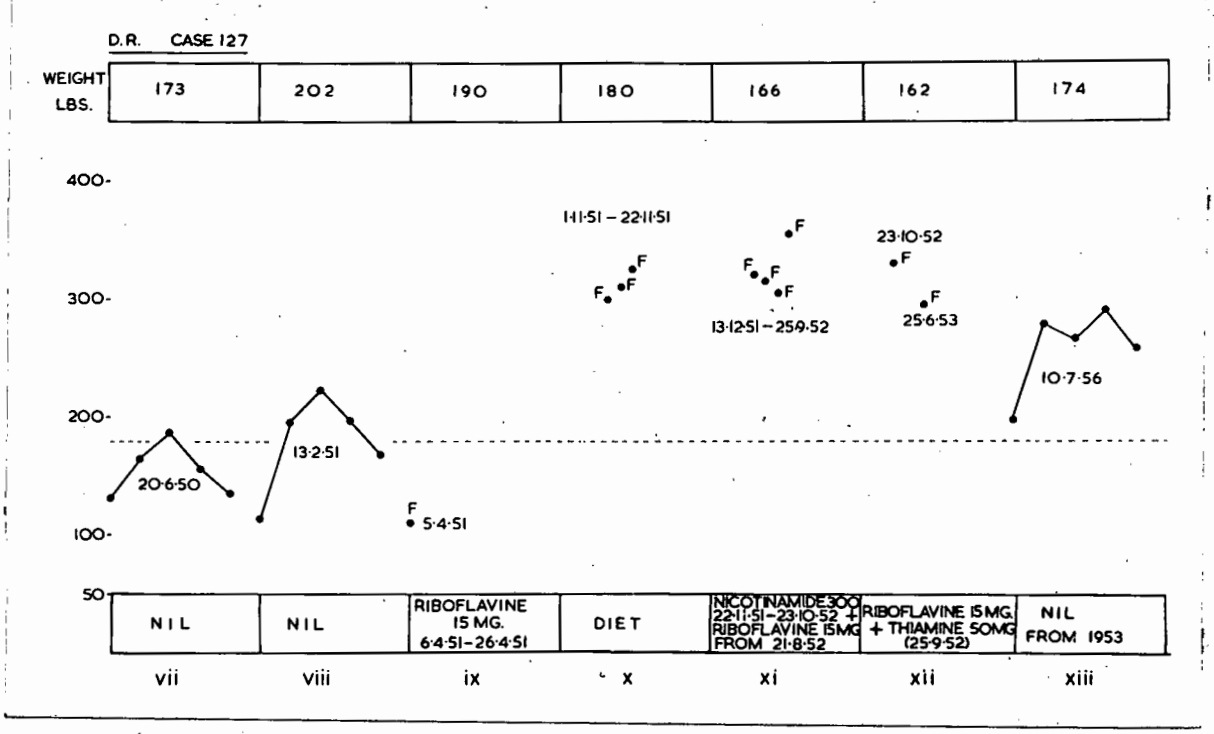
2) FASTING GLUCOSE LEVELS (denoted by F), are given consecutively, i.e. in chronological order but the span of time between the plotted fasting levels is not to scale.

3) DOSAGE stated in illustrations refers to the daily dose, e.g. Nicotinamide 500 mg. should be read as 'Nicotinamide 500 mg. daily'.

4) Each column in the graph is marked with a Roman numeral.

5) The AGE stated refers to the age at date when the patient was first seen.


D.R. E.F. AGE 43 YEARS GSH. 13081 CASE 127
WEIGHT LBS.
151
160
160
171
BLOOD GLUCOSE MG./100 ML.
400
300
200
100
50
3·9·47
21·9·47
10·9·47
F
28·8·47
F
F
21·8·47
14·10·47
7·11·47
19·11·47
2·11·48
30·11·49
TREATMENT
DIET
21·8·47 — 21·9·47
NICOTINAMIDE 500 MG.
26·9·47 — 7·11·47
NIL
NIL
NIL
i
ii
iii
iv
v
vi

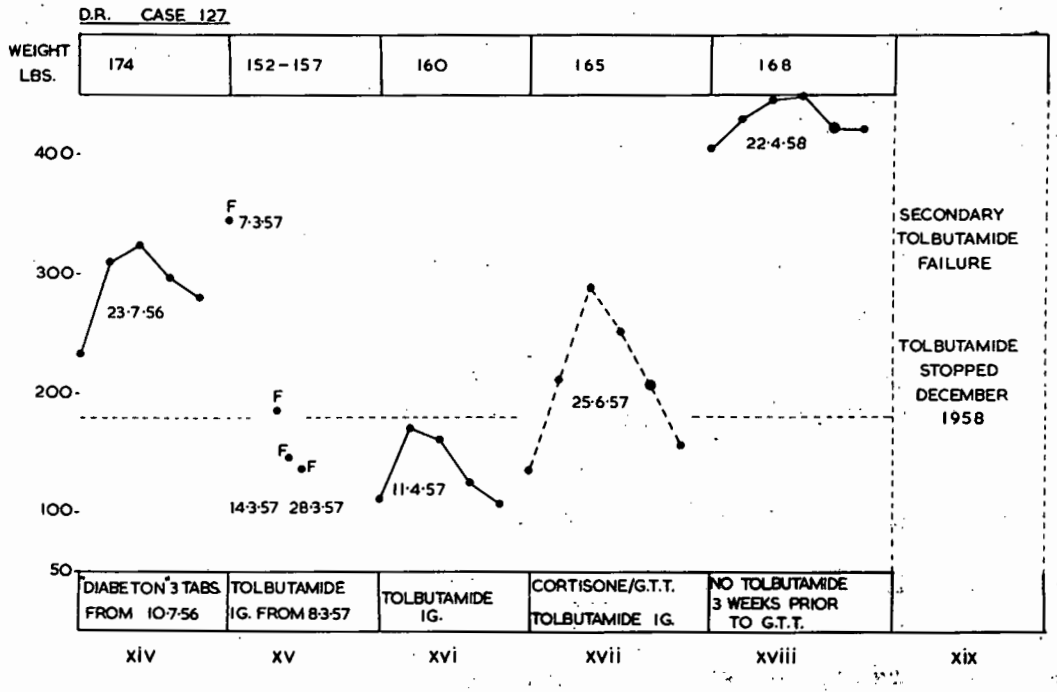

D.R. CASE 127
WEIGHT LBS.
173
202
190
180
166
162
174
400
300
200
100
50
1·11·51 – 22·11·51
F
F
F
F
F
F
F
13·12·51 – 25·9·52
23·10·52
F
F
25·6·53
10·7·56
20·6·50
13·2·51
F
5·4·51
NIL
NIL
RIBOFLAVINE 15 MG. 6·4·51–26·4·51
DIET
NICOTINAMIDE 300 22·11·51–23·10·52 + RIBOFLAVINE 15 MG FROM 21·8·52
RIBOFLAVINE 15 MG. + THIAMINE 50 MG (25·9·52)
NIL FROM 1953
vii
viii
ix
x
xi
xii
xiii

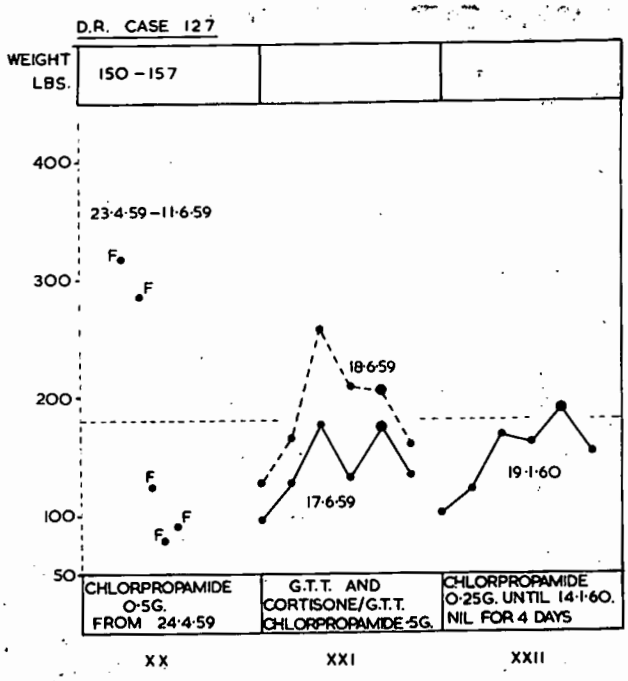
D.R. (Case 127), a European woman aged 43 years (1947).

The marked hyperglycaemic fasting levels and abnormal glucose tolerance tests are seen in (i).

A remission in glucose tolerance tests to normal: (iii) - (vii).

The relapse of hyperglycaemia (x), (xi), (xii), and markedly abnormal glucose tolerance tests are shown in (xiii) and (xiv).


D.R. CASE 127
WEIGHT LBS.
174
152 – 157
160
165
168
400
300
200
100
50
22·4·58
F 7·3·57
23·7·56
F
F F
14·3·57 28·3·57
11·4·57
25·6·57
SECONDARY TOLBUTAMIDE FAILURE
TOLBUTAMIDE STOPPED DECEMBER 1958
DIABETON 3 TABS. FROM 10·7·56
TOLBUTAMIDE 1G. FROM 8·3·57
TOLBUTAMIDE 1G.
CORTISONE/G.T.T. TOLBUTAMIDE 1G.
NO TOLBUTAMIDE 3 WEEKS PRIOR TO G.T.T.
XIV
XV
XVI
XVII
XVIII
XIX


D.R. CASE 127
WEIGHT LBS.
150 – 157
400
300
200
100
50
23·4·59 – 11·6·59
F
F
18·6·59
F
F F
17·6·59
19·1·60
CHLORPROPAMIDE 0·5G. FROM 24·4·59
G.T.T. AND CORTISONE/G.T.T. CHLORPROPAMIDE ·5G.
CHLORPROPAMIDE 0·25G. UNTIL 14·1·60. NIL FOR 4 DAYS
XX
XXI
XXII

D.R. (Case 127): (Cont'd).

An excellent response to tolbutamide is shown with low fasting levels (xv) and a remission to a normal glucose tolerance test while on tolbutamide (xvi).

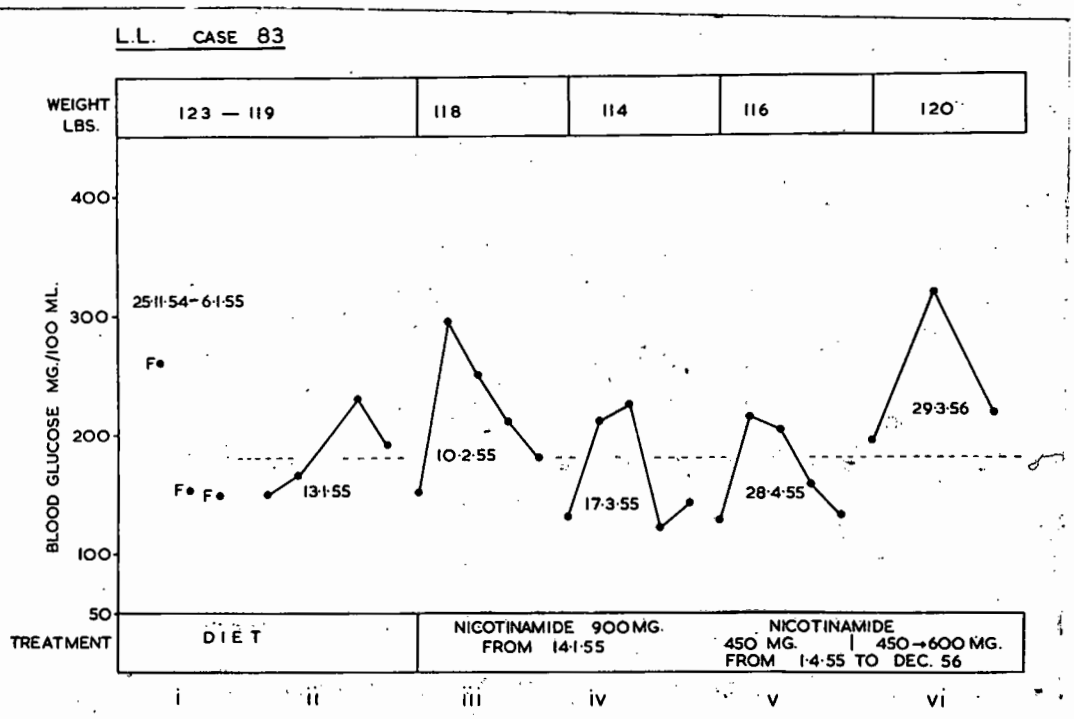
Relapse without tolbutamide (xviii).

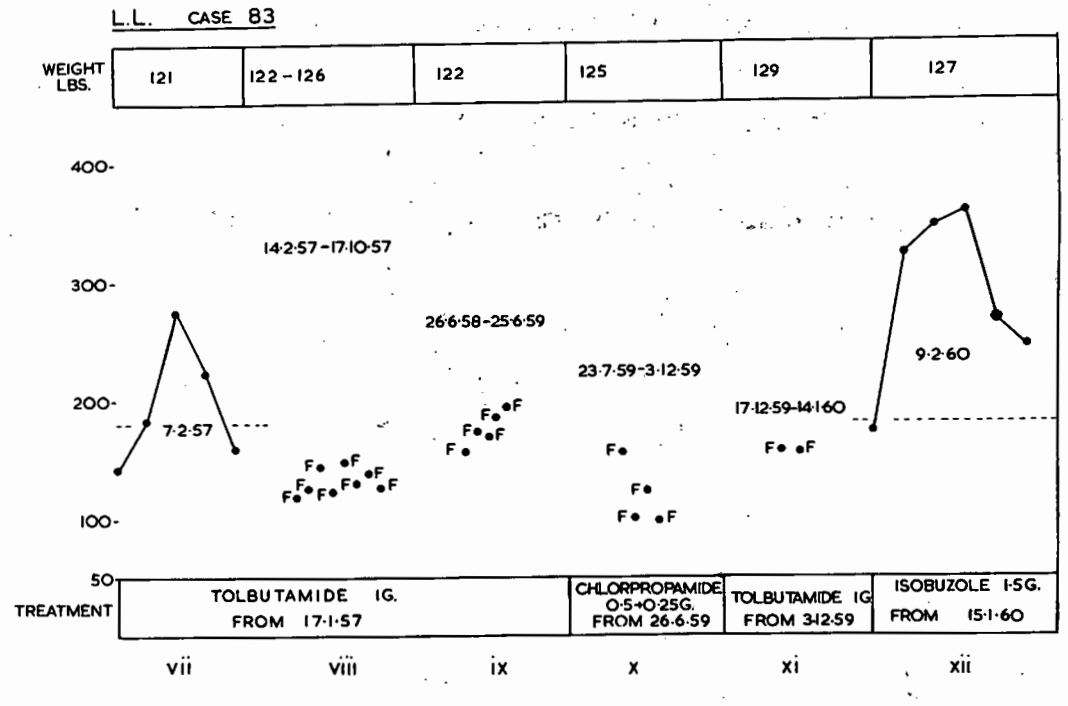
Delayed failure to tolbutamide (xix), but an excellent response to chlorpropamide (xx).

Another remission to near normal glucose tolerance test is seen with chlorpropamide (xxi).

The response to chlorpropamide is maintained (xxii) (Note no tabs. for 4 days).

(It is to be noted that an improvement in control was accompanied by an improvement in well-being).


L.L. CASE 83
WEIGHT LBS.
123 — 119
118
114
116
120
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
25·11·54–6·1·55
F
F F
13·1·55
10·2·55
17·3·55
28·4·55
29·3·56
TREATMENT
DIET
NICOTINAMIDE 900 MG. FROM 14·1·55
NICOTINAMIDE 450 MG. | 450→600 MG. FROM 1·4·55 TO DEC. 56
i
ii
iii
iv
v
vi


L.L. CASE 83
WEIGHT LBS.
121
122 – 126
122
125
129
127
400
300
200
100
50
14·2·57–17·10·57
7·2·57
26·6·58–25·6·59
23·7·59–3·12·59
17·12·59–14·1·60
9·2·60
F
TREATMENT
TOLBUTAMIDE 1G. FROM 17·1·57
CHLORPROPAMIDE 0·5+0·25G. FROM 26·6·59
TOLBUTAMIDE 1G. FROM 3·12·59
ISOBUZOLE 1·5G. FROM 15·1·60
vii
viii
ix
x
xi
xii

L.L. (Case 83), a European woman aged 58 years.

A remission was recorded with normal fasting and 2 hour level (iv) and (v).

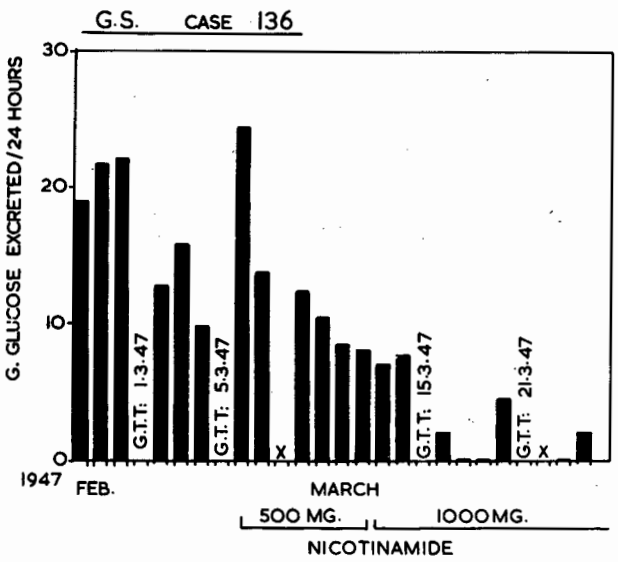
Then a relapse to an abnormal glucose tolerance test (vi).

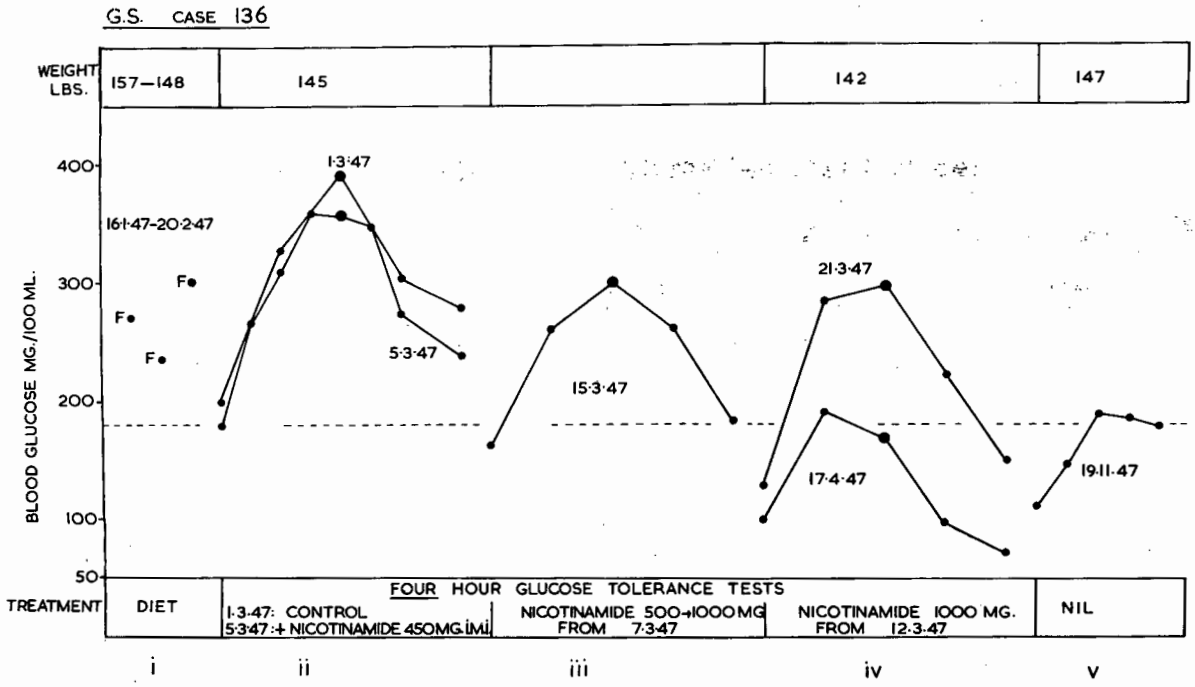
Although the fasting blood glucose levels were lowered by tolbutamide, a glucose tolerance test is still grossly abnormal: (vii) and (viii).

Later fasting levels show a tendency to rise on tolbutamide (ix) and are lowered by chlorpropamide (x).

Reversion to tolbutamide again causes a rise (xi).

Completely unsatisfactory control with isobuzole is shown (xii).


G.S. CASE 136
G. GLUCOSE EXCRETED/24 HOURS
30
20
10
0
G.T.T: 1·3·47
G.T.T: 5·3·47
G.T.T: 15·3·47
G.T.T: 21·3·47
X
X
1947
FEB.
MARCH
500 MG.
1000 MG.
NICOTINAMIDE


G.S. CASE 136
WEIGHT LBS.
157—148
145
142
147
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
16·1·47–20·2·47
F•
F•
F•
1·3·47
5·3·47
15·3·47
21·3·47
17·4·47
19·11·47
TREATMENT
DIET
FOUR HOUR GLUCOSE TOLERANCE TESTS
1·3·47: CONTROL
5·3·47: + NICOTINAMIDE 450 MG. I.M.
NICOTINAMIDE 500→1000 MG FROM 7·3·47
NICOTINAMIDE 1000 MG. FROM 12·3·47
NIL
i
ii
iii
iv
v

G.S. (Case 136), a European woman aged 53 years:

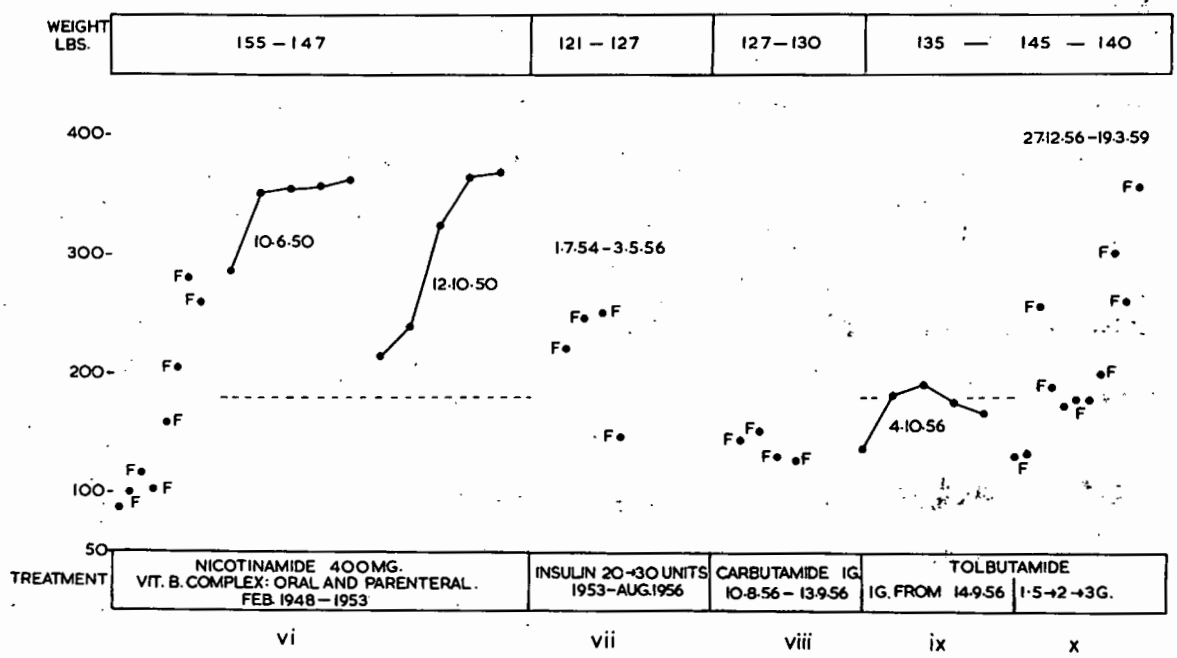
The reduction in the amount of glucose excreted daily in the initial part of the study is charted on the facing page.

An improvement in glucose tolerance tests is shown: (ii) - (v).

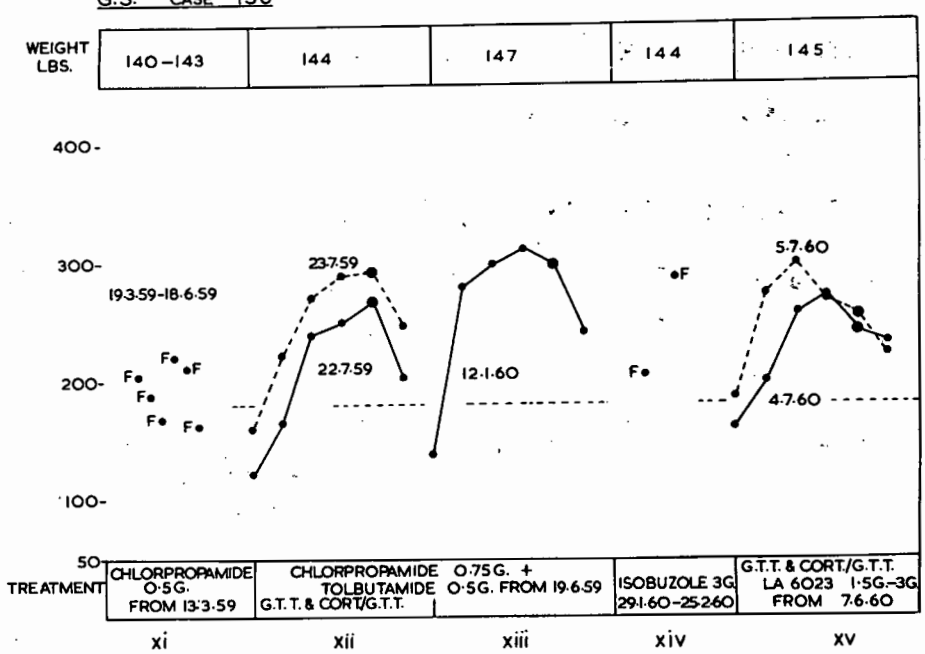
Note: Glucose tolerance tests in (ii), (iii) and (iv) are charted over a 4 hour period.

As usual, heavy dot marks the 2 hour figure.

G.S. CASE 136



G.S. CASE 136



G.S. (case 136): (Cont'd).

Maintenance of low fasting levels and a relapse in the severity of diabetes and of the abnormality of glucose tolerance tests are shown in (vi).

A good hypoglycaemic response to carbutamide is shown (viii).

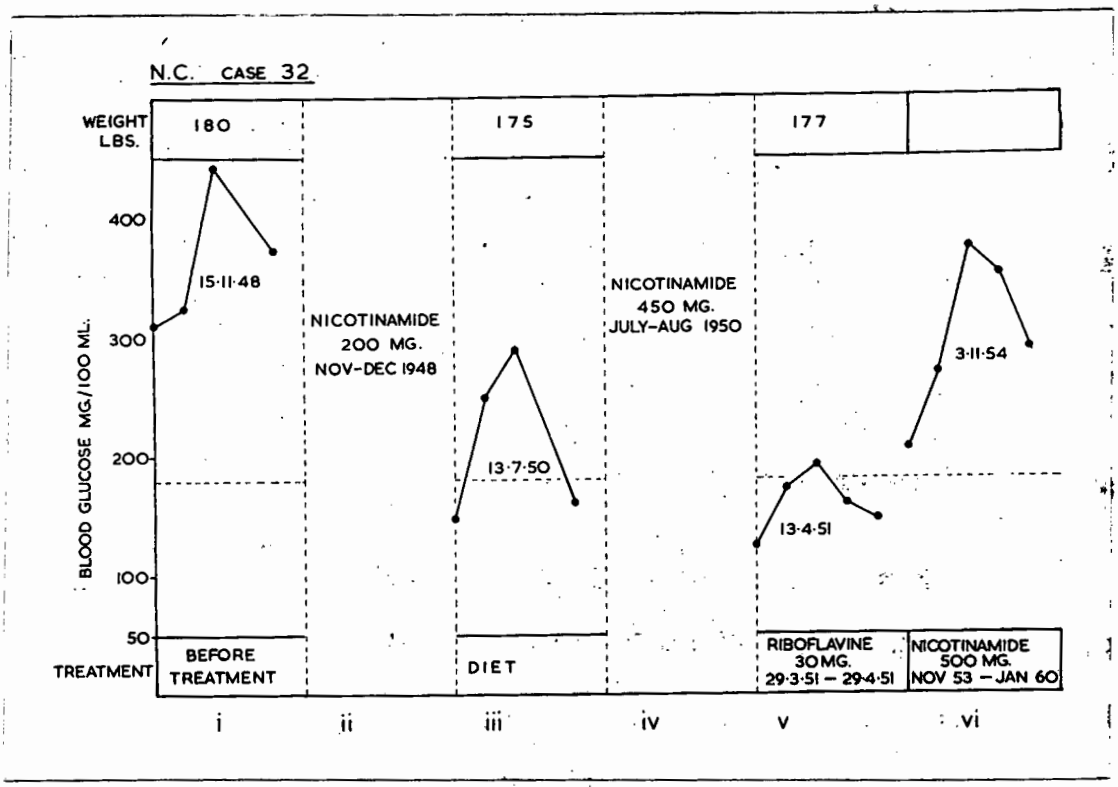
A near normal glucose tolerance test while on tolbutamide (ix).

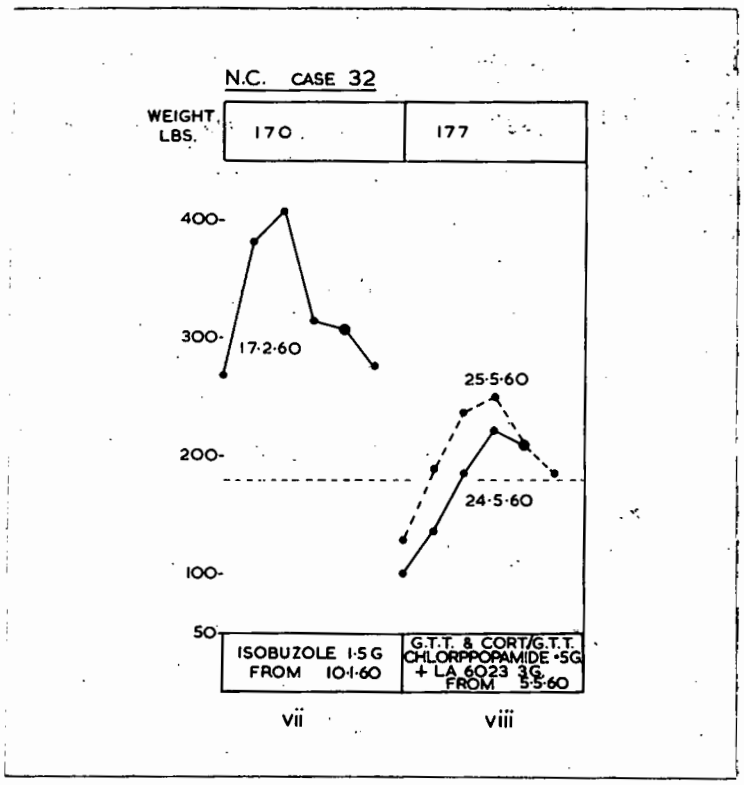
Delayed failure of response is seen in (x).

A moderate fasting response to chlorpropamide (xi) is enhanced by the addition of tolbutamide but the glucose tolerance tests (xii) and (xiii) show a severely abnormal form.

Elevation of fasting levels was noted on the sulphonylurea, isobuzole (xiv).

The glucose tolerance test (xv) on dimethylbiguanide appears slightly better than on the sulphonylureas.


N.C. CASE 32
WEIGHT LBS.
180
175
177
400
300
200
100
50
BLOOD GLUCOSE MG/100 ML.
15·11·48
13·7·50
13·4·51
3·11·54
NICOTINAMIDE 200 MG. NOV–DEC 1948
NICOTINAMIDE 450 MG. JULY–AUG 1950
TREATMENT
BEFORE TREATMENT
DIET
RIBOFLAVINE 30 MG. 29·3·51 – 29·4·51
NICOTINAMIDE 500 MG. NOV 53 – JAN 60
i
ii
iii
iv
v
vi


N.C. CASE 32
WEIGHT LBS.
170
177
400
300
200
100
50
17·2·60
25·5·60
24·5·60
ISOBUZOLE 1·5 G FROM 10·1·60
G.T.T. & CORT/G.T.T. CHLORPROPAMIDE ·5G. + LA 6023 3G. FROM 5·5·60
vii
viii

N.C. (Case 32), a European man aged 35 years.

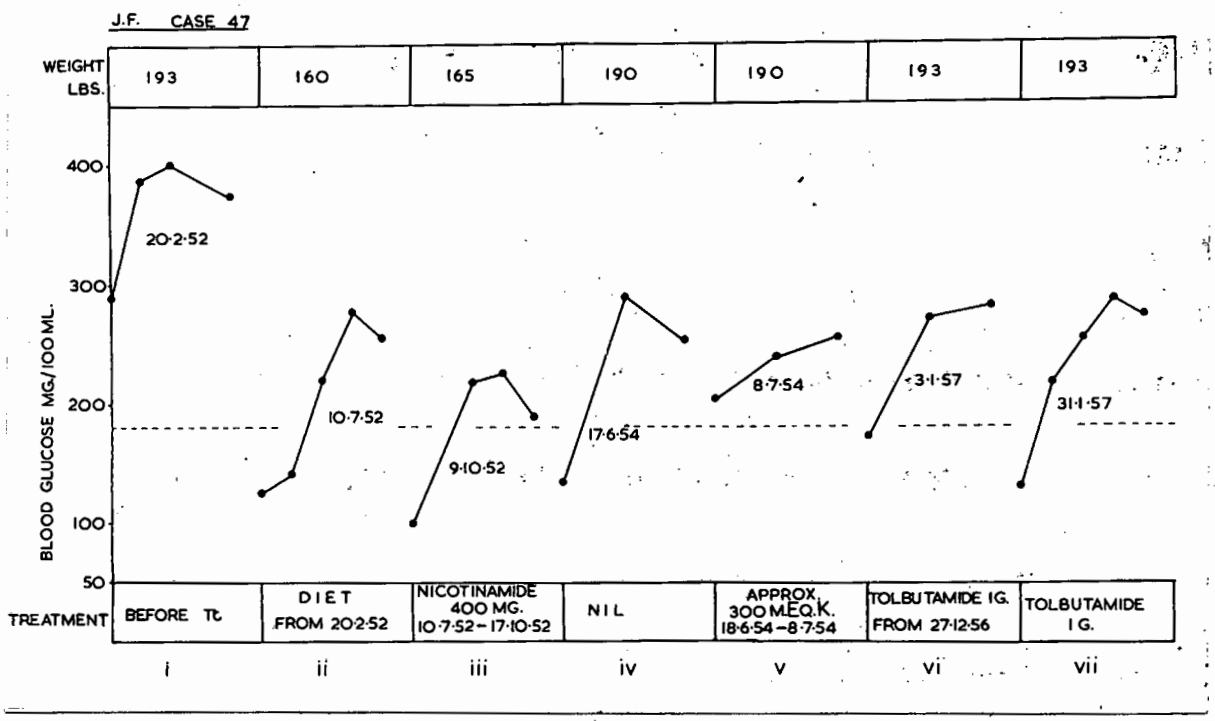
A remission in glucose tolerance test to normal is shown: (v).

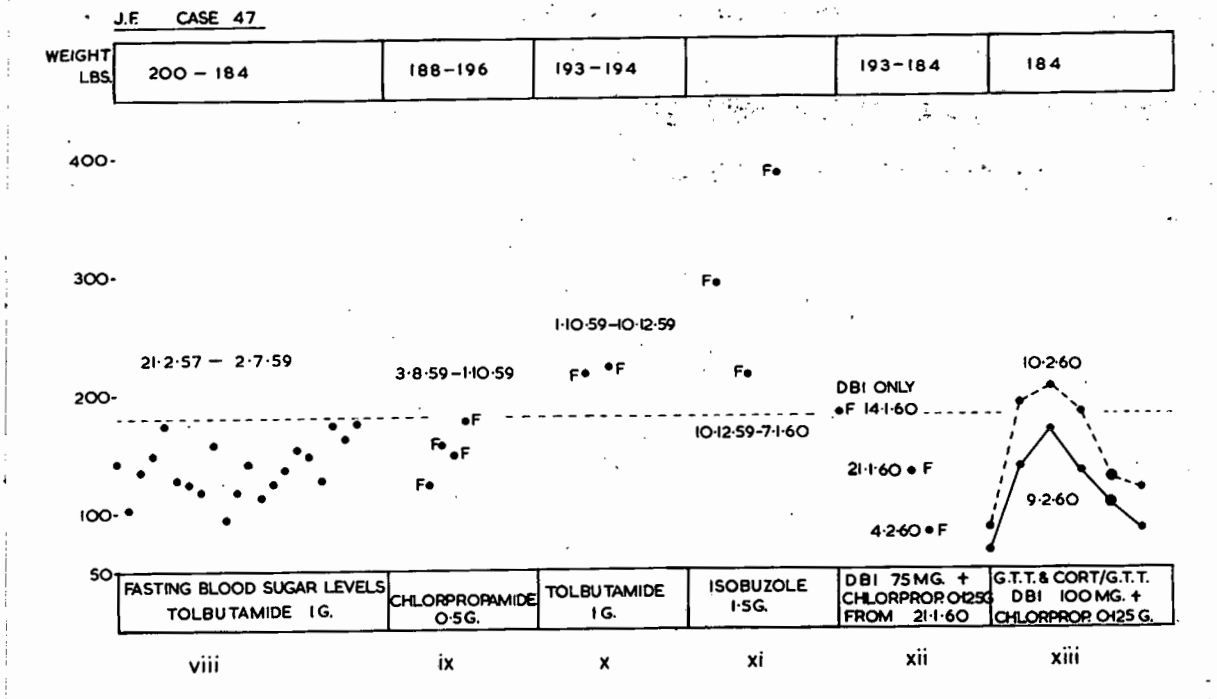
The relapse in severity of diabetes is seen in the next glucose tolerance test (vi).

A failure of response to a hypoglycaemic agent, isobuzolo, is recorded in glucose tolerance test (vii).

An excellent response to chlorpropamide and dimethylbiguanide was noted (viii).

(Subsequently the urine remained sugar free on LA 6023 1.5 G. daily alone; chlorpropamide alone had failed to do so).


J.F. CASE 47
WEIGHT LBS.
193
160
165
190
190
193
193
400
300
200
100
50
BLOOD GLUCOSE MG/100 ML.
20·2·52
10·7·52
9·10·52
17·6·54
8·7·54
31·1·57
31·1·57
TREATMENT
BEFORE Tt.
DIET FROM 20·2·52
NICOTINAMIDE 400 MG. 10·7·52 – 17·10·52
NIL
APPROX. 300 M.EQ.K. 18·6·54 – 8·7·54
TOLBUTAMIDE 1G. FROM 27·12·56
TOLBUTAMIDE 1 G.
i
ii
iii
iv
v
vi
vii


J.F. CASE 47
WEIGHT LBS.
200 – 184
188–196
193–194
193–184
184
400
300
200
100
50
21·2·57 – 2·7·59
3·8·59–1·10·59
1·10·59–10·12·59
10·12·59–7·1·60
DBI ONLY
F 14·1·60
21·1·60 • F
4·2·60 • F
10·2·60
9·2·60
FASTING BLOOD SUGAR LEVELS TOLBUTAMIDE 1G.
CHLORPROPAMIDE 0·5G.
TOLBUTAMIDE 1 G.
ISOBUZOLE 1·5G.
DBI 75 MG. + CHLORPROP. 0·125 FROM 21·1·60
G.T.T. & CORT/G.T.T. DBI 100 MG. + CHLORPROP. 0·125 G.
viii
ix
x
xi
xii
xiii

J.F. (Case 47), a European man aged 47 years.

Improvement in glucose tolerance tests (i) - (iii).

Glucose tolerance tests completely abnormal on tolbutamide (vi) and (vii) although satisfactory fasting levels are recorded (vii) and (viii).

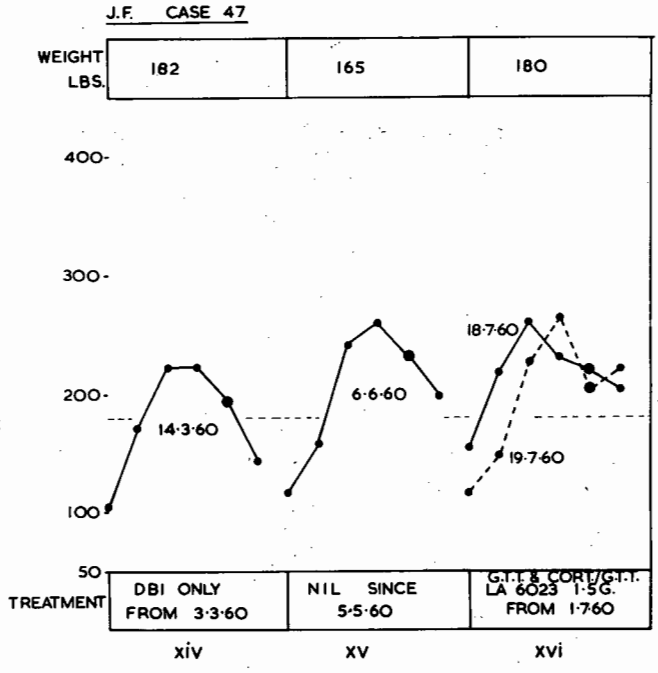
Moderate response only to chlorpropamide (ix).

Delayed failure of response to tolbutamide (x).

Further elevation of fasting level on isobuzole (xi).

A good response to phenethyldiguanide enhanced by the addition of chlorpropamide (xii).

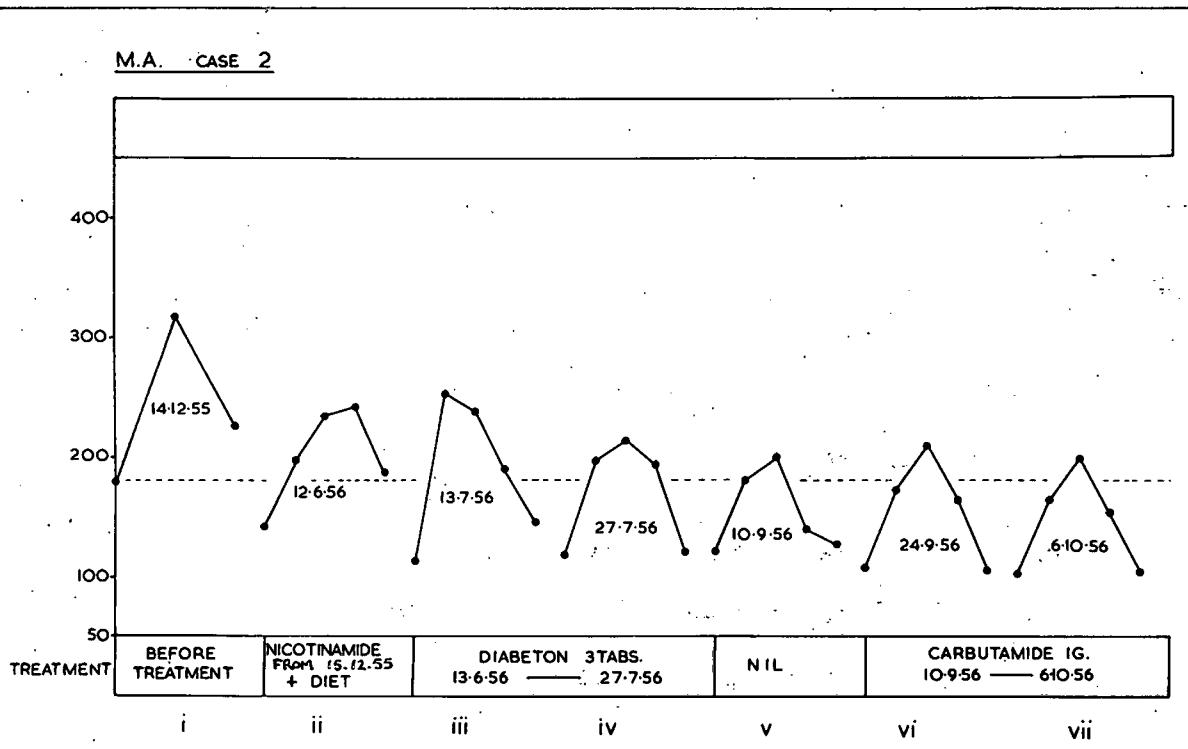
A normal glucose tolerance test on the combination of guanide and sulphonylurea (xiii).

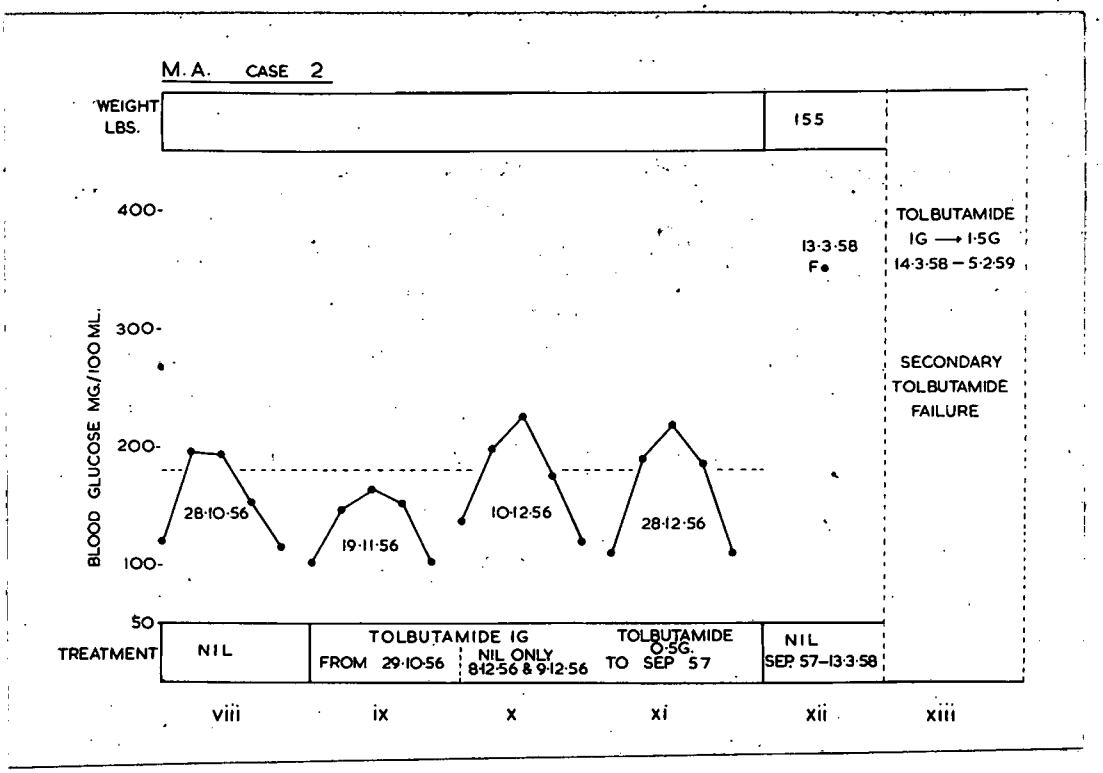

J.F. CASE 47
WEIGHT LBS.
182
165
180
400-
300-
200-
100
50
18·7·60
6·6·60
14·3·60
19·7·60
TREATMENT
DBI ONLY FROM 3·3·60
NIL SINCE 5·5·60
G.T.I. & CORT./G.T.I. LA 6023 1·5G. FROM 1·7·60
xiv
xv
xvi

J.F. (Case 47): (Cont'd).

Not such a good glucose tolerance test on DBI alone (xiv) or when this is discontinued (xv).

The response to another diguanide derivative is shown by an unsatisfactory glucose tolerance test (xvi).


M.A. CASE 2
400
300
200
100
50
14·12·55
12·6·56
13·7·56
27·7·56
10·9·56
24·9·56
6·10·56
TREATMENT
BEFORE TREATMENT
NICOTINAMIDE FROM 15.12.55 + DIET
DIABETON 3TABS. 13·6·56 —— 27·7·56
NIL
CARBUTAMIDE 1G. 10·9·56 —— 6·10·56
i
ii
iii
iv
v
vi
vii


M.A. CASE 2
WEIGHT LBS.
155
400-
300-
200-
100-
50
BLOOD GLUCOSE MG./100 ML.
28·10·56
19·11·56
10·12·56
28·12·56
13·3·58 F.
TOLBUTAMIDE 1G ⟶ 1·5G 14·3·58 — 5·2·59
SECONDARY TOLBUTAMIDE FAILURE
TREATMENT
NIL
TOLBUTAMIDE 1G FROM 29·10·56
NIL ONLY 8·12·56 & 9·12·56
TOLBUTAMIDE 0·5G. TO SEP 57
NIL SEP 57–13·3·58
viii
ix
x
xi
xii
xiii

M.A. (Case 2), a Coloured man aged 68 years.

(A patient with gout and diabetes).

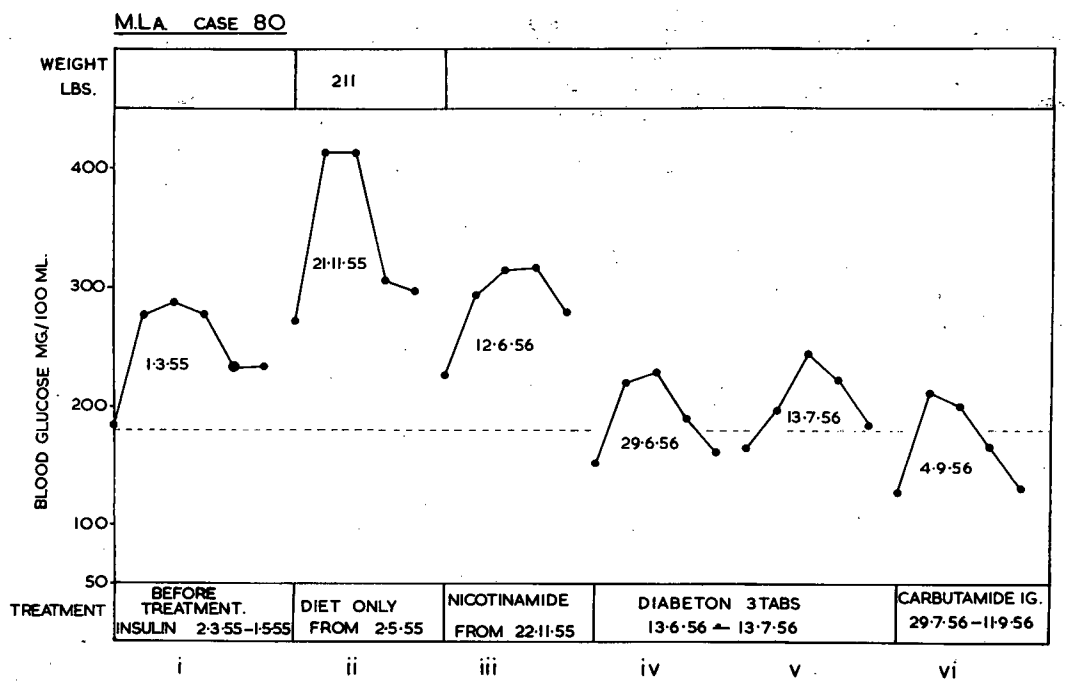
The evolution of a remission in glucose tolerance test towards normal is seen: (i) - (v).

The fasting and 2 hour levels are further depressed with hypoglycaemic agents carbutamide and tolbutamide while in remission (vi) - (ix).

Relapse in severity after being off tolbutamide for more than 6 months (xii).

Delayed failure of response to tolbutamide occurred (xiii).

Persistent glycosuria and blood glucose 323 mg. on tolbutamide on 24.3.60 (not charted).

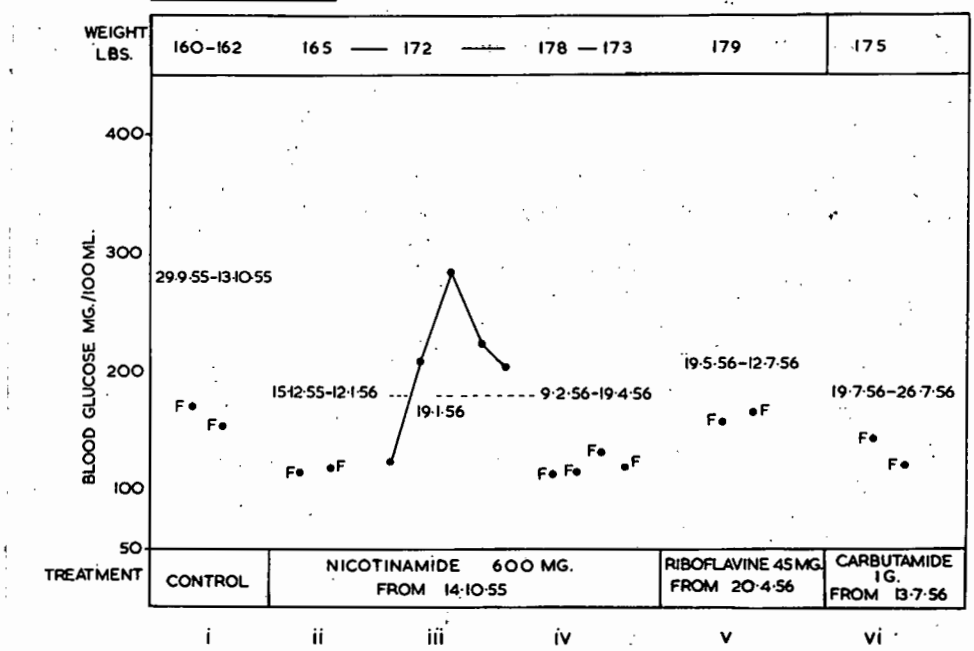

M.L.A. CASE 80
WEIGHT LBS.
211
400
300
200
100
50
BLOOD GLUCOSE MG/100 ML.
1·3·55
21·11·55
12·6·56
29·6·56
13·7·56
4·9·56
TREATMENT
BEFORE TREATMENT. INSULIN 2·3·55–1·5·55
DIET ONLY FROM 2·5·55
NICOTINAMIDE FROM 22·11·55
DIABETON 3 TABS 13·6·56 — 13·7·56
CARBUTAMIDE 1G. 29·7·56–11·9·56
i
ii
iii
iv
v
vi

M.Le. (Case 80), a Coloured man aged 46 years.

(A case of gout and diabetes).

After a tendency to remission was noted, there is a further lowering of the fasting and 2 hour figures giving rise to an almost normal glucose tolerance test (vi) on carbutamide.

C.M. CASE 95

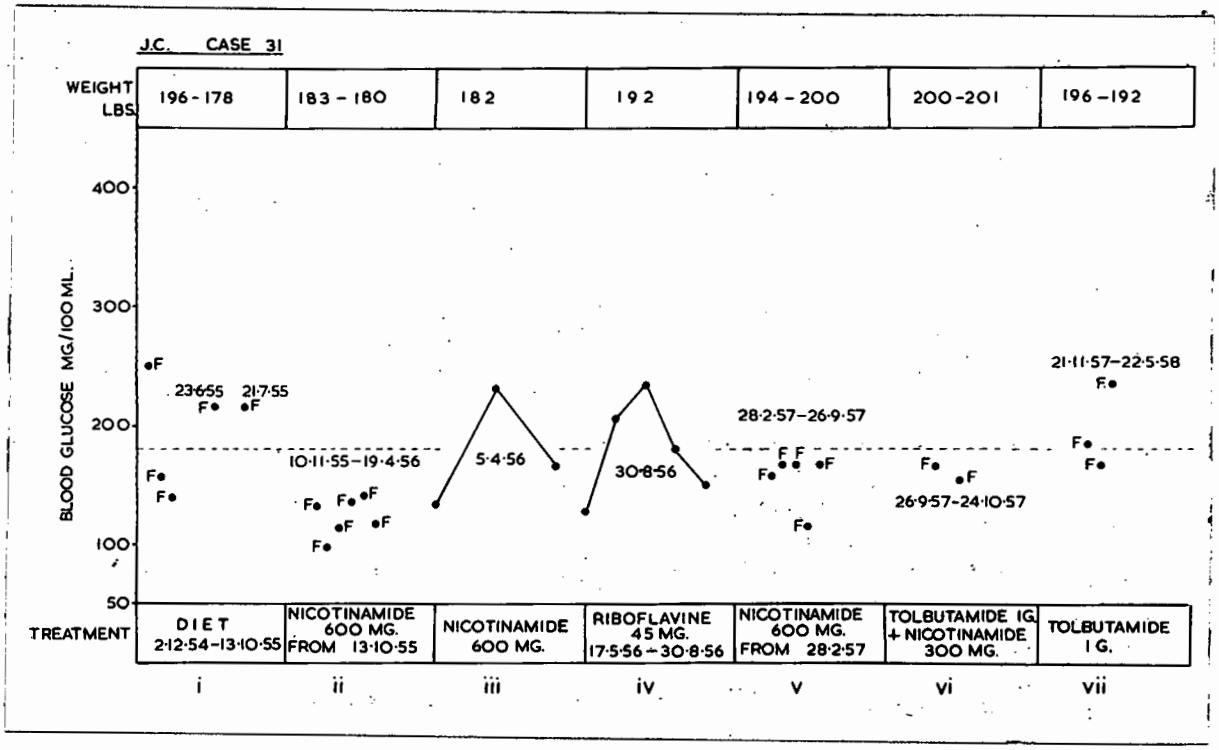

WEIGHT LBS.
160–162
165 — 172 — 178 — 173
179
175
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
29·9·55–13·10·55
15·12·55–12·1·56
19·1·56
9·2·56–19·4·56
19·5·56–12·7·56
19·7·56–26·7·56
F
TREATMENT
CONTROL
NICOTINAMIDE 600 MG. FROM 14·10·55
RIBOFLAVINE 45 MG. FROM 20·4·56
CARBUTAMIDE 1 G. FROM 13·7·56
i
ii
iii
iv
v
vi

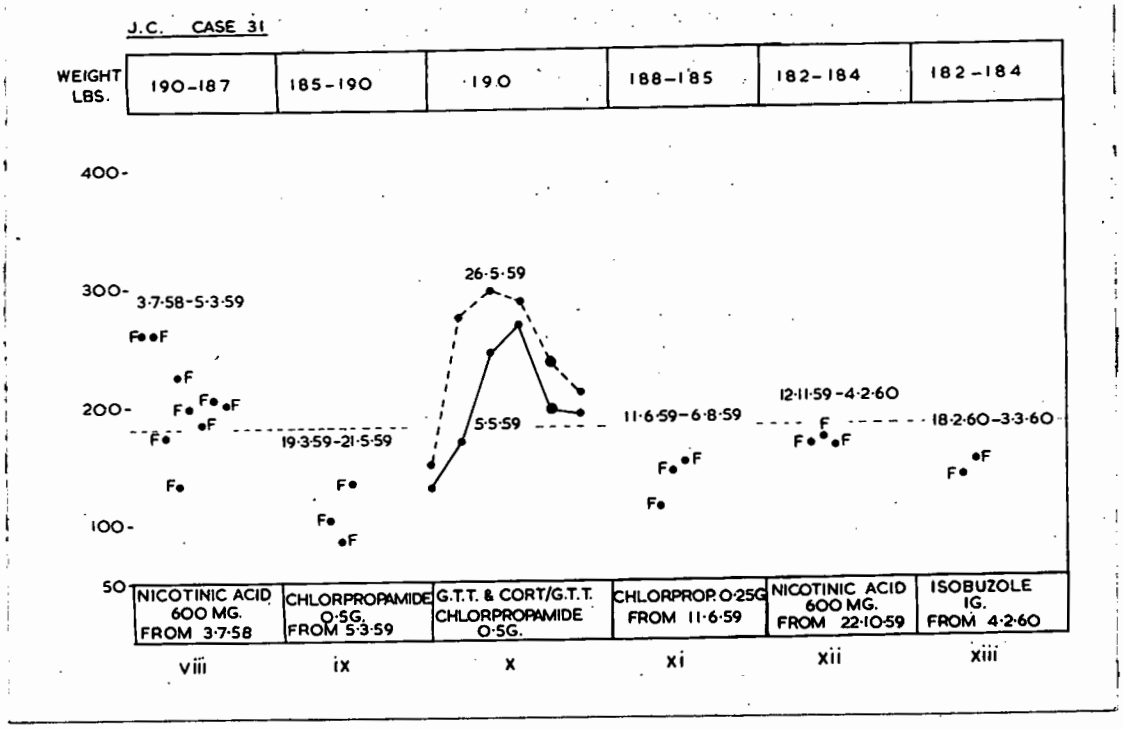
C.M. (Case 95), a European woman aged 51 years.

Normal fasting levels are recorded during a phase of remission (ii), (iii), (iv);

A glucose tolerance test, though, shows a high 2 hour level (iii).

Fasting levels on carbutamide (vi) are similar to those seen during the remission phase.


J.C. CASE 31
WEIGHT LBS.
196 - 178
183 - 180
182
192
194 - 200
200 - 201
196 - 192
BLOOD GLUCOSE MG./100 ML.
400
300
200
100
50
23·6·55
21·7·55
10·11·55 – 19·4·56
5·4·56
30·8·56
28·2·57 – 26·9·57
26·9·57 – 24·10·57
21·11·57 – 22·5·58
TREATMENT
DIET 2·12·54 – 13·10·55
NICOTINAMIDE 600 MG. FROM 13·10·55
NICOTINAMIDE 600 MG.
RIBOFLAVINE 45 MG. 17·5·56 – 30·8·56
NICOTINAMIDE 600 MG. FROM 28·2·57
TOLBUTAMIDE 1G. + NICOTINAMIDE 300 MG.
TOLBUTAMIDE 1 G.
i
ii
iii
iv
v
vi
vii


J.C. CASE 31
WEIGHT LBS.
190 – 187
185 – 190
190
188 – 185
182 – 184
182 – 184
400
300
200
100
50
3·7·58 – 5·3·59
19·3·59 – 21·5·59
26·5·59
5·5·59
11·6·59 – 6·8·59
12·11·59 – 4·2·60
18·2·60 – 3·3·60
NICOTINIC ACID 600 MG. FROM 3·7·58
CHLORPROPAMIDE 0·5G. FROM 5·3·59
G.T.T. & CORT/G.T.T. CHLORPROPAMIDE 0·5G.
CHLORPROP. 0·25G FROM 11·6·59
NICOTINIC ACID 600 MG. FROM 22·10·59
ISOBUZOLE 1G. FROM 4·2·60
viii
ix
x
xi
xii
xiii

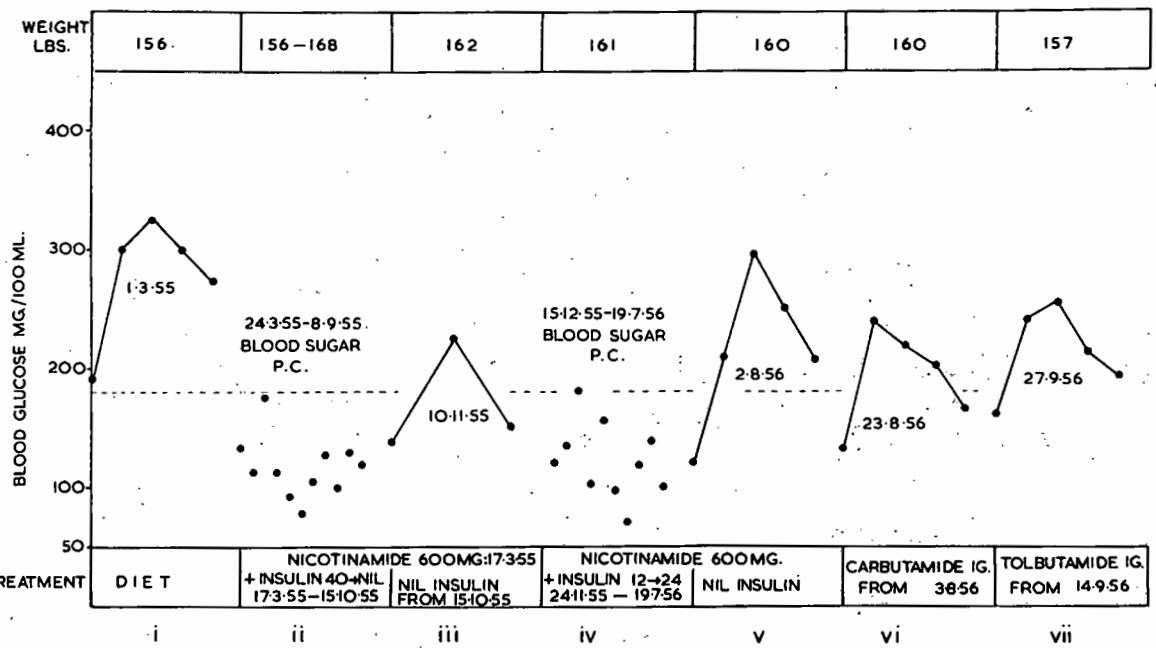
J.C. (Case 31), a European woman aged 65 years.

An improvement to low normal fasting glucose levels is recorded (i) - (iv).

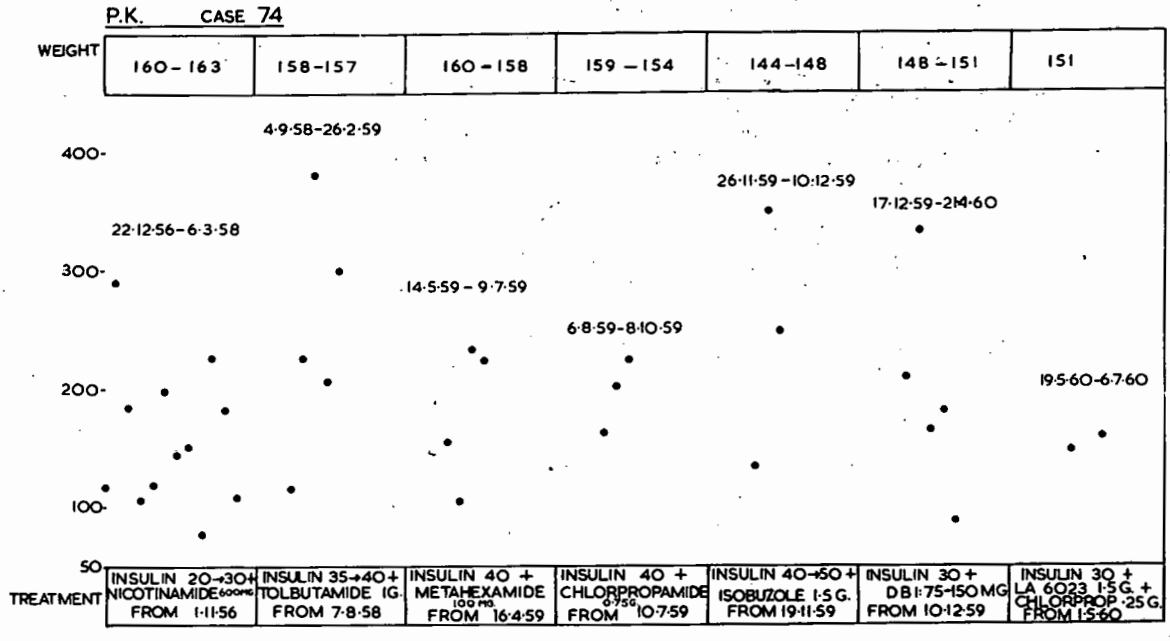
Then a gradual elevation in fasting levels is noted not influenced by tolbutamide (vii).
Chlorpropamide has lowered the fasting levels (ix) but a glucose tolerance test (x), in spite of the hypoglycaemic agent, shows a higher rise and a higher 2 hour level than in (ii) and (iv).

Later fasting glucose levels show a rise (xi) and (xii).
It is of interest to note that the fasting levels with isobuzole (xiii) were no higher than with chlorpropamide.

P.K. CASE 74



P.K. CASE 74



ALL BLOOD GLUCOSE LEVELS ARE APPROX 3 HOURS P.C.

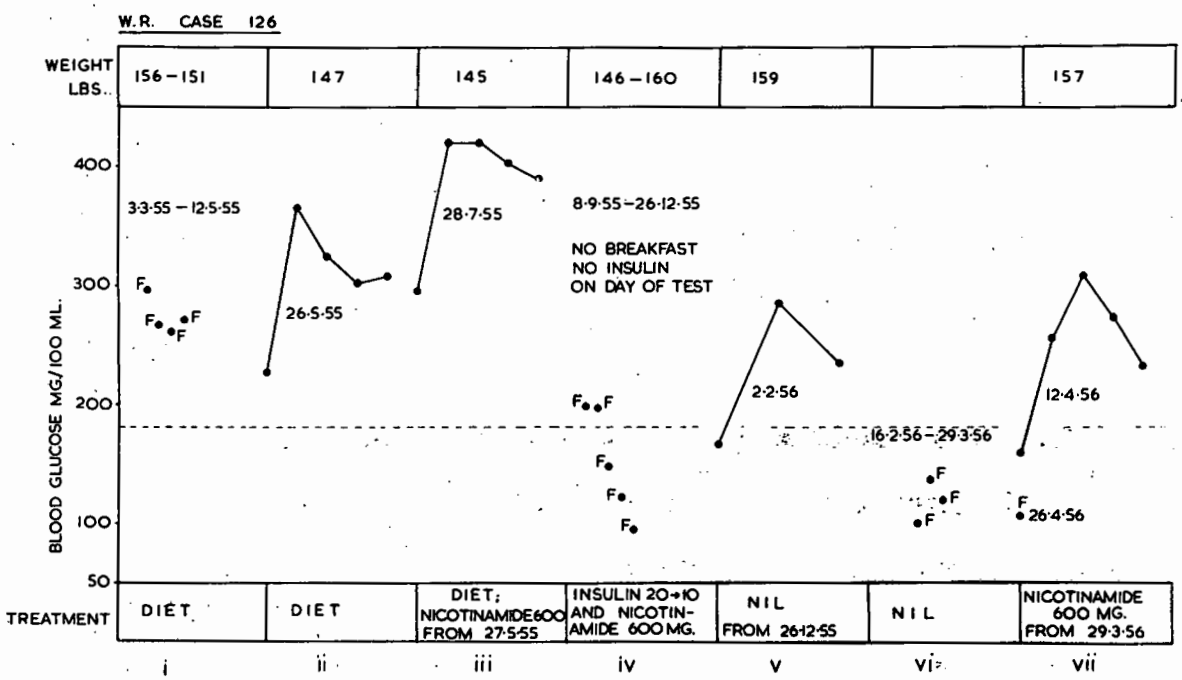
P.K. (Case 74). a European man aged 37 years.

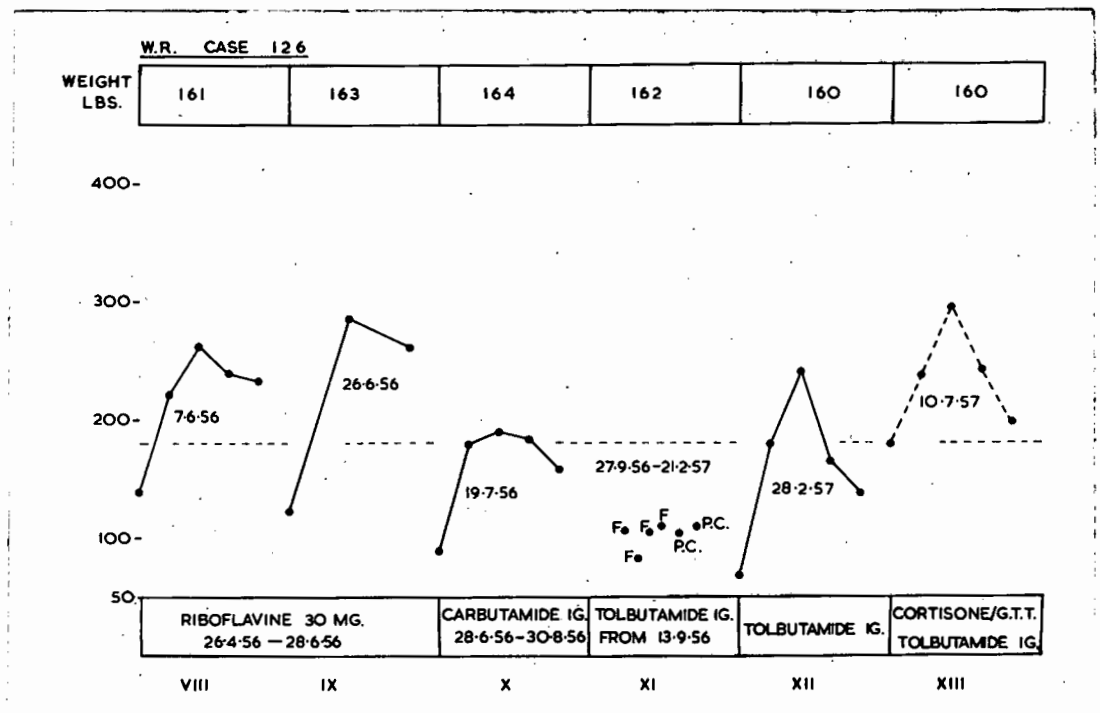
A remission occurred after insulin administration had stopped on 15.10.55 and glucose tolerance test (iii) is much better than (i). However, in (v) a grossly abnormal glucose tolerance test is recorded again in spite of a low fasting level.

Glucose tolerance tests on carbutamide (vi) and (vii) are still abnormal.

While taking insulin a trial of tolbutamide, metahexamide, chlorpropamide and isobuzole failed to influence the insulin requirement (viii) - (xii).

However, with the addition of DBI or IA 6023 (+ chlorpropamide) the hyperglycaemia was not so marked.


W.R. CASE 126
WEIGHT LBS.
156 – 151
147
145
146 – 160
159
157
BLOOD GLUCOSE MG/100 ML.
400
300
200
100
50
3·3·55 – 12·5·55
26·5·55
28·7·55
8·9·55 – 26·12·55
NO BREAKFAST
NO INSULIN
ON DAY OF TEST
2·2·56
16·2·56 – 29·3·56
12·4·56
26·4·56
TREATMENT
DIET
DIET
DIET; NICOTINAMIDE 600 FROM 27·5·55
INSULIN 20→10 AND NICOTINAMIDE 600 MG.
NIL FROM 26·12·55
NIL
NICOTINAMIDE 600 MG. FROM 29·3·56
i
ii
iii
iv
v
vi
vii

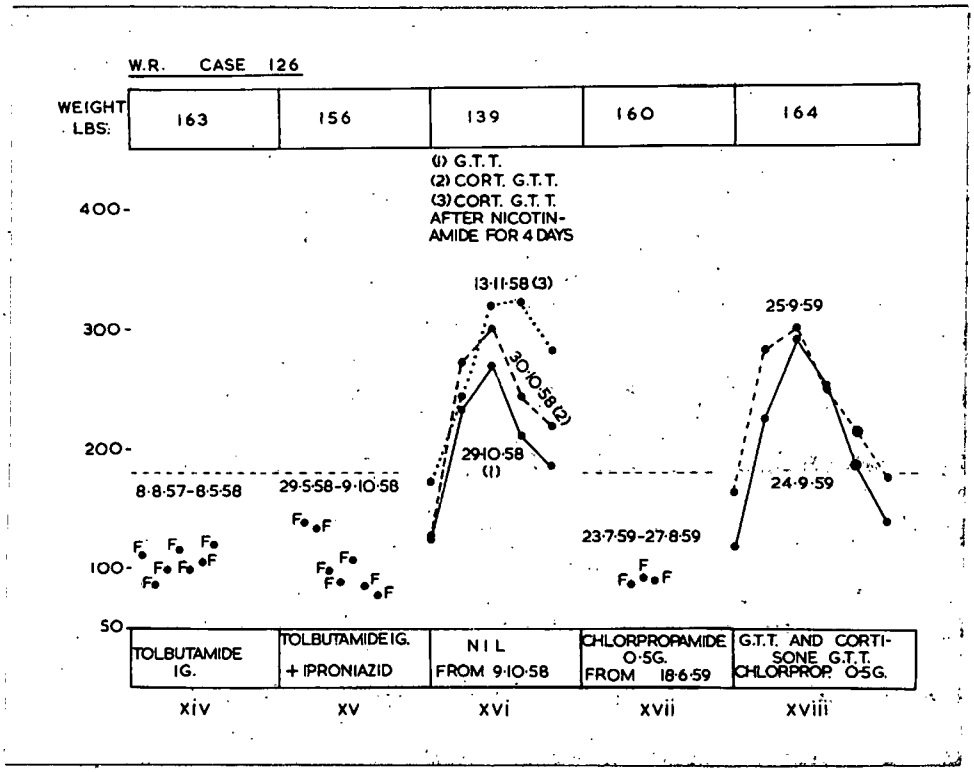

W.R. CASE 126
WEIGHT LBS.
161
163
164
162
160
160
400
300
200
100
50
7·6·56
26·6·56
19·7·56
27·9·56 – 21·2·57
28·2·57
10·7·57
P.C.
RIBOFLAVINE 30 MG. 26·4·56 – 28·6·56
CARBUTAMIDE IG. 28·6·56 – 30·8·56
TOLBUTAMIDE IG. FROM 13·9·56
TOLBUTAMIDE IG.
CORTISONE/G.T.T. TOLBUTAMIDE IG.
VIII
IX
X
XI
XII
XIII

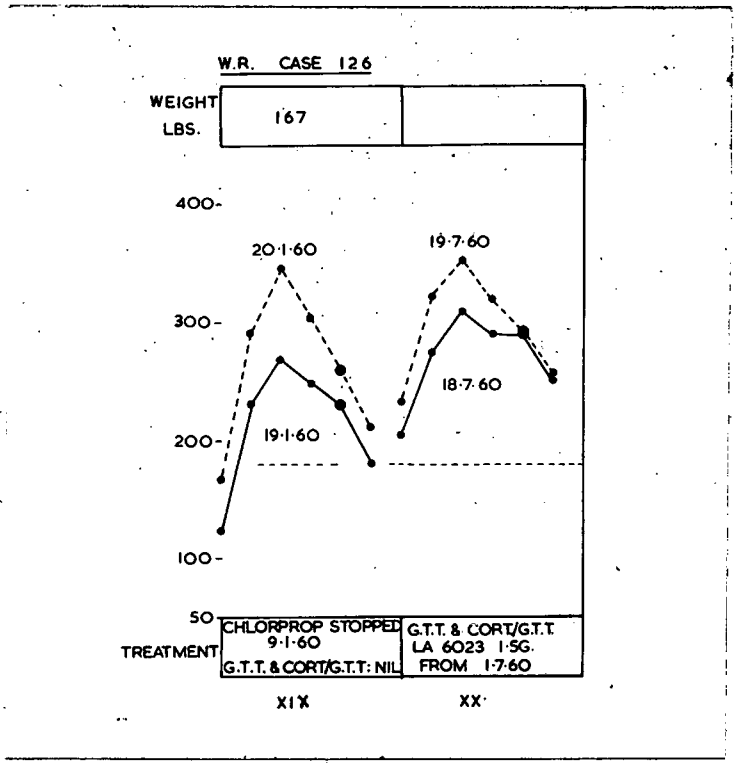
W.R. (Case 126), a European woman aged 51 years.

The severity of the diabetes is established by high fasting levels and glucose tolerance tests (i) - (iii).

Then after the termination of a course of insulin, low fasting levels are recorded, but the glucose tolerance tests remain grossly abnormal (v) - (ix).

On hypoglycaemic agents low fasting glucose levels are demonstrated (x) - (xii); the glucose tolerance curves vary slightly; low fasting levels and near normal 2 hour levels while on carbutamide (x) and tolbutamide (xii) but the peak is raised with tolbutamide.


W.R. CASE 126
WEIGHT LBS:
163
156
139
160
164
(1) G.T.T.
(2) CORT. G.T.T.
(3) CORT. G.T.T. AFTER NICOTINAMIDE FOR 4 DAYS
400-
300-
200-
100-
50
13·11·58 (3)
30·10·58 (2)
29·10·58 (1)
25·9·59
24·9·59
8·8·57-8·5·58
29·5·58-9·10·58
23·7·59-27·8·59
TOLBUTAMIDE 1G.
TOLBUTAMIDE 1G. + IPRONIAZID
NIL FROM 9·10·58
CHLORPROPAMIDE 0·5G. FROM 18·6·59
G.T.T. AND CORTISONE G.T.T. CHLORPROP. 0·5G.
XIV
XV
XVI
XVII
XVIII

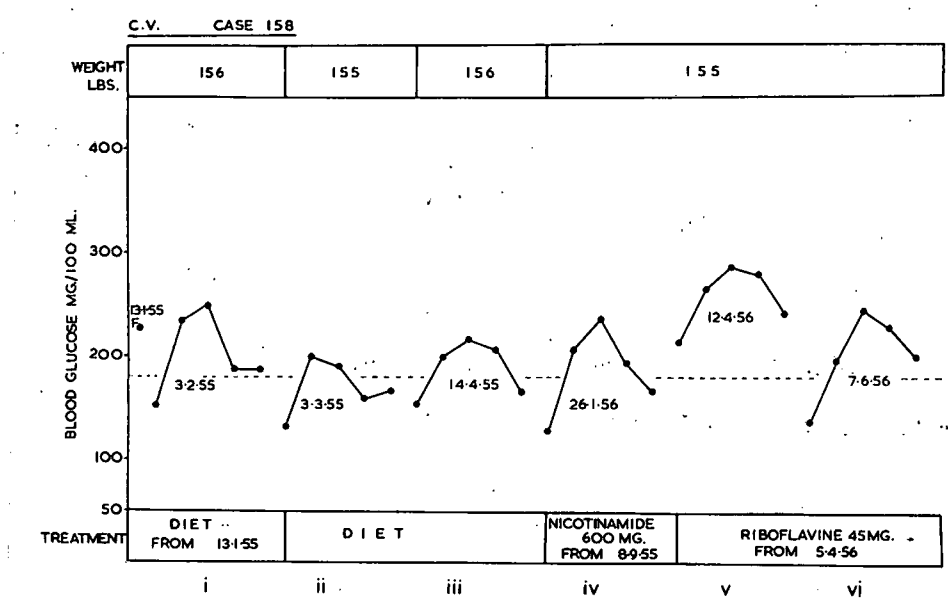

W.R. CASE 126
WEIGHT LBS.
167
400-
300-
200-
100-
50
20·1·60
19·1·60
19·7·60
18·7·60
TREATMENT
CHLORPROP STOPPED 9·1·60 G.T.T. & CORT/G.T.T: NIL
G.T.T. & CORT/G.T.T. LA 6023 1·5G. FROM 1·7·60
XIX
XX

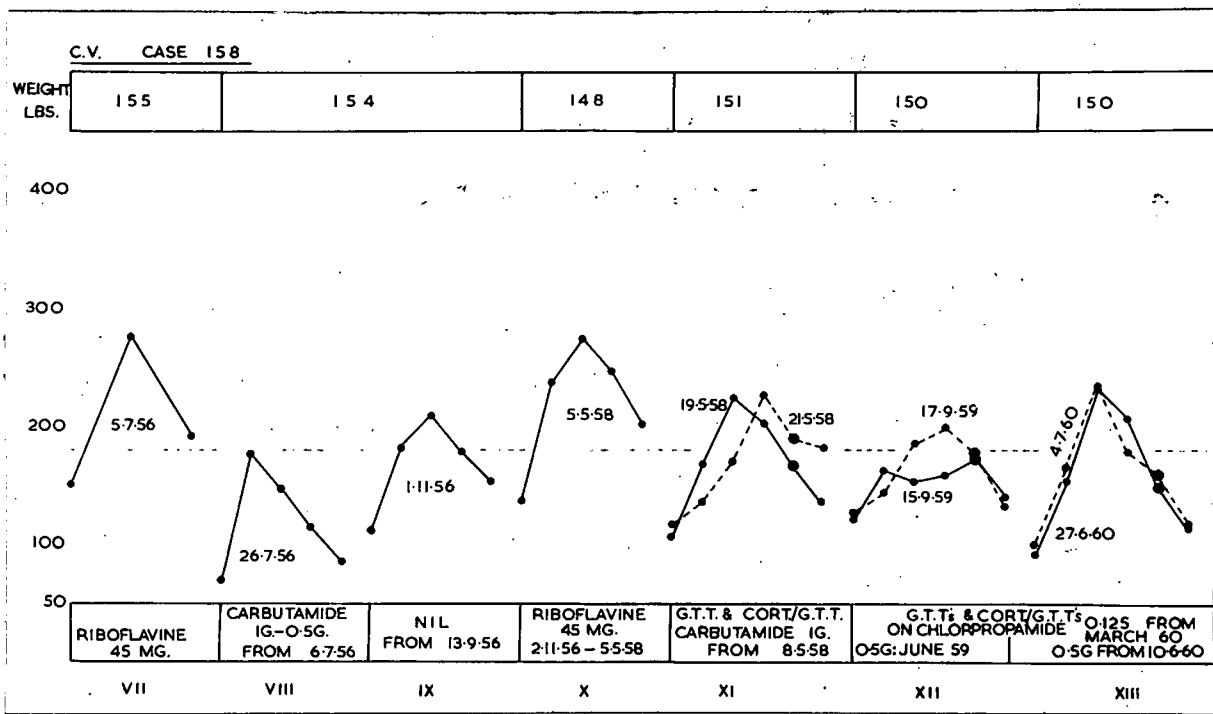
W.R. (Case 126): (Cont'd).

Low fasting levels persist (xiv) - (xix), but in spite of the low fasting level on chlorpropamide, a grossly abnormal glucose tolerance test (xviii) is recorded.

After stopping tolbutamide (xvi) or chlorpropamide (xix) the glucose tolerance tests show further elevation of the 2 hour levels when compared with the corresponding curves on tolbutamide (xii) and chlorpropamide (xviii).

The glucose tolerance test is abnormal in all respects on dimethylbiguanide (xx).


C.V. CASE 158
WEIGHT LBS.
156
155
156
155
400
300
200
100
50
BLOOD GLUCOSE MG/100 ML.
13·1·55
3·2·55
3·3·55
14·4·55
26·1·56
12·4·56
7·6·56
TREATMENT
DIET FROM 13·1·55
DIET
NICOTINAMIDE 600 MG. FROM 8·9·55
RIBOFLAVINE 45MG. FROM 5·4·56
i
ii
iii
iv
v
vi


C.V. CASE 158
WEIGHT LBS.
155
154
148
151
150
150
400
300
200
100
50
5·7·56
26·7·56
1·11·56
5·5·58
19·5·58
21·5·58
15·9·59
17·9·59
4·7·60
27·6·60
RIBOFLAVINE 45 MG.
CARBUTAMIDE 1G.–0·5G. FROM 6·7·56
NIL FROM 13·9·56
RIBOFLAVINE 45 MG. 2·11·56 – 5·5·58
G.T.T. & CORT/G.T.T. CARBUTAMIDE 1G. FROM 8·5·58
G.T.Ts & CORT/G.T.Ts ON CHLORPROPAMIDE 0·5G: JUNE 59
0·125 FROM MARCH 60 0·5G FROM 10·6·60
VII
VIII
IX
X
XI
XII
XIII

C.V. (CASE 158), a Coloured woman aged 49 years.

A brief remission to near normal in glucose tolerance test (ii) is not maintained (iii).

Abnormal glucose tolerance tests with a return to previously abnormal level (iv) - (vii).

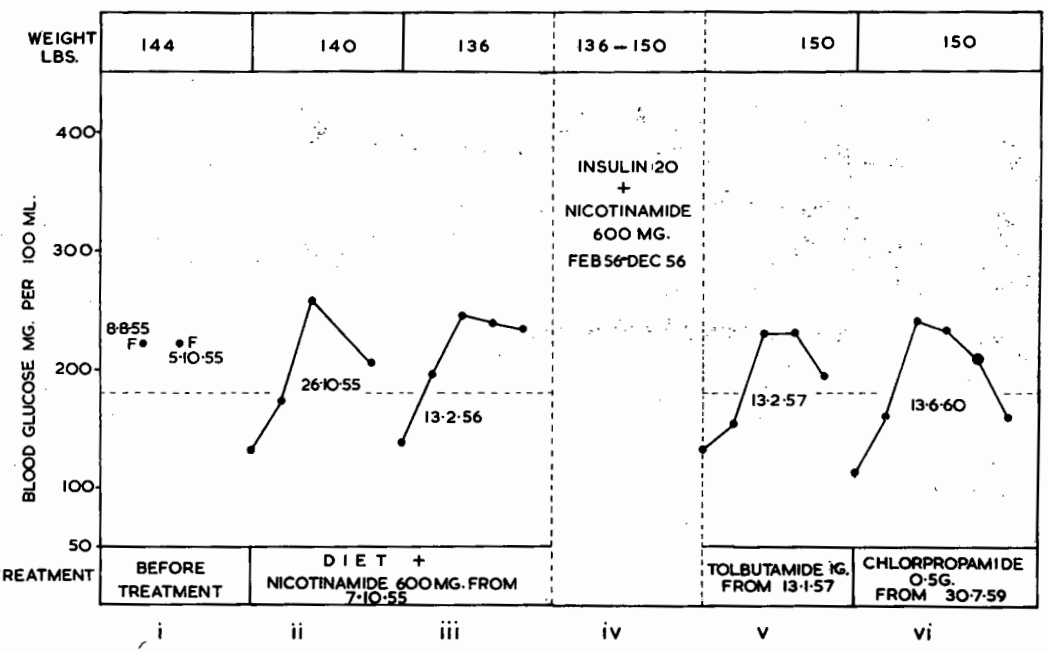
Remission to normal glucose tolerance test soon after starting carbutamide (viii).

Gradual aggravation of glucose tolerance test after stopping carbutamide (ix) and (x).

Response to second course of carbutamide: this time glucose tolerance test (xi) is not as good as glucose tolerance test (viii) in spite of low fasting levels.

The response to chlorpropamide is more or less equal to that of carbutamide. Glucose tolerance test (xii), 3 months after commencing chlorpropamide, and glucose tolerance test (xiii) one year after commencing chlorpropamide, shows a normal fasting and near normal 2 hour level.

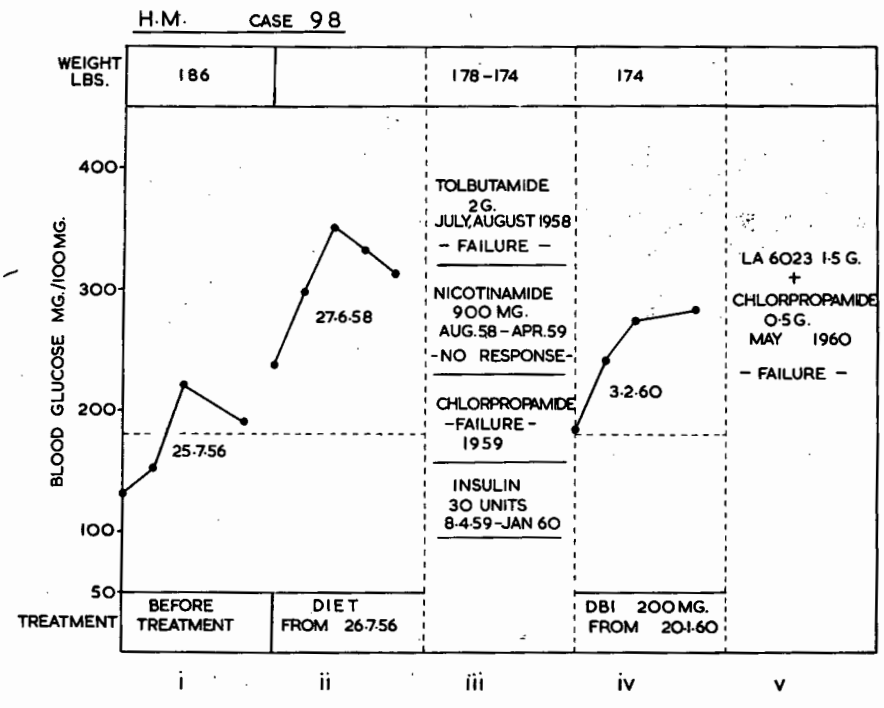
MY. L. CASE 81


WEIGHT LBS.
144
140
136
136 – 150
150
150
400
300
200
100
50
BLOOD GLUCOSE MG. PER 100 ML.
INSULIN 20 + NICOTINAMIDE 600 MG. FEB 56-DEC 56
8·8·55 F
F 5·10·55
26·10·55
13·2·56
13·2·57
13·6·60
TREATMENT
BEFORE TREATMENT
DIET + NICOTINAMIDE 600 MG. FROM 7·10·55
TOLBUTAMIDE 1G. FROM 13·1·57
CHLORPROPAMIDE 0·5G. FROM 30·7·59
i
ii
iii
iv
v
vi

My.L. Case 81, a European woman aged 45 years.

There was some reduction in the fasting glucose level while taking nicotinamide but glucose tolerance tests (ii) and (iii) were abnormal.

There was no appreciable difference in glucose tolerance test while taking tolbutamide or chlorpropamide.

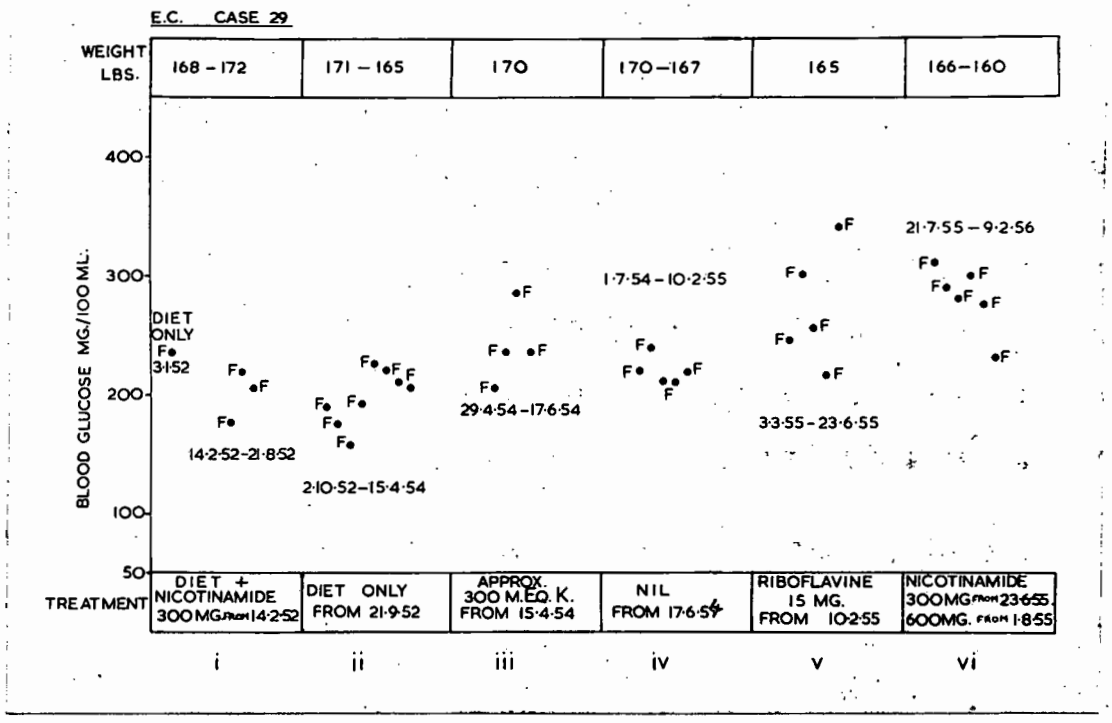

H.M. CASE 98
WEIGHT LBS.
186
178–174
174
BLOOD GLUCOSE MG./100 MG.
400
300
200
100
50
25.7.56
27.6.58
3.2.60
TOLBUTAMIDE 2G. JULY, AUGUST 1958 – FAILURE –
NICOTINAMIDE 900 MG. AUG. 58 – APR. 59 – NO RESPONSE –
CHLORPROPAMIDE – FAILURE – 1959
INSULIN 30 UNITS 8.4.59 – JAN 60
LA 6023 1·5 G. + CHLORPROPAMIDE 0·5 G. MAY 1960 – FAILURE –
TREATMENT
BEFORE TREATMENT
DIET FROM 26.7.56
DBI 200 MG. FROM 20.1.60
i
ii
iii
iv
v

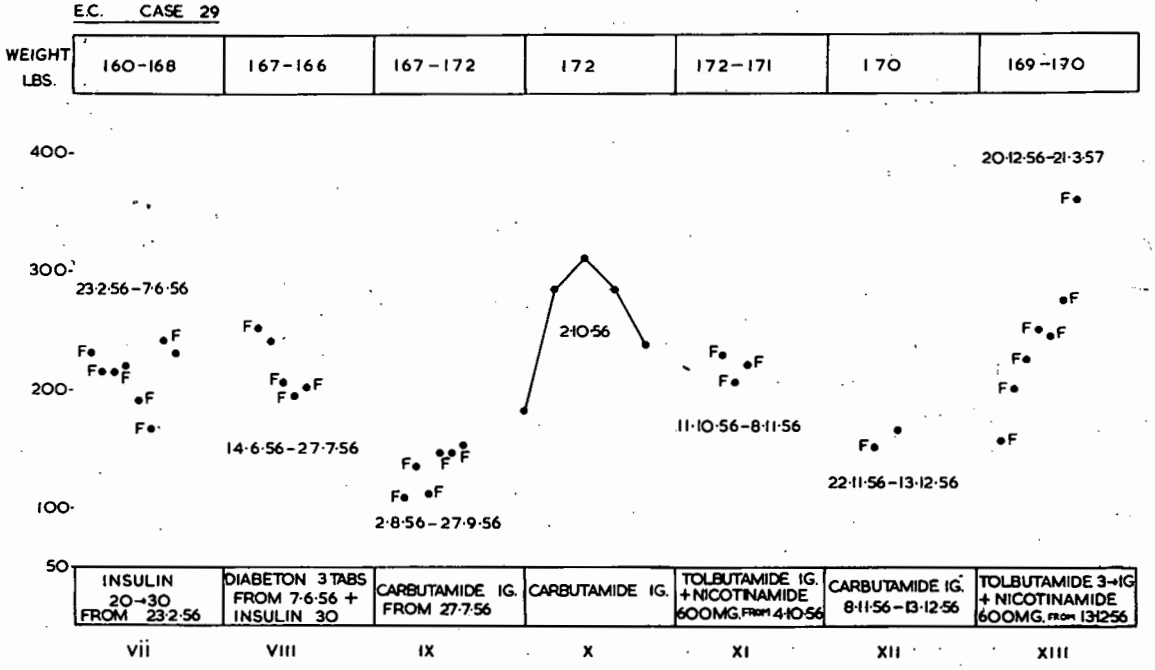
H.M. (Case 98):

This young European man was aged 37 years at onset of diabetes.

Failure of response to all oral medication is shown.

(On DBI and LA 6023, there was a reduction in insulin requirement).


E.C. CASE 29
WEIGHT LBS.
168 – 172
171 – 165
170
170 – 167
165
166 – 160
BLOOD GLUCOSE MG./100 ML.
400
300
200
100
50
DIET ONLY
F 31·52
14·2·52 – 21·8·52
2·10·52 – 15·4·54
29·4·54 – 17·6·54
1·7·54 – 10·2·55
3·3·55 – 23·6·55
21·7·55 – 9·2·56
TREATMENT
DIET + NICOTINAMIDE 300 MG. from 14·2·52
DIET ONLY FROM 21·9·52
APPROX. 300 M.EQ. K. FROM 15·4·54
NIL FROM 17·6·54
RIBOFLAVINE 15 MG. FROM 10·2·55
NICOTINAMIDE 300 MG. from 23·6·55. 600 MG. from 1·8·55
i
ii
iii
iv
v
vi

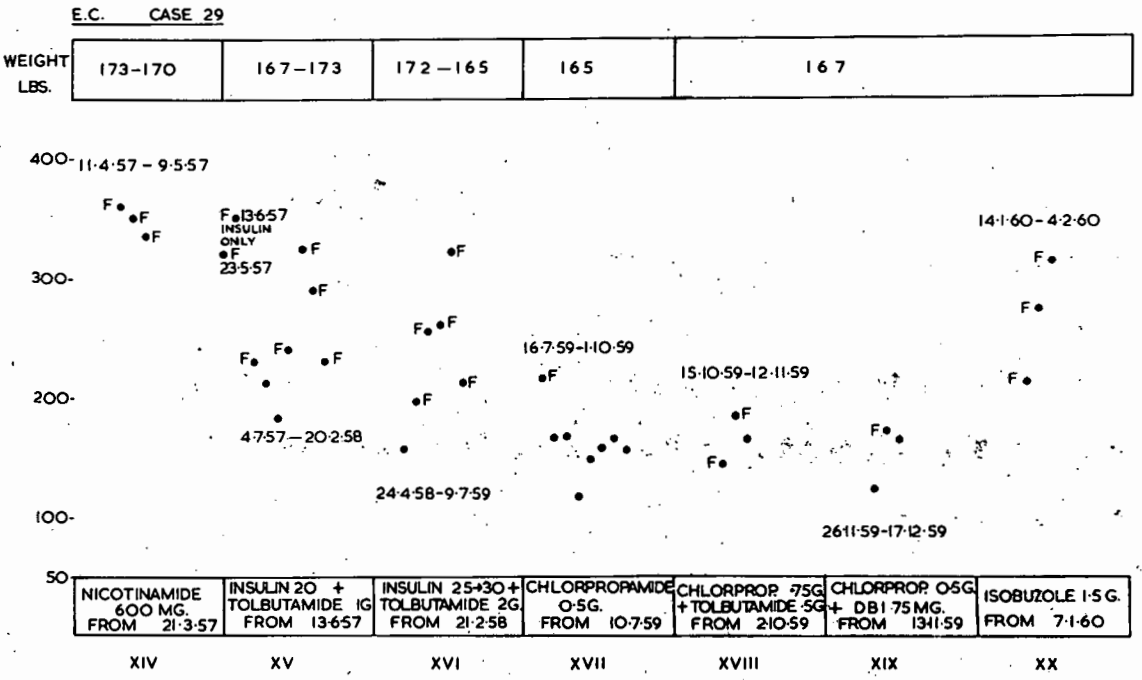

E.C. CASE 29
WEIGHT LBS.
160 – 168
167 – 166
167 – 172
172
172 – 171
170
169 – 170
400
300
200
100
50
23·2·56 – 7·6·56
14·6·56 – 27·7·56
2·8·56 – 27·9·56
2·10·56
11·10·56 – 8·11·56
22·11·56 – 13·12·56
20·12·56 – 21·3·57
INSULIN 20 → 30 FROM 23·2·56
DIABETON 3 TABS FROM 7·6·56 + INSULIN 30
CARBUTAMIDE 1G. FROM 27·7·56
CARBUTAMIDE 1G.
TOLBUTAMIDE 1G. + NICOTINAMIDE 600 MG. from 4·10·56
CARBUTAMIDE 1G. 8·11·56 – 13·12·56
TOLBUTAMIDE 3 → 1G. + NICOTINAMIDE 600 MG. from 13·12·56
vii
viii
ix
x
xi
xii
xiii

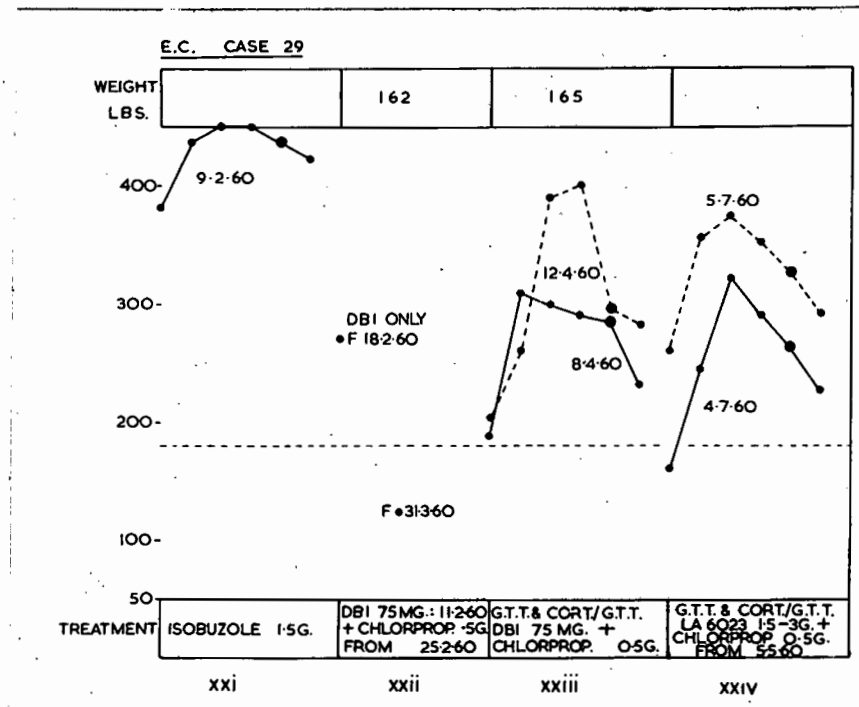
E.C. (Case 29), a European woman aged 55 years.

High fasting glucose levels are shown throughout (i) - (viii) until carbutamide is started (ix), but a glucose tolerance test on carbutamide is abnormal in all respects (x).

No response to tolbutamide is seen in (xi) and a satisfactory response to carbutamide is again shown in (xii).

On tolbutamide there is a gradual elevation in fasting levels (xiii).


E.C. CASE 29
WEIGHT LBS.
173–170
167–173
172–165
165
167
400
300
200
100
50
11·4·57 – 9·5·57
F 13·6·57 INSULIN ONLY
F 23·5·57
4·7·57 – 20·2·58
24·4·58 – 9·7·59
16·7·59 – 1·10·59
15·10·59 – 12·11·59
26·11·59 – 17·12·59
14·1·60 – 4·2·60
NICOTINAMIDE 600 MG. FROM 21·3·57
INSULIN 20 + TOLBUTAMIDE 1G FROM 13·6·57
INSULIN 25→30 + TOLBUTAMIDE 2G. FROM 21·2·58
CHLORPROPAMIDE 0·5G. FROM 10·7·59
CHLORPROP. ·75G. + TOLBUTAMIDE ·5G. FROM 2·10·59
CHLORPROP. 0·5G. + DBI 75 MG. FROM 13·11·59
ISOBUZOLE 1·5 G. FROM 7·1·60
XIV
XV
XVI
XVII
XVIII
XIX
XX


E.C. CASE 29
WEIGHT LBS.
162
165
400
300
200
100
50
9·2·60
DBI ONLY
F 18·2·60
12·4·60
8·4·60
5·7·60
4·7·60
F 31·3·60
TREATMENT
ISOBUZOLE 1·5G.
DBI 75 MG.: 11·2·60 + CHLORPROP. ·5G. FROM 25·2·60
G.T.T. & CORT/G.T.T. DBI 75 MG. + CHLORPROP. 0·5G.
G.T.T. & CORT/G.T.T. LA 6023 1·5–3G. + CHLORPROP 0·5G. FROM 5·5·60
XXI
XXII
XXIII
XXIV

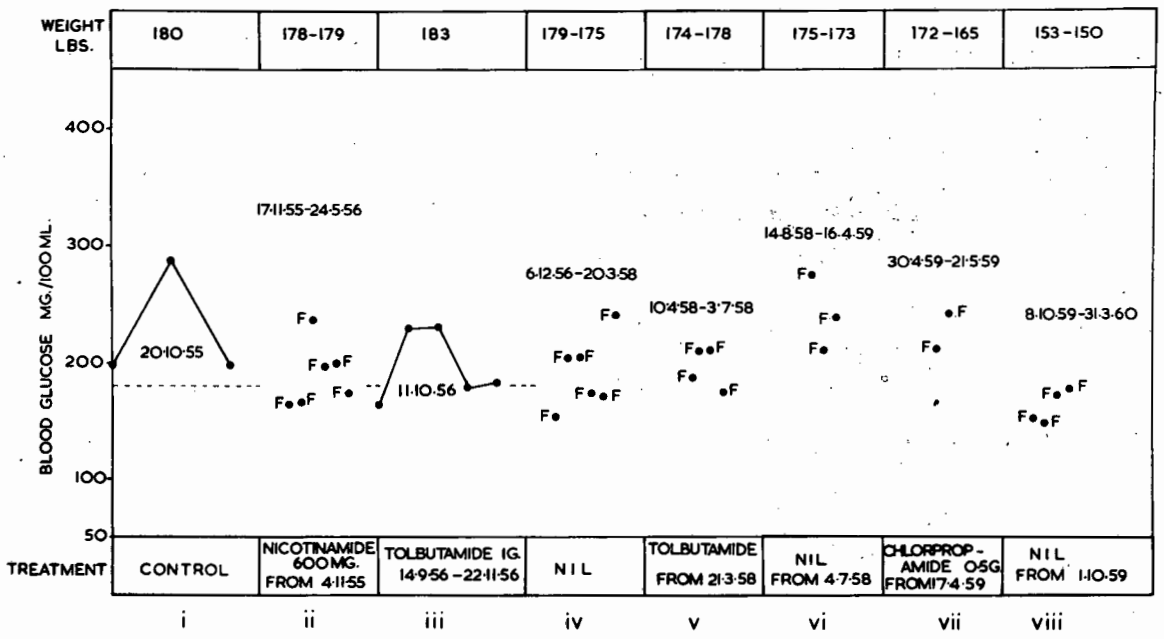
E.C. (Case 29): (Cont'd).

Hyperglycaemic levels are again shown (xiv), (xv), (xvi) until a moderately good response in fasting levels is seen with chlorpropamide (xvii) which was not significantly enhanced by tolbutamide (xviii) or DBI (xix).

Severely hyperglycaemic levels fasting and in glucose tolerance test were recorded on isobuzole (xx) and xxi).

On DBI + chlorpropamide (xxiii) and LA 6023 + chlorpropamide (xxiv) the glucose tolerance tests were severely abnormal.

I.U. CASE 156


WEIGHT LBS.
180
178-179
183
179-175
174-178
175-173
172-165
153-150
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
20·10·55
17·11·55-24·5·56
11·10·56
6·12·56-20·3·58
10·4·58-3·7·58
14·8·58-16·4·59
30·4·59-21·5·59
8·10·59-31·3·60
TREATMENT
CONTROL
NICOTINAMIDE 600 MG. FROM 4·11·55
TOLBUTAMIDE 1G. 14·9·56-22·11·56
NIL
TOLBUTAMIDE FROM 21·3·58
NIL FROM 4·7·58
CHLORPROPAMIDE 0·5G. FROM 17·4·59
NIL FROM 1·10·59
i
ii
iii
iv
v
vi
vii
viii

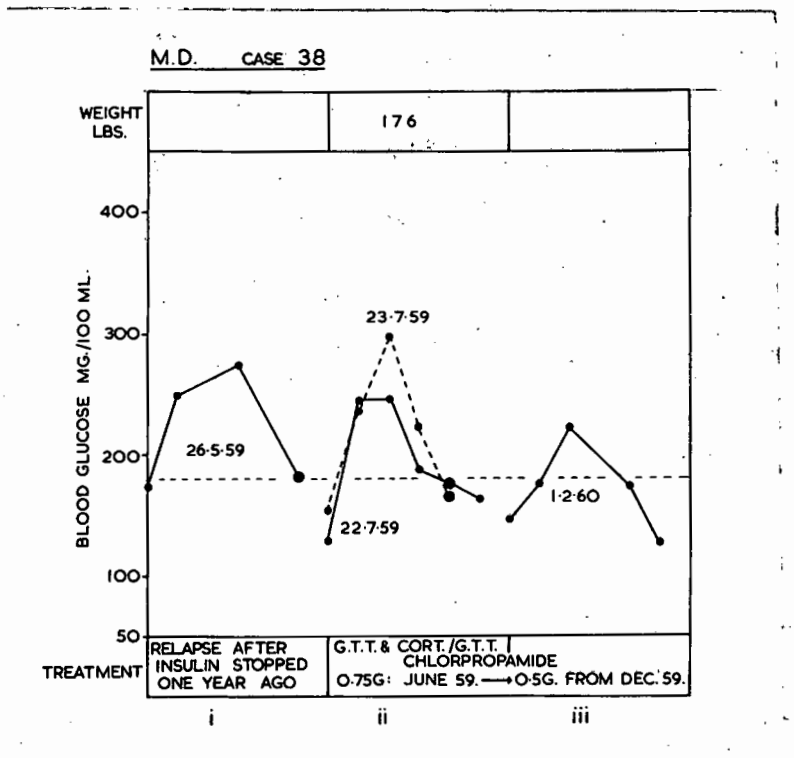
I.U. (Case 156), a European woman aged 67 years.

(A case of gout and diabetes).

There was no response to tolbutamide: glucose tolerance test (iii) or fasting blood glucose levels (v).

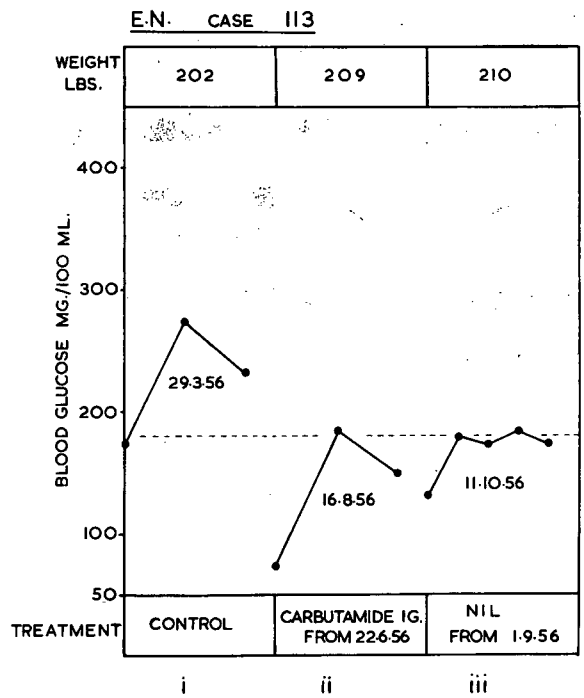
Chlorpropamide (vii) similarly produced no response.

This patient however, did show a reduction in fasting levels at a late stage (viii) with loss of weight.


M.D. CASE 38
WEIGHT LBS.
176
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
23·7·59
26·5·59
22·7·59
1·2·60
TREATMENT
RELAPSE AFTER INSULIN STOPPED ONE YEAR AGO
G.T.T. & CORT./G.T.T. CHLORPROPAMIDE
0·75G: JUNE 59. → 0·5G. FROM DEC. 59.
i
ii
iii

M.D. (Case 38), a European man aged 43 years.

A progressive improvement is shown in 2 glucose tolerance tests (ii) and (iii) following the commencement of chlorpropamide (in a man who had previously been receiving 60 units of insulin and had gone into a spontaneous remission followed by a relapse of diabetes).

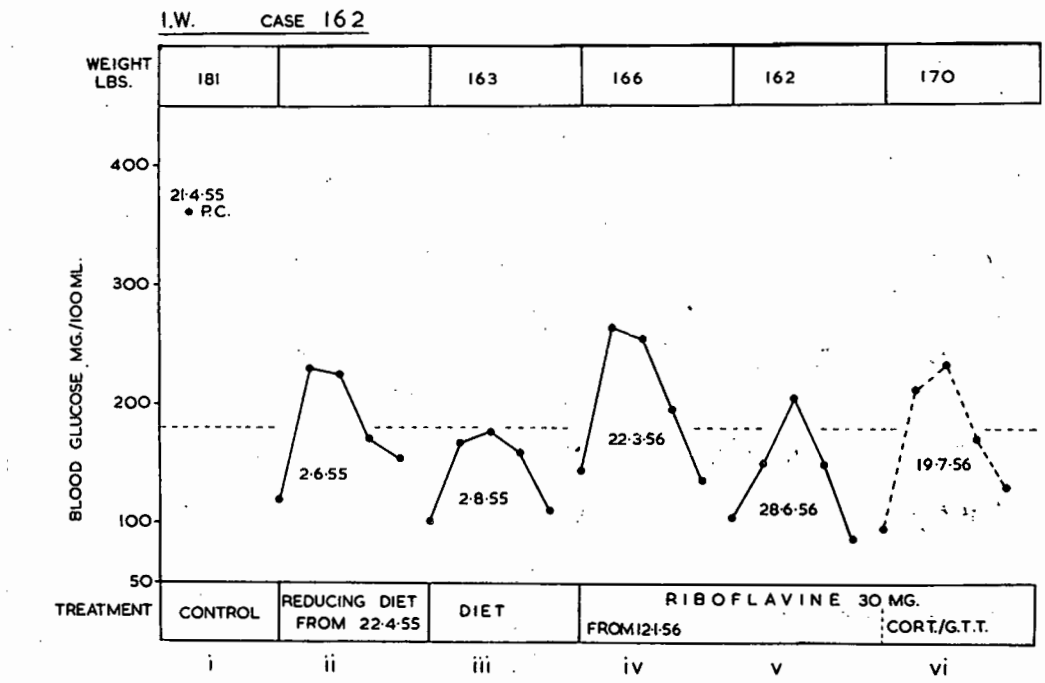

E.N. CASE 113
WEIGHT LBS.
202
209
210
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
29.3.56
16.8.56
11.10.56
TREATMENT
CONTROL
CARBUTAMIDE 1G. FROM 22.6.56
NIL FROM 1.9.56
i
ii
iii

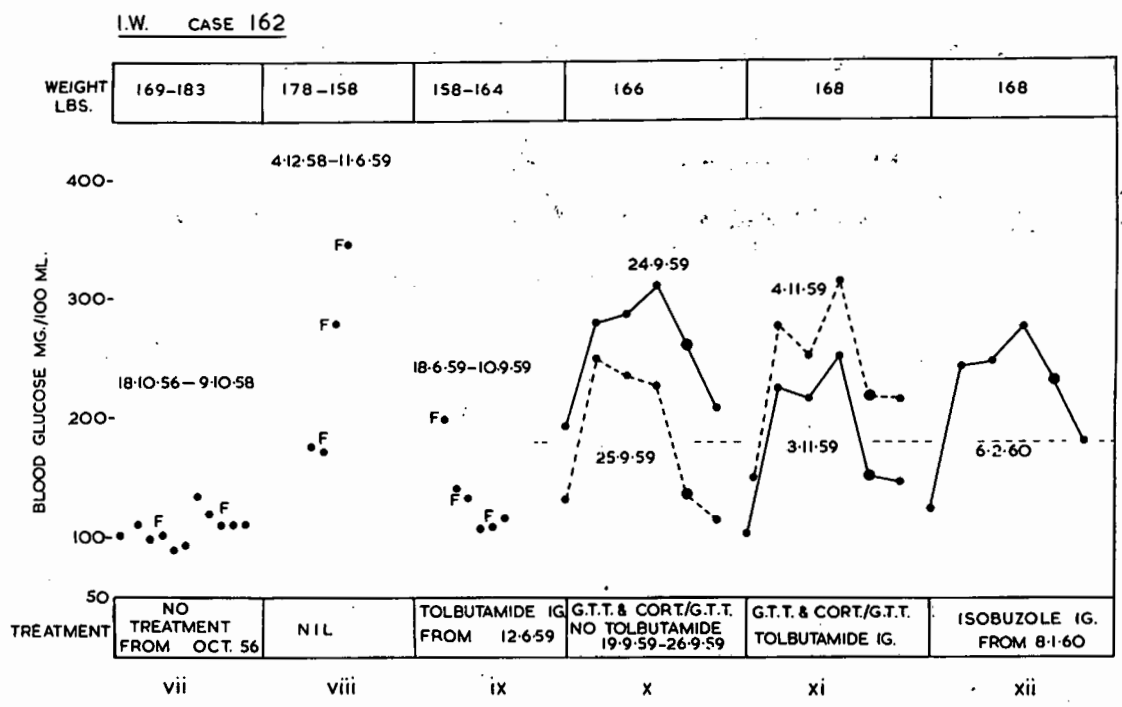
E.H. (Case 113), a European woman aged 58 years.

Glucose tolerance test (i) was done after a period of established diabetes (15 months).

Glucose tolerance test (ii) is much improved on carbutamide though of the same form as (i).

A tendency to relapse after stopping carbutamide is shown in (iii).


I.W. CASE 162
WEIGHT LBS.
181
163
166
162
170
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
21·4·55
• P.C.
2·6·55
2·8·55
22·3·56
28·6·56
19·7·56
TREATMENT
CONTROL
REDUCING DIET FROM 22·4·55
DIET
RIBOFLAVINE 30 MG. FROM 12·1·56
CORT./G.T.T.
i
ii
iii
iv
v
vi


I.W. CASE 162
WEIGHT LBS.
169–183
178–158
158–164
166
168
168
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
4·12·58–11·6·59
18·10·56–9·10·58
18·6·59–10·9·59
24·9·59
25·9·59
4·11·59
3·11·59
6·2·60
F
TREATMENT
NO TREATMENT FROM OCT. 56
NIL
TOLBUTAMIDE IG. FROM 12·6·59
G.T.T. & CORT./G.T.T. NO TOLBUTAMIDE 19·9·59–26·9·59
G.T.T. & CORT./G.T.T. TOLBUTAMIDE IG.
ISOBUZOLE IG. FROM 8·1·60
vii
viii
ix
x
xi
xii

I.W. (Case 162), a European woman aged 58 years.

Remission to normal glucose tolerance test (iii).

Fluctuations in glucose tolerance tests (iv) - (vi).

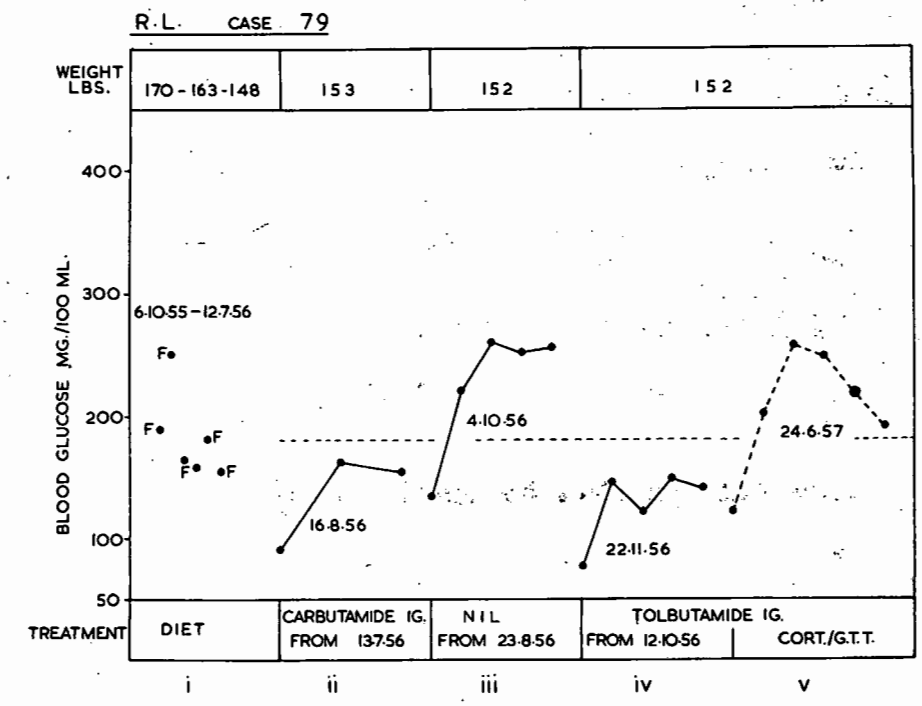
Relapse in diabetes (viii) after low normal fasting levels (vii).

An excellent response to tolbutamide (ix).

Relapse after stopping tolbutamide for one week (x).

An improved glucose tolerance test on tolbutamide (note low fasting level and near normal 2 hour level.

Not such a good glucose tolerance test on another hypoglycaemic agent isobuzole (xii). Note the low fasting level has been maintained but the 2 hour level is definitely abnormal.


R.L. CASE 79
WEIGHT LBS.
170 - 163 - 148
153
152
152
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
6-10-55 – 12-7-56
F
F
F
F
F
16-8-56
4-10-56
22-11-56
24-6-57
TREATMENT
DIET
CARBUTAMIDE IG. FROM 13-7-56
NIL FROM 23-8-56
TOLBUTAMIDE IG. FROM 12-10-56
CORT./G.T.T.
i
ii
iii
iv
v

R.L. (Case 79), a European woman aged 59 years.

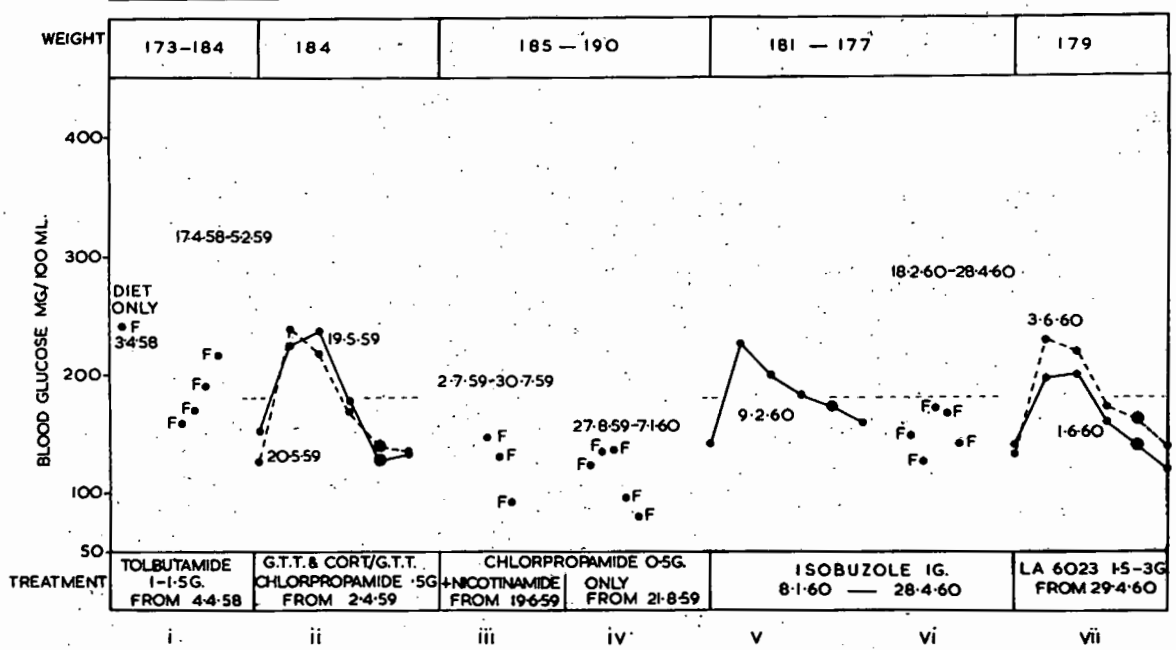
Normal fasting levels are not achieved with diet and weight loss (i).

On carbutamide there is a marked reduction of the fasting glucose level (ii).

The glucose tolerance tests on carbutamide (ii) and tolbutamide (iv) are almost identical: a low fasting level but an elevated 2 hour level.

Off carbutamide the glucose tolerance test (iii) is more abnormal.

J.G. CASE 52

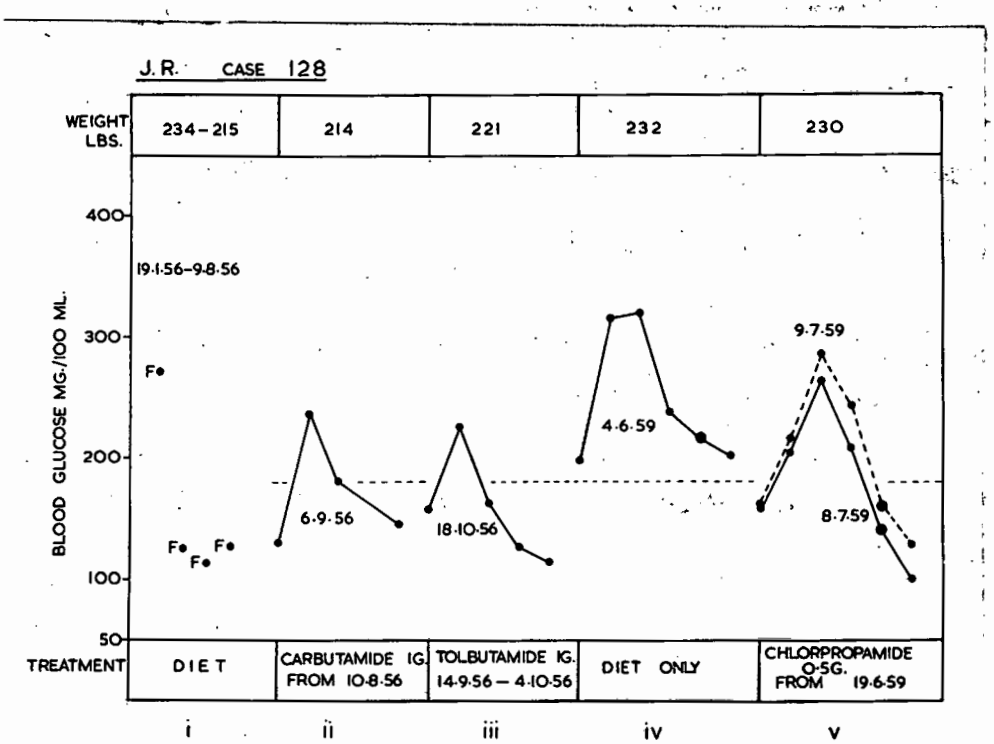

WEIGHT
173–184
184
185 — 190
181 — 177
179
BLOOD GLUCOSE MG/100 ML.
400
300
200
100
50
17·4·58–5·2·59
DIET ONLY
F
3·4·58
19·5·59
20·5·59
2·7·59–30·7·59
27·8·59–7·1·60
9·2·60
18·2·60–28·4·60
3·6·60
1·6·60
TREATMENT
TOLBUTAMIDE 1–1·5G. FROM 4·4·58
G.T.T. & CORT/G.T.T. CHLORPROPAMIDE ·5G FROM 2·4·59
CHLORPROPAMIDE 0·5G. +NICOTINAMIDE FROM 19·6·59
ONLY FROM 21·8·59
ISOBUZOLE 1G. 8·1·60 — 28·4·60
LA 6023 1·5–3G FROM 29·4·60
i
ii
iii
iv
v
vi
vii

J.G. (Case 52), a European man aged 54 years.

No response was seen to tolbutamide (i), but a good response was recorded to chlorpropamide: glucose tolerance test (ii) and fasting levels in (iii) and (iv).

On isobuzole the glucose tolerance test response (v) was reasonably good but there was an elevation of fasting levels (vi).

An excellent response in glucose tolerance test (vii) was recorded to dimethylbiguanide.


J.R. CASE 128
WEIGHT LBS.
234–215
214
221
232
230
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
19·1·56–9·8·56
F
F F
F
6·9·56
18·10·56
4·6·59
9·7·59
8·7·59
TREATMENT
DIET
CARBUTAMIDE 1G. FROM 10·8·56
TOLBUTAMIDE 1G. 14·9·56 – 4·10·56
DIET ONLY
CHLORPROPAMIDE 0·5G. FROM 19·6·59
i
ii
iii
iv
v

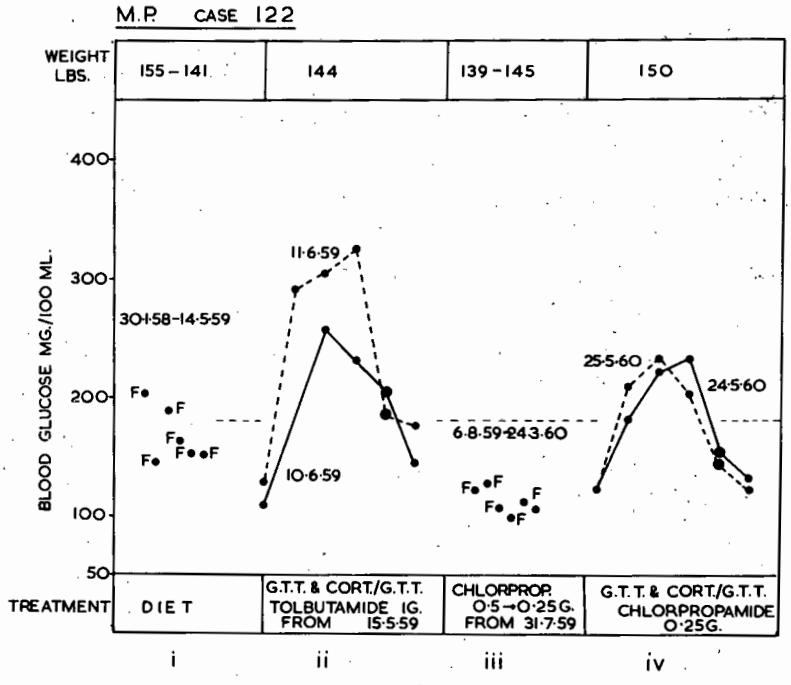
J.R. (Case 128), a European woman aged 59 years.

Glucose tolerance curves (ii) on carbutamide and (iii) on tolbutamide are practically normal apart from the high ½ hour figure in both instances.

(This period may correspond with a remission in diabetes due to weight loss).

Glucose tolerance test (iv) is completely abnormal again (after weight has been gained).

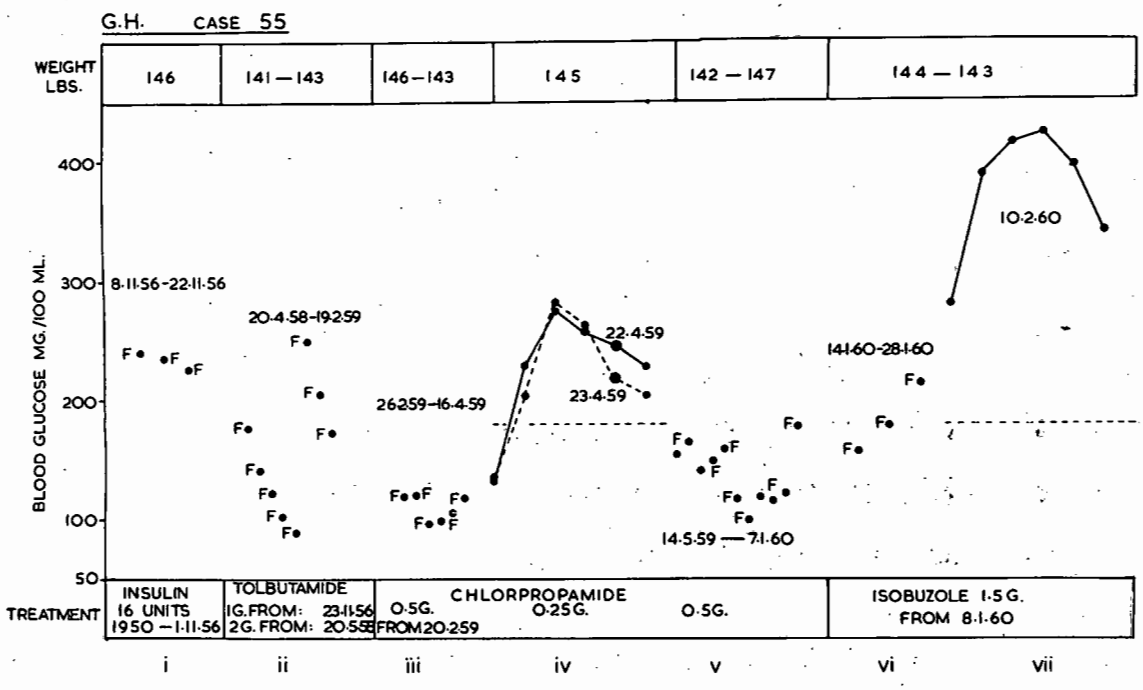
Glucose tolerance test (v) on chlorpropamide is much improved.

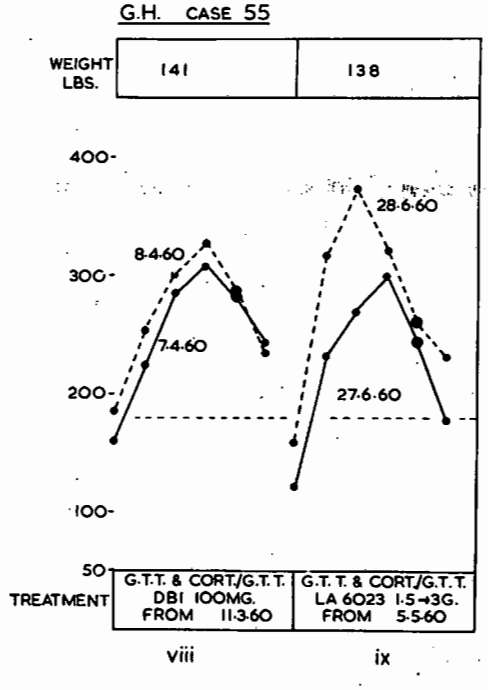

M.P. CASE 122
WEIGHT LBS.
155 – 141
144
139 – 145
150
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
30·1·58–14·5·59
11·6·59
10·6·59
6·8·59–24·3·60
25·5·60
24·5·60
F
TREATMENT
DIET
G.T.T. & CORT./G.T.T. TOLBUTAMIDE 1G. FROM 15·5·59
CHLORPROP. 0·5→0·25G. FROM 31·7·59
G.T.T. & CORT./G.T.T. CHLORPROPAMIDE 0·25G.
i
ii
iii
iv

M.P. (Case 122), a European woman aged 60 years.

This patient showed a good hypoglycaemic response to tolbutamide and chlorpropamide.

The glucose tolerance test on chlorpropamide (iv) was better than that on tolbutamide (ii).


G.H. CASE 55
WEIGHT LBS.
146
141 — 143
146 — 143
145
142 — 147
144 — 143
BLOOD GLUCOSE MG./100 ML.
400
300
200
100
50
8-11-56-22-11-56
20-4-58-19-2-59
26-2-59-16-4-59
22-4-59
23-4-59
14-5-59 — 7-1-60
10-2-60
14-1-60-28-1-60
TREATMENT
INSULIN 16 UNITS 19-5-0 — 1-11-56
TOLBUTAMIDE 1G. FROM: 23-11-56 2G. FROM: 20-5-58
CHLORPROPAMIDE 0·5G. FROM 20-2-59 0·25G. 0·5G.
ISOBUZOLE 1·5G. FROM 8-1-60
i
ii
iii
iv
v
vi
vii


G.H. CASE 55
WEIGHT LBS.
141
138
400
300
200
100
50
8-4-60
7-4-60
28-6-60
27-6-60
TREATMENT
G.T.T. & CORT./G.T.T. DBI 100MG. FROM 11-3-60
G.T.T. & CORT./G.T.T. LA 6023 1·5→3G. FROM 5-5-60
viii
ix

G.H. (Case 55), a European woman aged 52 years.

A good response to tolbutamide is followed by delayed failure (ii).

An excellent response in fasting levels to chlorpropamide is seen (iii) but the glucose tolerance test is grossly abnormal (iv).

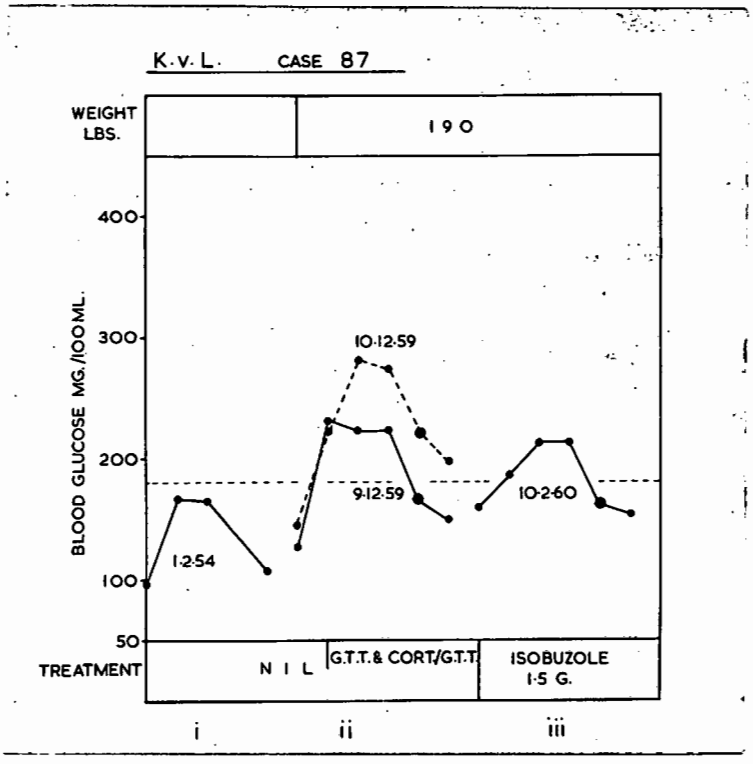
Fasting levels on chlorpropamide later (v) are not quite as good.

On isobuzole there is the development of grossly abnormal fasting blood glucose levels (vi) and glucose tolerance test (vii).

On DBI (viii) and dimethylbiguanide (ix) the response in glucose tolerance tests was similar to that seen with chlorpropamide (iv).

G.K. (Case 76), a European man aged 48 years.

Glucose tolerance tests on tolbutamide and after discontinuing tolbutamide are almost identical. (See page 212).


K.v.L. CASE 87
WEIGHT LBS.
190
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
10-12-59
9-12-59
10-2-60
1-2-54
TREATMENT
NIL
G.T.T. & CORT/G.T.T.
ISOBUZOLE 1·5 G.
i
ii
iii

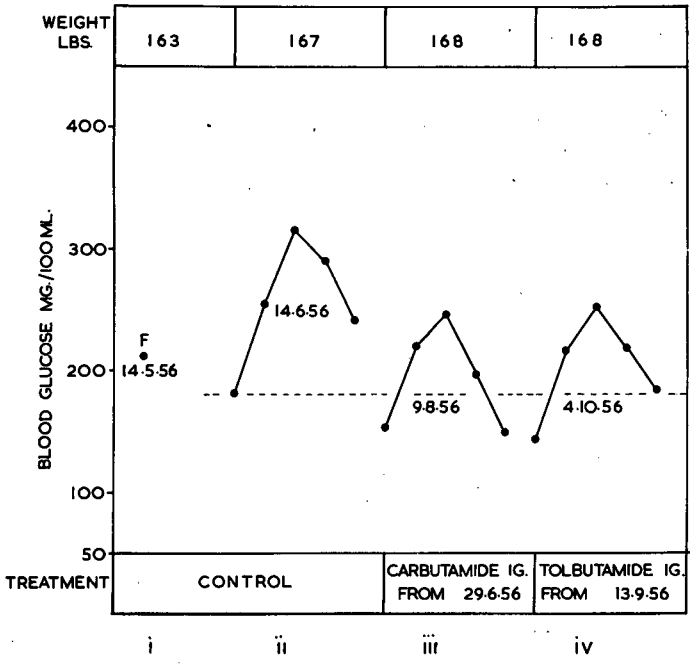
K.v.L. (case 87), a European man aged 58 years.

A glucose tolerance test (i) in 1954 had established previous renal glycosuria.

Glucose tolerance test (ii) shows a diabetic type of curve 5 years later.

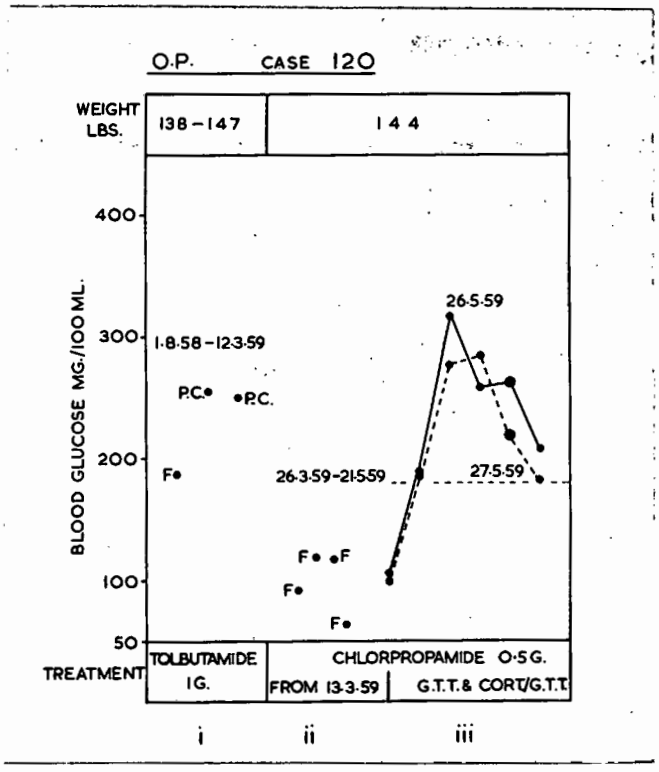
On isobuzole the glucose tolerance test (iii) is practically unchanged.

G. SA. CASE 134


WEIGHT LBS.
163
167
168
168
400
300
200
100
50
BLOOD GLUCOSE MG/100 ML.
F
14.5.56
14.6.56
9.8.56
4.10.56
TREATMENT
CONTROL
CARBUTAMIDE IG. FROM 29.6.56
TOLBUTAMIDE IG. FROM 13.9.56
i
ii
iii
iv

G. Sa. (Case 134), a Coloured woman aged 44 years.

The response as measured by glucose tolerance test was better to carbutamide (iii) than to tolbutamide (iv).

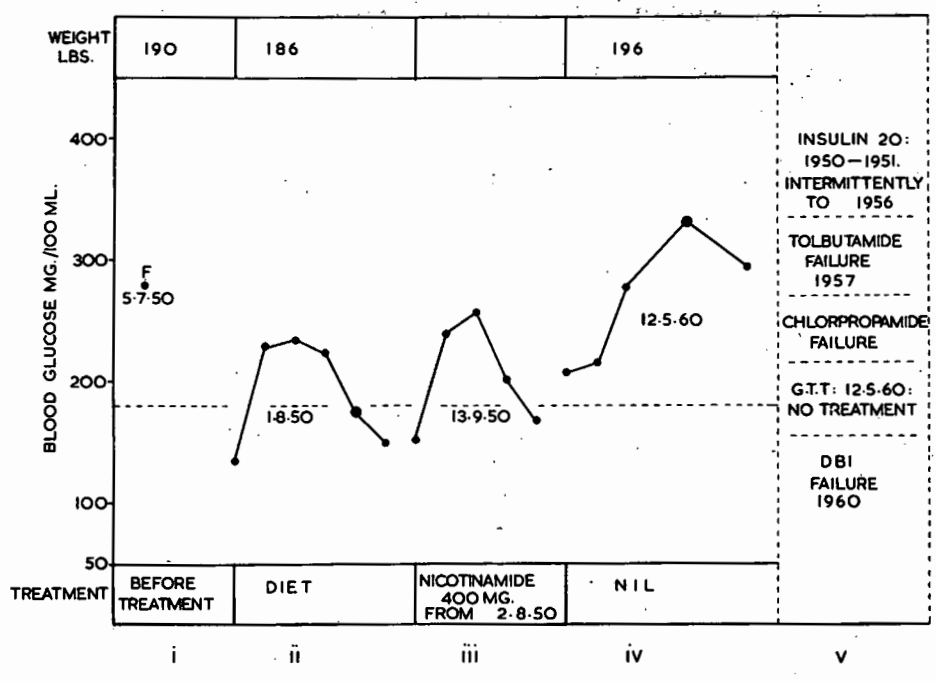

O.P. CASE 120
WEIGHT LBS.
138 – 147
144
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
1·8·58 – 12·3·59
P.C.
P.C.
F
26·3·59 – 21·5·59
26·5·59
27·5·59
F
F
F
F
TREATMENT
TOLBUTAMIDE 1G.
CHLORPROPAMIDE 0·5 G.
FROM 13·3·59
G.T.T. & CORT/G.T.T.
i
ii
iii

O.P. (Case 120), a European woman aged 65 years.

There was failure of response to tolbutamide (i), but an excellent response in fasting levels to chlorpropamide (ii).

Glucose tolerance test though, was grossly abnormal (iii).

H. MR. CASE 97


WEIGHT LBS.
190
186
196
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
F
5·7·50
1·8·50
13·9·50
12·5·60
INSULIN 20: 1950—1951. INTERMITTENTLY TO 1956
TOLBUTAMIDE FAILURE 1957
CHLORPROPAMIDE FAILURE
G.T.T: 12·5·60: NO TREATMENT
DBI FAILURE 1960
TREATMENT
BEFORE TREATMENT
DIET
NICOTINAMIDE 400 MG. FROM 2·8·50
NIL
i
ii
iii
iv
v

H.Mr. (Case 97), a European man aged 35 years.

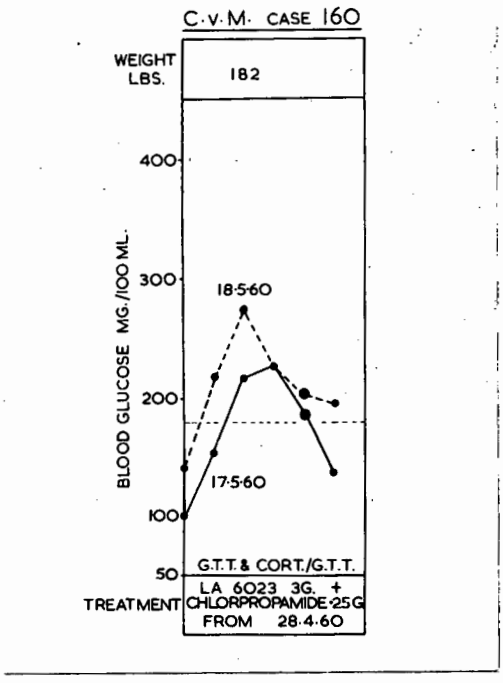
Progressive worsening of glucose tolerance tests are shown (ii, (iii), (iv).

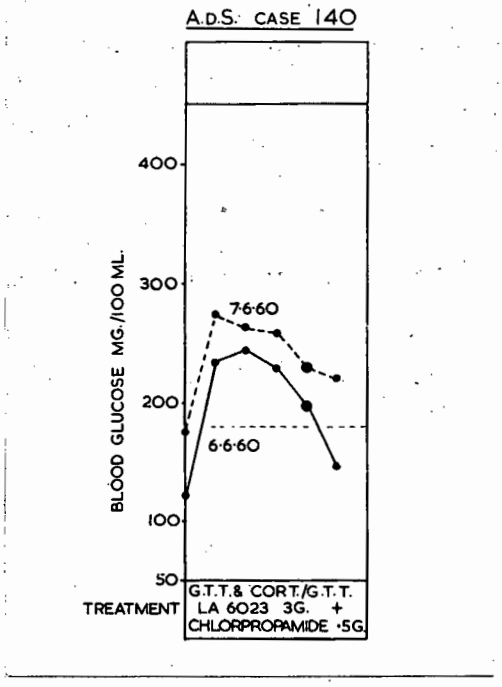
No response was seen to tolbutamide, chlorpropamide or DBI.

A.d.S. (Case 140), a European man aged 52 years.

(This man, previously on insulin, failed to respond to a trial of all the sulphonylureas: tolbutamide, chlorpropamide, metahexamide, isobuzole).

His control with chlorpropamide + dimethylbiguanide was good and the glucose tolerance test as well was reasonably good. (See illustration next page).


C.V.M. CASE 160
WEIGHT LBS.
182
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
18·5·60
17·5·60
G.T.T. & CORT./G.T.T.
TREATMENT
LA 6023 3G. + CHLORPROPAMIDE·25G FROM 28·4·60


A.D.S. CASE 140
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
7·6·60
6·6·60
TREATMENT
G.T.T.& CORT./G.T.T. LA 6023 3G. + CHLORPROPAMIDE ·5G.

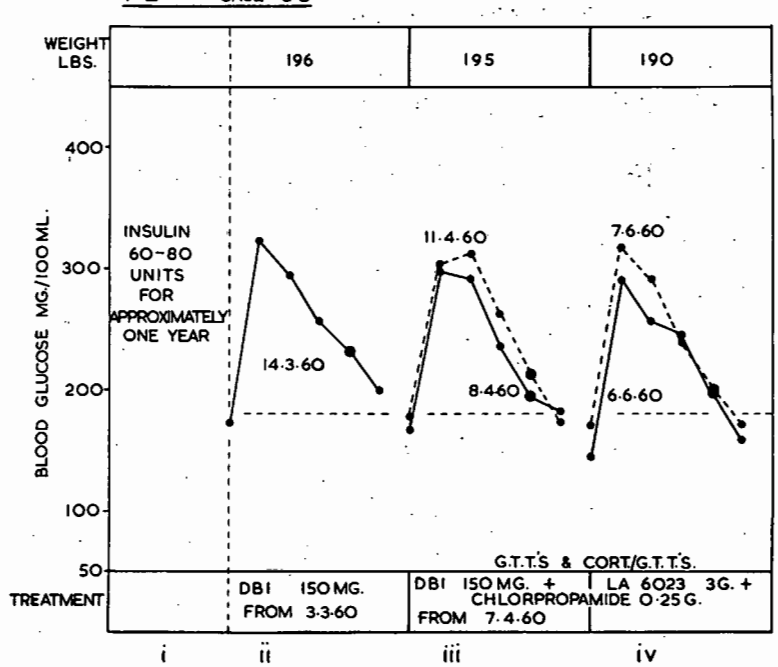
C.v.M. (Case 160), a European man aged 63 years.

(There was a failure of reponse to a trial of all the sulphonylureas: tolbutamide, chlorpropamide, metahexamide and isobuzole in this patient who was taking insulin 45 units daily. Insulin could be discontinued after starting the concurrent administration of LA 6023 and chlorpropamide).

Glucose tolerance test showed an excellent response to dimethylbiguanide + chlorpropamide.

On withdrawal of chlorpropamide he remained sugar free.

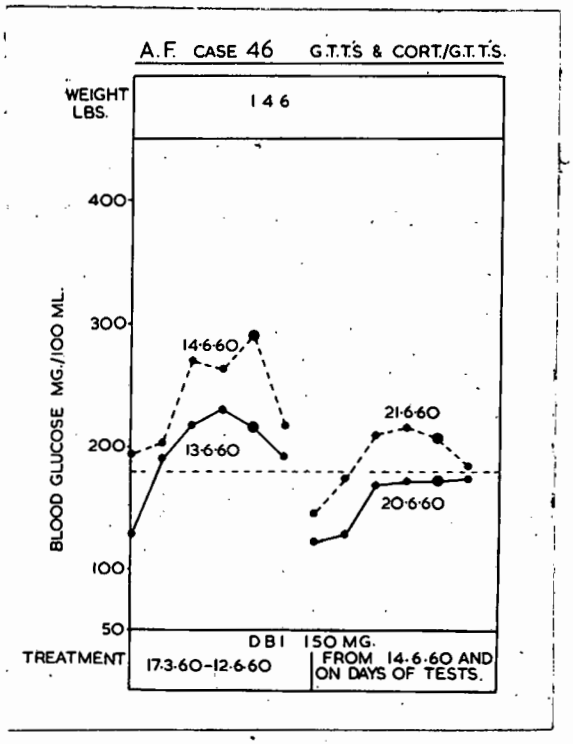
P.L. CASE 88


WEIGHT LBS.
196
195
190
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
INSULIN 60-80 UNITS FOR APPROXIMATELY ONE YEAR
14.3.60
11.4.60
8.4.60
7.6.60
6.6.60
G.T.T.'S & CORT/G.T.T.'S.
TREATMENT
DBI 150 MG. FROM 3.3.60
DBI 150 MG. + CHLORPROPAMIDE 0.25 G. FROM 7.4.60
LA 6023 3G. +
i
ii
iii
iv

P.L. (Case 88), a European man aged 58 years.

(There had been poor control on insulin 60 - 80 units. On DBI or dimethylbiguanide better blood glucose levels were recorded).

Glucose tolerance tests on DBI alone (ii) or DBI + chlorpropamide (iii) or dimethylbiguanide + chlorpropamide (iv) were all almost identical and equally abnormal.


A.F. CASE 46 G.T.T.'S & CORT/G.T.T.'S.
WEIGHT LBS.
146
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
14·6·60
13·6·60
21·6·60
20·6·60
DBI 150 MG.
FROM 14·6·60 AND ON DAYS OF TESTS.
TREATMENT
17·3·60–12·6·60

A.F. (Case 46), a Coloured woman aged 55 years.

This patient, with diabetes of 2 years' duration, was previously on insulin.

She showed an excellent response to DBI: fasting and glucose tolerance test 13.6.60.
(This was done when the patient omitted DBI from the previous day).

On. 20.6.60. the glucose tolerance test has been lowered by taking DBI 50 mg. before glucose on the days of glucose tolerance tests.

RESULTS: PHARMACOLOGICAL AGENTS IN DIABETES:

The preceding illustrations clearly demonstrate the hypoglycaemic action of the various agents used. These patients are a representative reflection of the total group studied, and have been selected for presentation as they illustrate the following features of particular interest in my study:

1. Response and failure of response to pharmacological substances,

2. Remission,

3. Comparative effect of the various hypoglycaemic agents and other substances in this study.

The hypoglycaemic action of pharmacological agents has been firmly established in the literature and these studies amply confirm this point.

The Value of Long Term Studies in assessing Hypoglycaemic Agents:

The value of the method of investigation which I have used here in assessing the response or failure of response of a diabetic patient to pharmacological agents over a long period has been demonstrated in my publication on chlorpropamide in diabetes with special reference to tolbutamide-failed cases (Herman et al 1960).

Patients in whom primary or secondary tolbutamide failure had been demonstrated were treated with chlorpropamide. Of 51 patients who had previously had tolbutamide, 43 failed to respond to this drug. In this latter group there were 18 primary tolbutamide failures and 25 secondary failures. The test imposed on chlorpropamide in this trial was therefore a very stringent one. An excellent response to chlorpropamide was obtained in 20 of the 43 tolbutamide failures and a partial response in a further 14. Chlorpropamide was often found to be effective where there was primary or secondary tolbutamide failure.

The reports on the action of carbutamide and tolbutamide in diabetes by Jackson et al (1956 and 1957) include some of the patients I had studied over a period of years. The value of long term assessment of hypoglycaemic action is again demonstrated.

The above reports deal with the effective hypoglycaemic action of the sulphonylureas, carbutamide, tolbutamide and chlorpropamide.

Isobuzole, a thiadiazole derivative, synthesised by Chubb et al (1959) and resembling the original product used by Janbon (1942) more closely than any other hypoglycaemic agent at present in use, was not found to be an effective hypoglycaemic agent in the patients in whom it was used (Herman 1960).

The guanidine derivatives might be effective where the sulphonylureas have failed to produce a satisfactory response. This was well demonstrated in C.v.M. (Case 160) an elderly man on insulin who failed to respond to all the available sulphonylureas. His response to both phenethylbiguanide and later to dimethylbiguanide was excellent and his control was

better than when he was taking 45 units of insulin.

The following patients, too, who had failed to respond to the sulphonylureas, showed satisfactory control on the diguanides: P.L. (Case 88), N.C. (Case 32), A.F. (Case 46).

A few other patients - an intermediate group of diabetics aged 30 to 40 years at onset of diabetes - who had failed to show a hypoglycaemic response to the sulphonylureas, showed this unsatisfactory response to the biguanides also, e.g. P.K. (Case 74), H.M. (Case 98), H.Mr.(Case 97). These patients had been observed over a long period of time and resembled N.C. (Case 32) in age of onset and type of diabetes, but not in their type of response to the guanides.

The Value of Glucose Tolerance Tests in assessing Hypoglycaemic Action:

The action of the pharmacological hypoglycaemic agents was put to the most stringent test, the glucose tolerance test. Many of the cases who were on the pharmacological agents had glucose tolerance tests done before treatment as well as when receiving treatment. Fluctuations in glucose tolerance tests had already been noted in many of these patients over a period of years.

The glucose tolerance tests portrayed in this study have been a better index of the extent of improvement than the fasting blood glucose levels. Thus when a patient was thought to show a 'partial response' to a hypoglycaemic agent as judged by fasting glucose estimations the glucose tolerance test often revealed the gross abnormality.

Where patients had shown a return of the fasting glucose levels to normal or near normal (e.g. a feature often demonstrated in the illustrations was a dramatic fall in the fasting levels from 300 mg. to 100 mg. under the influence of the

hypoglycaemic agent) the glucose tolerance tests showed 2 types of response:

1. A well-marked lowering of the fasting blood glucose level but the rest of the curve remained elevated and often grossly abnormal.

2. Marked improvement or remission to a normal glucose tolerance curve.

The patients showing these responses are listed.

1. A well-marked lowering of the fasting glucose level but the rest of the curve remained elevated and often grossly abnormal: 9 patients.

Case	Name	Column no. in graph	Hypoglycaemic agent
83	L.L.	(vii)	Tolbutamide
		(xii)	Isobuzole
136	G.S.	(xii)	Chlorpropamide + tolbutamide
		(xiii)	Chlorpropamide + tolbutamide
		(xv)	LA 6023
47	J.F.	(vii)	Tolbutamide
120	O.P.		Chlorpropamide
31	J.C.	(x)	Chlorpropamide
126	W.R.	(xviii)	Chlorpropamide
29	E.C.	(x)	Carbutamide
		(xxiii)	DBI + Chlorpropamide
		(xxiv)	LA 6023 + Chlorpropamide
122	M.P.	(ii)	Tolbutamide
55	G.H.	(iv)	Chlorpropamide
		(viii)	DBI
		(ix)	LA 6023

2. Glucose tolerance tests showing marked improvement or remissions to normal while being treated with hypoglycaemic agents: 14 patients.

Case	Name	Col. no. in graph	Hypoglycaemic Agent	Comment
127	D.R.	(xvi)	Tolbutamide	Completely normal G.T.T.
		(xxi)	Chlorpropamide	Near normal G.T.T.
136	G.S.	(ix)	Tolbutamide	Near normal G.T.T.
32	N.C.	(viii)	LA 6023 + chlorpropamide	Near normal G.T.T.
47	J.F.	(xiii)	DBI + chlorpropamide	Completely normal G.T.T.
2	M.A.	(vii)	Carbutamide	Normal G.T.T.
		(ix)	Tolbutamide	Normal G.T.T.
80	M.La.	(vi)	Carbutamide	Near normal G.T.T.
126	W.R.	(x)	Carbutamide	Near normal G.T.T.
		(xii)	Tolbutamide	Near normal G.T.T.
113	E.N.	(ii)	Carbutamide	Improved G.T.T. (Form of G.T.T. resembles previous G.T.T.)
79	R.L.	(ii)	Carbutamide	Near normal G.T.T.
		(iv)	Tolbutamide	Near normal G.T.T. (Form of G.T.T. resembles previous G.T.T.)
52	J.G.	(ii)	Chlorpropamide	G.T.T. with normal F and 2 hr. levels
		(vii)	LA 6023	
128	J.R.	(v)	Chlorpropamide	High peak; but good 2 hr. level.
122	M.P.	(iv)	Chlorpropamide	Low Fasting and 2 hr. level.
76	G.K.		Tolbutamide	Mildly abnormal only
38	M.D.	(iii)	Chlorpropamide	Much improved G.T.T.

Examination of Groups 1 and 2 indicates that 4 patients had at one time shown a remission in glucose tolerance test to normal or near normal while being treated with a hypoglycaemic agent, and at another time had shown severe impairment in glucose tolerance test in spite of a good response judged by fasting levels only.

These 4 patients were:

G.S. Case 136
J.F. Case 47
W.R. Case 126
M.P. Case 122

DISCUSSION OF THE RESULTS:

The most interesting outcome of the results is that patients have shown improvement in the glucose tolerance test to near normal or normal.

It has been generally accepted that the glucose tolerance test does not improve with the hypoglycaemic agent; that there is merely lowering of the blood glucose level.

The 4 patients who showed both types of response in glucose tolerance tests clearly demonstrate that a change in the form of the glucose tolerance curve does occur, and in several of the patients listed in Group 2, the fasting and 2 hour levels were shown to be within normal limits.

If further evidence for remission to a normal glucose tolerance test on a hypoglycaemic agent is required, Mrs. D.R. (Case 127) (See page 102) demonstrates this phenomenon perfectly.

On 11.4.57 a completely normal glucose tolerance test (xvi) was seen after tolbutamide had been given for one month. Her fasting blood glucose before that was over 300 mg., and abnormal glucose tolerance tests, (e.g. on 23.7.56 (xiv) where the 2 hour level was near 300 mg.), had been established over a period. When tolbutamide was omitted for 3 weeks, a glucose tolerance test (xviii) on 22.4.58 with a 2 hour level in the vicinity of 400 mg. was noted. After this, another much improved glucose tolerance test on chlorpropamide (xxi) was seen at a time when she had developed

secondary tolbutamide failure with fasting glucose levels again at 300 mg.

Thus fluctuations from grossly abnormal to normal curves have been demonstrated in this case.

It seems that we may have to alter our previously held concept that an improvement in glucose tolerance test does not occur.

If a normal glucose tolerance curve had been recorded in patients who showed only a mild aberration of the glucose tolerance test it might be argued that this phenomenon was merely a manifestation of the blood glucose lowering effect of the drug; but the most striking responses were seen in patients with gross abnormalities of the glucose tolerance test.

It is possible that the reports in the literature of the type of changes seen in the glucose tolerance tests have been misleading. In a report on the results of a joint investigation of the oral anti-diabetogenic preparation, tolbutamide,

(D.860), held at Frankfurt/M on 8.12.55 and 8.3.56, several workers (G. Stötter, G. Mohnike, W. Creutzfeldt, R. Seus, St. Schlagintweit and H. Ulrich) contributed their experiences on the results of glucose tolerance tests in patients with tolbutamide. It was stated that with the Staub-Traugott tolerance test the trend of the blood glucose curve was practically identical in diabetes with and without tolbutamide; only the level varied.

Granville-Grossman et al (1959) reported their experience on glucose tolerance tests in 11 patients who had been treated with chlorpropamide for 6 weeks. The first glucose tolerance test was done before the course of chlorpropamide and the second some weeks or months after completion of the course, when the patients were well controlled on diet. They reported that all the blood sugar levels of the glucose tolerance test had fallen after chlorpropamide, but that the curve was still abnormal.

Duncan et al (1956) carried out oral glucose tolerance tests before and during treatment

with carbutamide (BZ 55) in 10 successfully treated cases. They reported that carbutamide was without effect either on glucose tolerance or on the rate of its absorption. Thus, the mean of the oral glucose tolerance curves obtained in 10 responsive patients before and during treatment with carbutamide show 2 parallel curves throughout their whole extent.

It is difficult to reconcile my findings on changes in the glucose tolerance test with the reports of the German workers on tolbutamide, and the work at Edinburgh on BZ 55 (Duncan et al 1956), and of others, (Granville-Grossman 1959) and also with the generally accepted view.

Some comments can be made:-

In this study a long term observation of individual diabetics was undertaken and the course of fluctuations in glucose tolerance test of each diabetic was well-known. It was therefore not necessary to give an average of results obtained in a group of patients. Inclusion of all diabetics with varying responses and giving the result in the average may be misleading.

Was it possible that the inclusion of patients showing 2 contrasting types of responses in glucose tolerance test (like those seem in this investigation) would obscure the results seen, i.e. if Groups 1 and 2 were averaged would this not obscure the result seen in the group with remissions in diabetes ?

The report of changes in glucose tolerance tests observed before and during BZ 55 therapy by Duncan et al (1956) was based on the changes produced in glucose tolerance tests after a 5 to 10 day period of treatment. In the report by Granville-Grossman (1959) the second series of glucose tolerance tests was done after the completion of a 6 week course of treatment and is thus not comparable to my group where patients were still being treated at the time of the glucose tolerance tests.

It is possible that the presently held concept that there is no improvement in glucose tolerance is based on short term studies such as the one by Duncan et al (1956). It seems that this may be the very significant point of difference between my study and those of others. Whereas most reports of this nature were made on short term studies only, my study was

conducted on patients, many of whom had had investigations on fluctuations in glucose tolerance tests over a period of years (e.g. In the group showing remissions in glucose tolerance tests there were 6 patients whose course had been observed by me for 5 - 12 years).

The Influence of NICOTINAMIDE on the FASTING blood GLUCOSE level of patients on Pharmacological agents:

The administration of nicotinamide concurrently with a hypoglycaemic agent was not found to enhance its hypoglycaemic action; on the contrary, an examination of the results seemed to suggest that an elevation in fasting glucose level might have been induced when nicotinamide was administered as well as a sulphonylurea drug.

The Nicotinamide Response in Relation to the Response to Hypoglycaemic agents:

Nicotinamide and Hypoglycaemic Agents:

		Tolbutamide			
Name	Case	Response	2ndary Failure	Chlorpropamide Response	Comments.
D.R.	127	Excellent	Yes	Excellent	
G.S.	136	Satisfactory	Yes	Satisfactory	
M.A.	2	Good	Yes	Not tried	
L.L.	83	Satisfactory	Yes	Satisfactory	
J.F.	47	Satisfactory	Yes	Satisfactory	
J.C.	31	Satisfactory	Yes	Satisfactory	
N.C.	32	No response	-	No response	Biguanide response good
M.La.	80	-	-	-	Carbutamide response good
C.M.	95	-	-	-	Carbutamide response good

An analysis of the responses to hypoglycaemic agents in 9 cases who had shown a satisfactory remission with nicotinamide revealed that 6 of these cases had shown an initial response to tolbutamide and 2 to carbutamide. N.C. (Case 32) had failed to show any response to the sulphonylureas, but subsequently showed a good response to

dimethylbiguanide.

All of the 6 cases who showed an initial response to tolbutamide and were followed up for a period of years showed a secondary failure of response to tolbutamide.

Thus 6 patients who had shown a remission followed by a relapse in diabetes (before the pharmacological agents had been prescribed) showed a satisfactory or excellent response to tolbutamide initially. This response gradually gave way to complete failure of response with a progressive rise in fasting glucose levels, sometimes to 300 mg. or more.

This finding may be significant: a remission and a relapse of diabetes has been noted twice in the same patients. Has the diabetes changed in some way, i.e. towards the severe type or juvenile type ?

This does not appear to be the likely explanation because 5 of these patients who were tried on another sulphonylurea drug, chlorpropamide, showed a response which could be classed satisfactory or excellent.

SUMMARY:

1. In this section the hypoglycaemic action of the various agents has been demonstrated. The following were found to be effective hypoglycaemic agents:

(a) Tolbutamide

(b) Carbutamide

(c) Chlorpropamide.

Isobuzole was not found to be an effective hypoglycaemic agent in the patients in whom it was used.

2. The guanidine derivatives may be effective where the sulphonylureas have failed.

3. Chlorpropamide may be effective where there was primary or secondary tolbutamide failure.

4. The fasting glucose level, although a very good index of whether a patient showed response or not to a hypoglycaemic agent, was not as good an index as the glucose tolerance test of the extent of improvement.

5. In the glucose tolerance tests it was seen that the hypoglycaemic agents produced a change when compared with glucose tolerance tests done previously. Where a good response in fasting level was seen :

(i) In 9 patients there was merely a lowering of the fasting blood glucose levels, the later figures of the glucose tolerance test remaining elevated.

(ii) In 14 patients a marked improvement in glucose tolerance test was noted to normal or near normal.

VI.

A STUDY OF CARBOHYDRATE TOLERANCE IN GOUT

A STUDY OF CARBOHYDRATE TOLERANCE IN GOUT.

GOUT AND DIABETES MELLITUS:

There exists a large group of diabetics in whom the disturbance of carbohydrate metabolism is not dependent on insulin lack (Bornstein et al 1951 (a) and (b)). Recent advances in our knowledge have failed to throw much light on this group, and the metabolic lesion in diabetes-mellitus-without-insulin-deficiency still remains unknown.

The discovery of alloxan-induced diabetes (Dunn et al 1943) opened up a new field for investigation and acted as a stimulus to research workers in their attempt to discover some naturally occurring diabetogenic agent either in the diet or as a result of a disturbance of internal metabolism.

The formula of alloxan resembles the pyrimidine part of the uric acid molecule and it is possible that a substance such as alloxan or one closely related to it occurs in man as a result of nucleo-protein breakdown (Loubatieres 1954).

It seems reasonable to expect that such a product may occur to excess in a derangement of nucleo-protein metabolism, e.g. as in gout.

Accordingly the following investigation is concerned with the study of carbohydrate tolerance in gout.

MATERIALS AND METHODS:

Patients who were known to have gout were asked to report for a blood sugar test after a 12 hour fast. At first a modified glucose tolerance test, (i.e. fasting, 1 and 2 hour levels) was also done on all the patients. Subsequently only those with a suspiciously high fasting blood sugar level were asked to report back for a modified glucose tolerance test.

82 patients who were ambulant reported for a fasting blood sugar test, and 46 of these had a modified glucose tolerance test done as well.

The control group was made up of 27 ambulant non-gouty arthritic patients attending the

Groote Schuur Hospital Out-patients' Department. These patients were similarly asked to report for fasting blood glucose estimations.

The same technician did the tests on the gouty and control groups.

The method used throughout was the Hagedorn-Jensen method using blood obtained from the fingertip.

(This investigation of carbohydrate tolerance in gout was conducted during the period October 1955 to June 1956.

Patients who were found to have diabetes were referred to the diabetic clinic where they were studied further and were still the subjects of further observations which have continued to the time of writing).

<u>The Criteria For Abnormality Of The Glucose Tolerance Test:</u>

The generally accepted figures for the upper limit of normality in the glucose tolerance test by the Hagedorn-Jensen method (using capillary blood) are (Rosenthal et al 1950, Lawrence 1947) :-

Fasting blood glucose	120 mg.
1 hour level	200 mg.
2 hour level	120 mg.

To allow for the possible presence of reducing substances other than glucose in gouty patients (vide DISCUSSION page 170), I have used even more rigid criteria of abnormality than indicated above, viz.:

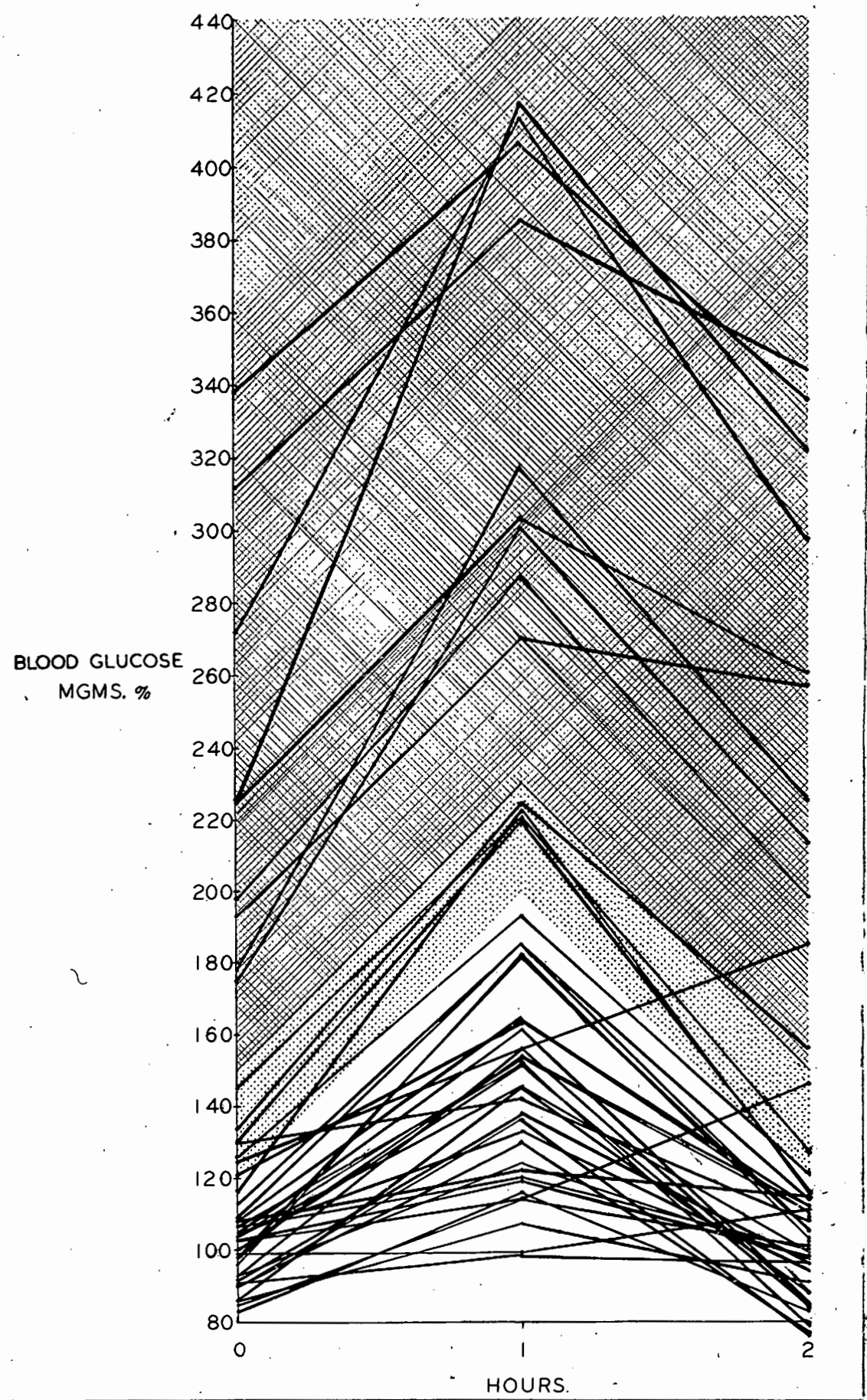
Fasting blood glucose:	greater than 150 mg.
1 hour level:	greater than 230 mg.
2 hour level:	greater than 150 mg.

I RESULTS IN THE GOUTY PATIENTS:

There were 10 definite diabetics (i.e. 12%) in the group of 82 gouty patients (by all the stringent criteria).

An elevated fasting blood glucose level is probably the most conclusive test for diabetes mellitus (Rosenthal et al 1950).

Fasting blood glucose levels of 120 - 150 mg. have to be considered presumptively abnormal and it is interesting to record that the fasting blood sugar was over 120 mg. in 32 patients (39 %) of the gouty group.


GLUCOSE TOLERANCE CURVES IN GOUTY PATIENTS
BLOOD GLUCOSE
MGMS. %
440
420
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
0
1
2
HOURS.

The following is an analysis of the results of the tests in these 32 patients who, according to our usually accepted criteria, have to be considered diabetic or pre-diabetic:

10 (as stated above) were definite diabetics.

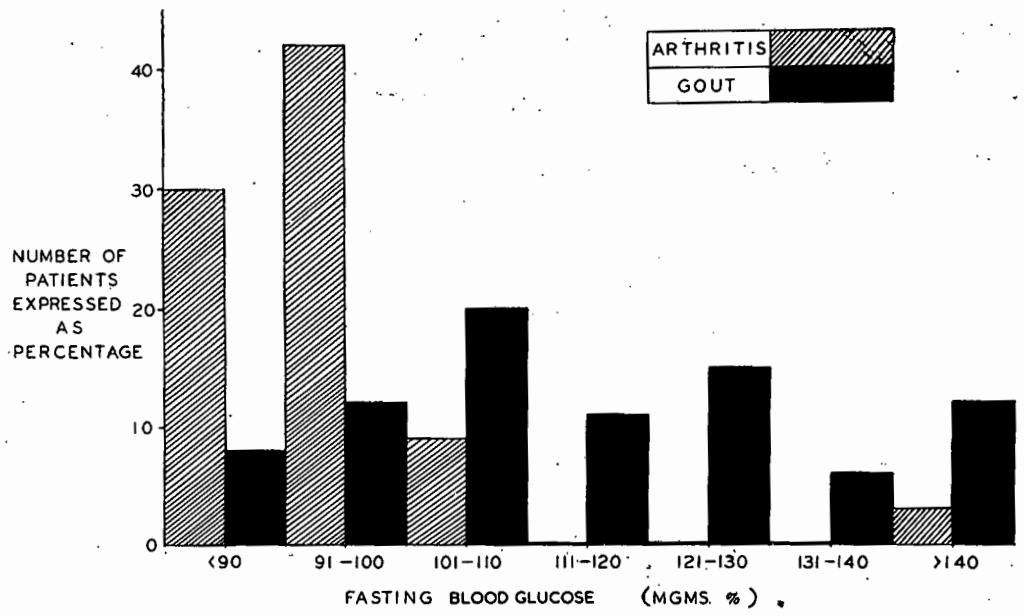
Of the remaining 22 patients with fasting blood glucose values over 120 mg., 3 patients had a high one hour level (approximately 220 mg.) and a further 2 had a high 2 hour level (185 mg. and 146 mg.).

Two more patients with fasting blood glucose suspiciously high (168 mg. and 138 mg.) failed to report back for a glucose tolerance test.

Thus by less rigid criteria, there may be an additional 7 diabetics, making a total of 17 diabetics (21 %) out of 82 gouty patients; the remaining 15 gouty patients may be in a pre-diabetic phase.

See facing page for glucose tolerance tests obtained in 46 of these gouty patients.

A COMPARISON BETWEEN FASTING BLOOD GLUCOSE LEVELS OF AUTHOR'S GOUTY AND CONTROL ARTHRITIC GROUP OF PATIENTS.



II RESULTS IN THE CONTROL GROUP OF ARTHRITIC PATIENTS:

In the control group of arthritic patients (excluding gouty patients), only one patient out of 27 had a fasting blood sugar value over 110 mg. This patient was found to be diabetic.

A comparison between the fasting blood sugar values of both groups shows clearly that the gouty group has higher fasting blood sugar values than the arthritic group (See Fig. facing page).

DISCUSSION OF THE RESULTS:

There are 3 possible explanations for this high incidence of abnormal carbohydrate tolerance in gout:-

1. that it is purely coincidental and not related to gout per se.

2. that an intermediary product of nucleo-protein breakdown resulting from the disturbance of metabolism in gout acts as a diabetogenic agent or that the

metabolic aberration responsible for gout is also responsible for a subsidiary abnormality in carbohydrate metabolism.

3. that gout and diabetes are gene-linked.

In discussing the first of these possible explanations for the high incidence of abnormal carbohydrate tolerance in gout, viz. that it is purely coincidental, the effect of various factors influencing glucose tolerance must be investigated.

These factors will be considered under the following headings:-

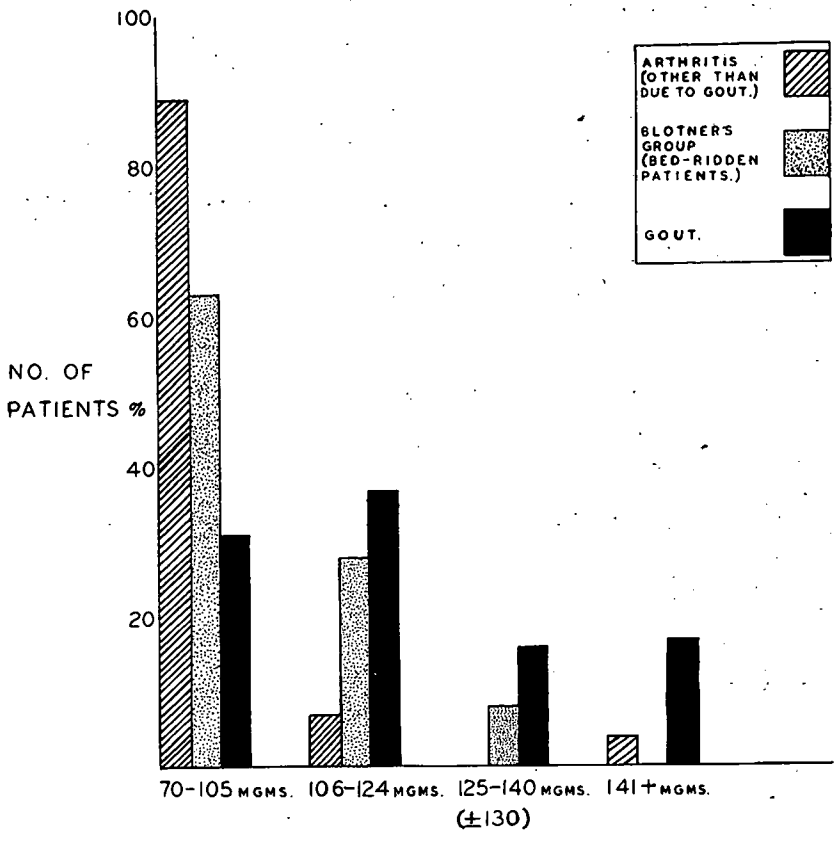
(i) Activity.
(ii) Diet.
(iii) Obesity.
(iv) Sex.
(v) Age.
(vi) Inclusion of non-glucose reducing substances.
(vii) Treatment with cortisone.

(i) <u>Activity:</u>

It has been shown by Blotner (1945) that prolonged confinement to bed is responsible for an abnormal carbohydrate tolerance and that resumption

FIG. 3.

A COMPARISON OF F.B.S. LEVELS OF
A GROUP OF AMBULANT GOUTY PATIENTS AND
A GROUP OF AMBULANT ARTHRITIS PATIENTS AND
A GROUP OF BED-RIDDEN PATIENTS.



FASTING BLOOD SUGAR LEVELS.

of activity causes a reversion to normal.

In my study, the blood sugar tests were made on ambulent out-patients.

It is interesting to compare the fasting blood sugar values in Blotner's bed-ridden patients with those of my 2 groups of patients (See Fig. facing page). Although the majority of Blotner's patients had an abnormal carbohydrate tolerance, the fasting blood sugar tests were normal.

(ii) Diet:

It is generally accepted that a severely restricted diet can impair glucose tolerance (Conn 1940, Himsworth 1935).

The daily carbohydrate intake need not be as high as suggested by Conn, i.e. 300 G. Crucial figures for daily carbohydrate intake are probably between 50 G. - 125 G. (Mosenthal et al 1950, Irving et al 1954).

It seems likely that the normal diet of an adequately nourished patient (such as those in this study), need not be augmented before doing a glucose

tolerance test. However, where an abnormal glucose tolerance test was obtained, the patient was asked about his diet. The carbohydrate intake was found to be well above 125 G. and usually in the region of 300 G.

(Gouty patients who were found to have a diabetic glucose tolerance test were referred to the diabetic clinic for follow-up. Diabetes was confirmed and several of these patients had glucose tolerance tests repeated (one or more), one week after being on a diet containing 300 G. carbohydrate daily).

(iii) Obesity:

Gouty patients on the whole belong to the obese group.

The majority of arthritics in the control group were of the obese type also.

It is a well known fact that the majority of diabetic patients of the maturity-onset type are (or have been) obese (Joslin 1952).

Hospital reports on the incidence of diabetes in obesity are conflicting and very often misleading

because some patients included in the obese group may come to hospital only because sugar is found in their urine (Embleton 1938).

(iv) Sex:

After the age of 45 years, the incidence of diabetes mellitus in females is about twice that in males (National Health Survey U.S.A. 1935 - 36). Before that age, sex is not an important factor.

Gout affects males mainly, and thus the finding of an increased incidence of abnormal carbohydrate tolerance in a predominantly male group enhances the significance of this finding.

The gouty group consisted of 74 males and 8 females. The number of definite diabetics in this group was made up of 9 males and 1 female, i.e. sex did not really have any siginificant influence.

In the arthritic group, there were 4 males and 23 females. The sex bias, such as it is, was therefore in favour of more diabetics in the control group.

(v) Age:

The following table shows the age composition of the gouty and the arthritic groups.

AGE	GOUTY GROUP			ARTHRITIC GROUP		
	No.	%	Diabetic	No.	%	Diabetic
Under 30	2	2.4%	-	2	7.4%	-
31 - 40	13	16 %	-	4	14.8%	1
41 - 50	23	28 %	4	7	25.9%	-
51 - 60	23	28 %	4	9	33.3%	-
61 - 70	14	17 %	2	4	14.8%	-
71 & over	7	8.5%	1	1	3.7%	-

A comparison of the ages of the 2 groups shows a fairly similar age distribution pattern.

Rosenthal et al (1950) found that sugar tolerance in old age did not differ from that in younger persons: "In the aged there was no impairment of glucose tolerance. This is contrary to accepted beliefs, which have been largely based on hospitalised individuals." (Compare Blotner 1945).

(vi) Inclusion of non-glucose reducing substances.

Uric acid and creatinine levels which may be raised in gout would produce an insignificant effect on the determined blood sugar levels.

Thus it was found that 9.4 mg. of uric acid produced a reducing value which was negligible, viz. 1 mg.% by the Hagedorn-Jensen method. 15.6 mg. creatinine produced a reducing value of only 9 mg.% (Hiller, Linder and van Slyke 1925).

This has again been confirmed recently: "The reducing value of uric acid and creatinine in the ambulant gouty patient would thus not be more than 5 mgms. as a liberal estimate (G.C. Linder - Personal communication, 1956)."

(vii) The Effect of Cortisone:

Patients with arthritis and gout are often treated with cortisone.

Some of the arthritic patients in the control group had cortisone without any obvious impairment.

of carbohydrate tolerance as gauged by fasting blood sugar levels.

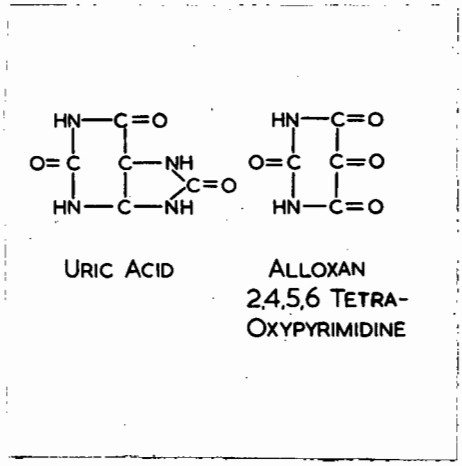
It seems possible that gouty patients are unduly susceptible to the diabetogenic effect of cortisone, i.e. that the gouty group may be pre-diabetic. This is discussed further in the Pathogenesis of Diabetes-in-Gout.

Even when all these modifying factors are taken into account, they still do not explain this increased incidence of abnormal carbohydrate tolerance and high fasting blood sugar values in gout. Thus, some factor, specifically related to gout, may be responsible for this abnormality in carbohydrate metabolism.

It is to be noted that the report by Weiss et al (1957) that a high percentage of gouty patients have elevated blood sugar levels, adds support to the findings of my investigation.

A DISCUSSION OF THE PATHOGENESIS OF DIABETES IN GOUT:

The structural formulae of uric acid and alloxan are shown:



URIC ACID

ALLOXAN
2,4,5,6 TETRA-
OXYPYRIMIDINE

Alloxan is one of the best known and most studied of diabetogonic agents in animals (Dunn et al 1943), and it has been clearly shown that man is as susceptible as other species (Conn et al 1948).

The difficulty in detecting alloxan in human plasma may be due to its extreme reactivity (Loubatieres 1954).

It has been suggested that alloxan or a related substance may occur as an intermediary product

in metabolism (Lazarow 1949).

The pyrimidine ring of uric acid resembles alloxan structurally and may be diabetogenic by virtue of its configuration at positions 1, 2 and 3.

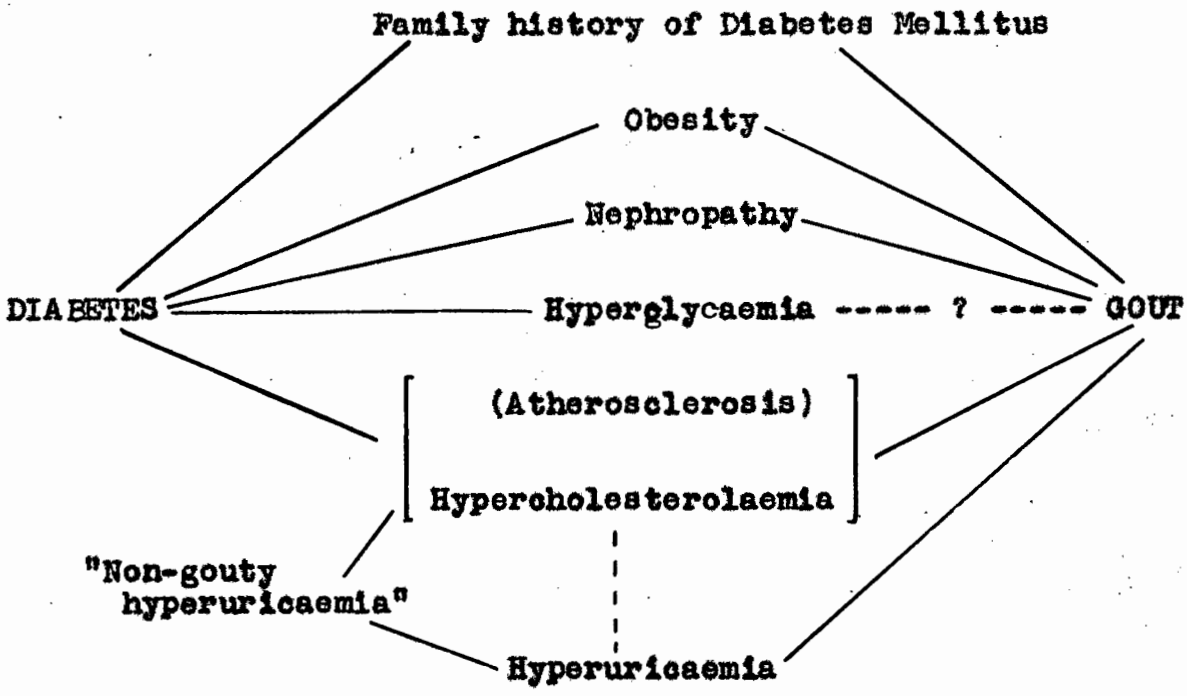
Diabetes mellitus has been induced in glutathione deficient rabbits by injecting them with uric acid (Griffiths 1948 and 1950).

A remarkable correlation between gout and diabetes exists in the pigeon where the injection of alloxan was shown to cause the development of diabetes mellitus and an intense form of visceral gout (Goldner et al 1945, Goldner 1945).

In man, the number of patients with gout occurring in association with diabetes mellitus was found by Joslin (1952) to be small, viz. less than 1 in 1500. (See Addendum at end of this Section for further experience at our diabetic clinic). However, a high incidence of diabetes mellitus has been reported in the families of patients with gouty arthritis (Ishmael 1945).

Apart from the fact that gout and diabetes mellitus are both disturbances of metabolism, they share certain other features, viz: Both conditions occur more commonly in association with obesity; their late complications too are similar, e.g. kidney-disease with the emphasis on vascular sclerosis; there is an increased incidence of hypertension; and there is a high incidence of hypercholesterolaemia with accompanying coronary atherosclerosis in both conditions.

The features that are common to both gout and diabetes can be shown diagrammatically as follows:



A follow-up of those patients in the gouty group who were found to be diabetic, showed that they belonged to the maturity-onset-type of diabetes. All but one responded to the usual forms of treatment, viz. diet or oral hypoglycaemic agents. The one exception who required insulin was a Bantu. The occurrence of either gout or diabetes in the Bantu race is said to be rare; the finding of the two together is therefore surprising and perhaps significant.

Preliminary observations (See SECTION VII) by the author seem to suggest that gouty patients may be unduly prone to the diabetogenic effect of cortisone. This does not appear to be so in the arthritic group, some of whom had cortisone.

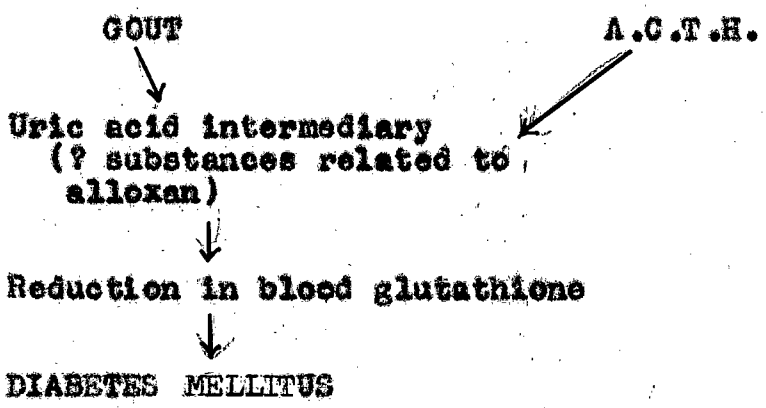
Conn et al (1948 (a) and (b)) have suggested that the abnormality of carbohydrate metabolism following cortisone administration parallels the increased production of uric acid (Forsham et al 1948), and presumably, also an increased production of intermediaries in uric acid metabolism.

This would add support to the hypothesis that some intermediary product of purine metabolism in gout is responsible for the development of the abnormality in carbohydrate metabolism. Cortisone may accentuate this abnormality.

Conn et al (1948 (a) and (b), 1949) have shown a reduction in blood glutathione during A.C.T.H. administration. Alloxan also produces a prompt and severe reduction in glutathione (Leech et al 1945).

Diabetes has been induced with uric acid in glutathione deficient rabbits (Griffiths 1948).

A possible mechanism of production of diabetes in gout could be diagrammatically shown thus:



SUMMARY:

A high incidence of abnormal carbohydrate tolerance was found in a group of 82 ambulant gouty patients. The fasting blood sugar levels were significantly higher in the gouty patients as compared with the control group of arthritics.

The significance of this and the pathogenesis of diabetes in gout are discussed in this article.

(See Addendum on next page).

ADDENDUM:

In our diabetic clinic there were a further 4 cases of diabetes in association with gout. (These were noted after the completion of my study of carbohydrate tolerance in gout, and are not included in the figures in this study).

(i) S.A. (Case 1), a Coloured man aged 51 years.

Glucose tolerance test: 280, 353, 420, 409, 361.

(ii) H.W. (Case 164), a European man aged 69 years.

(Discussed in Section VII).
Treated with large dose of insulin.

(iii) A.M. (Case 99), a European man aged 47 years.

Glucose tolerance test:
F 130 mg., 1 hour 226 mg., 2 hour 170 mg.
(This patient had previously had diabetic fasting levels and had been treated as a diabetic).

(iv) M.G. (Case 139), a European woman.

(Diabetes established for 2 years. First attack of typical acute gouty arthritis in metatarso-phalangeal joint at age of 72 years occurred while receiving the sulphonylurea drugs).

VII.

STUDIES ON THE EFFECTS OF THE ADRENAL CORTICAL STEROIDS ON CARBOHYDRATE METABOLISM IN MAN

STUDIES ON THE EFFECTS OF THE ADRENAL CORTICAL STEROIDS ON CARBOHYDRATE METABOLISM IN MAN:

Hitherto we have been dealing with the effects in man of physiological or pharmacological agents which are believed to improve carbohydrate tolerance by virtue of their hypoglycaemic action.

We now come to the adrenal cortical steroids. Their effect on carbohydrate metabolism has been extensively studied in vitro, in intact experimental animals and in man. The corticosteroids have been shown to be diabetogenic largely by virtue of their ability to stimulate increased hepatic gluconeogenesis (Thorn et al 1957).

The time lapse between the administration of the hormones and the first appearance of evidence suggesting increased gluconeogenesis is approximately one to three hours and is the same in the intact human organism and in tissues isolated from treated animals.

Thorn et al (1957) have listed some effects of glucocorticoids on tissues:

(i) Increased glycogen deposition (liver),

(ii) Increased glucose output (liver),

(iii) Increased glucose synthesis from pyruvate (liver),

(iv) Increased release of amino-acids (muscle, liver),

(v) Decreased lipogenesis (liver, mammary gland, carcass).

These authors point out that they are as yet unable to assign discrete metabolic sites to any of these effects, let alone suggest a primary site of corticosteroid action which could account for all their known metabolic effects.

CORTICOSTEROIDS AND DIABETES IN MAN:

The high incidence of abnormal glucose tolerance in patients with Cushing's syndrome (which is associated with gluco-corticoid excess) is well known.

Fajans and Conn (1954) have reported that glucose tolerance tests carried out shortly

after the administration of gluco-corticoids may unmask a group of potential diabetic patients, as yet compensated but approaching decompensation, i.e. they have used the diabetogenic effect of cortisone as a means of testing whether diabetes would develop in the future. This method of establishing whether a subject is 'pre-diabetic' has stimulated great interest and extensive studies on these lines have been undertaken in various centres. Conn himself has stated that it would take many years to establish whether subjects diagnosed as being pre-diabetic by this test would in fact develop diabetes later.

In this thesis, the object was not to repeat the work that has been done by Conn on the enhancement of the glucose tolerance test in normal subjects, but rather to use cortisone as a means of further elucidating certain problems which occurred in the course of this study :

Thus, in the investigations carried out in the present study, the cortisone/glucose tolerance

test was used as a means of further investigating carbohydrate tolerance in the following types of patients.

A group of gouty patients were tested in this way.

Some of the proven diabetics showed a remission in diabetes which persisted in spite of withholding treatment for diabetes, i.e. a spontaneous remission; in others, a remission was induced and maintained by using hypoglycaemic agents. What would be the influence of cortisone on the glucose tolerance test in these cases ?

Still others were referred to the diabetic clinic who had been previously considered diabetics (and treated as such, e.g. with insulin). However, in the course of the investigations a normal glucose tolerance test was recorded. In the follow-up studies, cortisone was used to test whether they were merely in a latent phase of the disease.

MATERIALS AND METHODS:

The Patients in this Study:

Observations on the action of cortico-steroids on carbohydrate tolerance were made in the following groups of patients :-

I. A group of gouty patients (11 patients).

II. Patients who were found to show remission in diabetes, either induced by hypoglycaemic agents or spontaneously.
(Included in this group were a few patients who might be considered to be latent or potential diabetics, for reasons stated in the text).

METHODS OF STUDY:

Cortisone/glucose tolerance tests were performed on all patients in Group I and Group II (except one gouty patient (H.W. Case 164) who had received cortisone as a therapeutic measure only.

THE CORTISONE/GLUCOSE TOLERANCE TEST:

Preparation for Cortisone/glucose tolerance test:

Patients were prepared for the standard glucose tolerance tests as described in SECTION II of the thesis. After the preliminary glucose tolerance test, an augmented test was performed the next day, as a general rule. Cortisone acetate was given orally in doses of 50 mg. or 2.5 mg. (if the patient weighed more than 1 0 lbs.) 8 and a half hours and again 2 hours before the second standard glucose tolerance test.

Where the patients were being treated with hypoglycaemic agents, these were omitted on the morning of the test only.

The dates of the glucose tolerance tests are recorded in the illustrations (pages 193-222) so that the few departures from the pattern of glucose tolerance tests on consecutive days is clarified.

In a few of the patients with gout and a few patients with a previously suspicious glucose tolerance curve cortisone was used to test whether a frankly abnormal or diabetic glucose tolerance test would be provoked, without the prior repetition of the standard glucose tolerance test.

INTERPRETATION AND PURPOSE OF THE CORTISONE/GLUCOSE TOLERANCE TEST IN THIS STUDY:

Interpretation:

The stringent criteria used for the diagnosis of diabetes by the standard glucose tolerance test have been discussed in SECTION II of the thesis. Emphasis was laid on the fasting and 2 hour figures which had to be over 150 mg. (in the standard glucose tolerance test) for the diagnosis of a diabetic curve.

As several of the patients in this study were known to have had a diabetic curve on a previous occasion or occasions, the cortisone/glucose

tolerance test was not used as a method of diagnosing diabetes, but rather to study the influence of its diabetogenic action on the form of the glucose tolerance test.

Conn (1958) has stated that his criteria (in the enhanced glucose tolerance test) for the diagnosis of 'pre-diabetes' cannot be regarded as a definite method of early diagnosis of diabetes: only time would tell whether diabetes would evolve. In this study, no definite classification for the abnormal levels of the cortisone enhanced glucose tolerance test are given. I have paid attention to alterations produced in each individual curve by cortisone and have evaluated them separately.

The Object of these Tests:

(a) In the gouty group the object was to see whether cortisone would produce considerable enhancement or whether a frankly diabetic curve could be produced in those in whom a previously abnormal glucose tolerance test had not been demonstrated.

(b) In the patients in remission the object was to see whether a definitely diabetic curve could be induced with cortisone.

(c) In the patients treated with hypoglycaemic agents, the object was to see how the hypoglycaemic agents influenced the form of the cortisone/glucose tolerance test. Some of the same patients also had cortisone/glucose tolerance tests done when not receiving the hypoglycaemic agent.

CORTICO-STEROIDS IN GOUT:

Introduction:

In the preceding section, a study of carbohydrate tolerance in gout showed a high incidence of diabetic glucose tolerance tests (12%) by the rigid criteria used in the study.

21% of the gouty patients studied would have been considered diabetic by generally accepted criteria for the diagnosis of diabetes.

It is noteworthy that 39% of the patients had a fasting glucose level above 120 mg. (the generally accepted figure for the upper limit of normal) as compared with 4% in a control group of arthritic patients.

Would the use of cortisone in gouty patients reveal that an abnormality in carbohydrate tolerance could be easily provoked in this group ? Was there merely a narrow dividing line between normal and abnormal carbohydrate metabolism in patients who show the existence of the error of metabolism of gout ?

Cortisone in the Gouty Patients of this Study:

Adrenal cortical steroids could be expected to potentiate the abnormalities of the glucose tolerance curves of mild and latent diabetes in gout and so possibly help to confirm a borderline case, or to predict the later development of overt diabetes. The object was to see whether gouty patients were particularly susceptible to the diabetogenic effect of cortisone.

RESULTS:

11 gouty patients were studied. The following is a summary of the results found in these patients and is followed by illustrations of the glucose tolerance tests and cortisone/glucose tolerance tests.

SUMMARY OF RESULTS: GROUP I. GOUTY PATIENTS:

J.E. (42): Cortisone had induced diabetes. (See illustration and case report page 193 showing G.T.T's during and following Cortisone Therapy).

H.W. (164): Diabetes was cortisone-induced or enhanced.

W.M. (96): Moderate aggravation of diabetic curve.

M.I. (66): (a) Moderate enhancement when in a state of remission: Diabetic curve.
(b) A paradoxical curve when further weight is lost.

G.J.W.(166): Diabetic type of curve in a patient who had previously been found to have a fasting glucose level 121 mg.

A.S. (145): Moderate enhancement to a diabetic type of curve.

V.B. (22): Moderate enhancement with cortisone but curve is not diabetic.

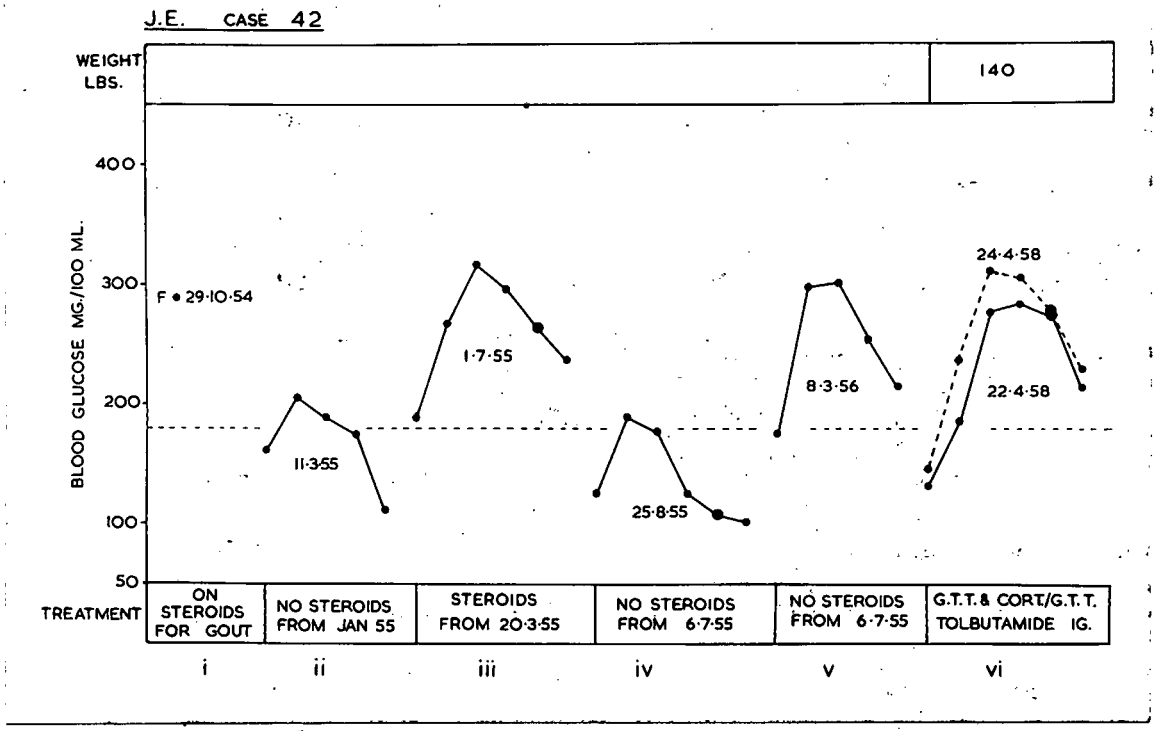
J.Ad. (7): Mild enhancement.

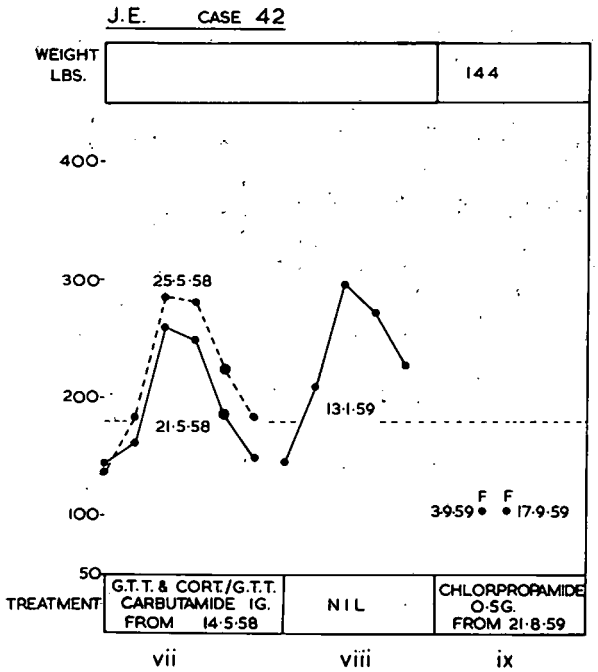
J.L. (91): Mild enhancement.

G.W. (161): Mild enhancement in a patient who previously had an abnormal glucose tolerance test.

H.N. (111): Mild enhancement in a case of hyperuricaemia.

ILLUSTRATIONS AND CASE REPORTS FOLLOW:


J.E. CASE 42
WEIGHT LBS.
140
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
F • 29·10·54
11·3·55
1·7·55
25·8·55
8·3·56
24·4·58
22·4·58
TREATMENT
ON STEROIDS FOR GOUT
NO STEROIDS FROM JAN 55
STEROIDS FROM 20·3·55
NO STEROIDS FROM 6·7·55
NO STEROIDS FROM 6·7·55
G.T.T. & CORT/G.T.T. TOLBUTAMIDE IG.
i
ii
iii
iv
v
vi


J.E. CASE 42
WEIGHT LBS.
144
400
300
200
100
50
25·5·58
21·5·58
13·1·59
F 3·9·59 •
F • 17·9·59
TREATMENT
G.T.T. & CORT./G.T.T. CARBUTAMIDE IG. FROM 14·5·58
NIL
CHLORPROPAMIDE 0·5G. FROM 21·8·59
vii
viii
ix

J.E. Case 42. Coloured man aged 42 years.

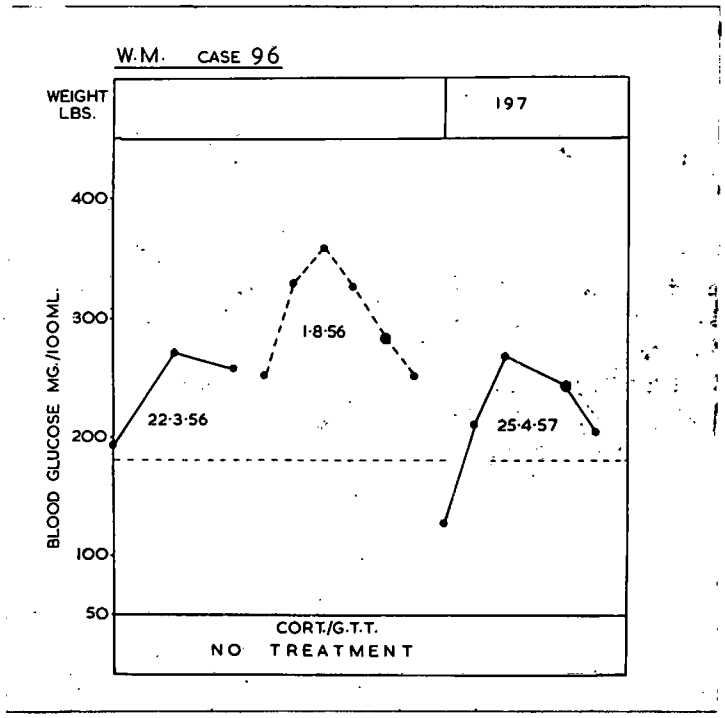
(This case illustrates the evolution of diabetes during cortico-steroid therapy).

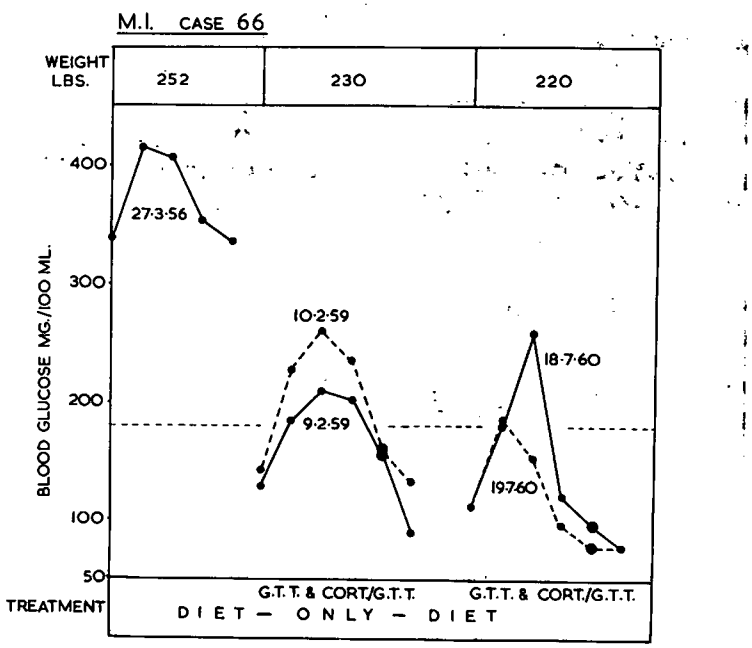
This young, healthy looking carpenter had severe gout for which he received meticorten. He developed symptoms of diabetes and a high fasting glucose level (29.10.54) while taking meticorten. A glucose tolerance test in March 1955 (ii) after meticorten had been discontinued showed a mild abnormality only of glucose tolerance test, but following steroids for 3 months a markedly abnormal glucose tolerance test again developed (iii) (1.7.55).

When steroids were stopped, a remarkable remission to a normal glucose tolerance test (iv) on 25.8.55 is noted.

On 8.3.56, in spite of the fact that steroids are withheld a grossly abnormal glucose tolerance test (v) has spontaneously evolved. (The abnormality of the glucose tolerance test is not much influenced by the administration of tolbutamide or carbutamide (Compare vi, vii, viii). Cortisone has produced only a moderate enhancement of the glucose tolerance test in (vi) and (vii), when the patient was being treated with hypoglycaemic agents).

H.W. Case 164. This elderly European man aged 69 years was first seen in April 1957 with a history of diabetes of 9 months' duration. He had been receiving treatment with meticorten for gout which had become manifest one month prior to the onset of diabetes. The diabetes was relatively resistant to insulin and control on 80 units insulin was poor (Blood glucose estimations: 315 mg., 184 mg., 186 mg.); while he was taking 3 tablets meticorten daily. On discontinuing steroids his diabetes rapidly improved and insulin could be stopped. Steroid therapy, in this gouty patient, had brought on diabetes or caused an exacerbation of a previously subclinical diabetes. When last seen he was being satisfactorily controlled with one of the sulphonylurea drugs.
(Patient H.W. was not included in the figures of the study on carbohydrate tolerance in gout - see Addendum to that Section).


W.M. CASE 96
WEIGHT LBS.
197
400
300
200
100
50
BLOOD GLUCOSE MG./100ML.
22·3·56
1·8·56
25·4·57
CORT./G.T.T.
NO TREATMENT


M.I. CASE 66
WEIGHT LBS.
252
230
220
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
27·3·56
10·2·59
9·2·59
18·7·60
19·7·60
TREATMENT
G.T.T. & CORT/G.T.T.
G.T.T. & CORT./G.T.T.
DIET — ONLY — DIET

W.M. Case 96, a Coloured man aged 45 years.

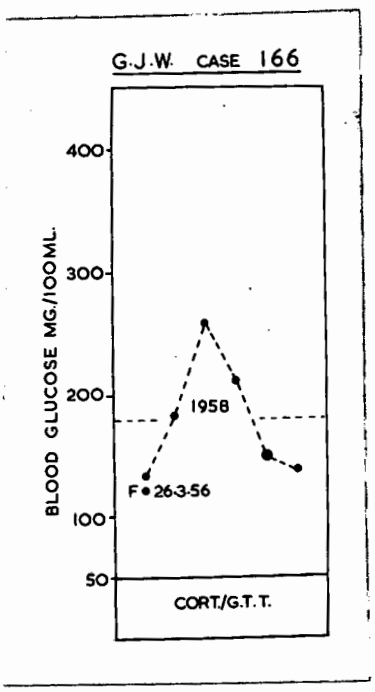
This patient has GOUT. On 22.3.56 there was a diabetic curve and following cortisone there was marked enhancement of the glucose tolerance test. A glucose tolerance test in 1957 still showed a considerably elevated 2 hour figure, in addition to a high one hour level, although the fasting level was normal.

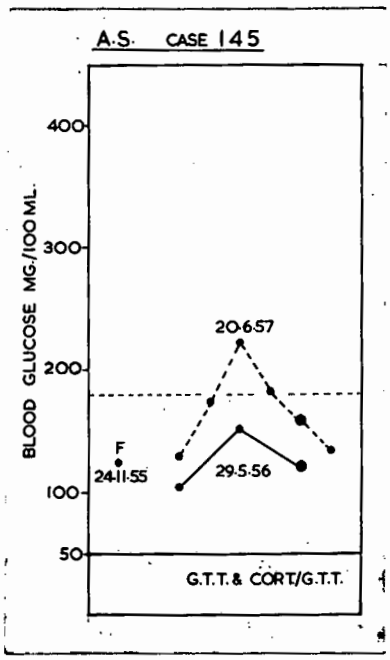
M.I. Case 66, A European man aged 51 years.

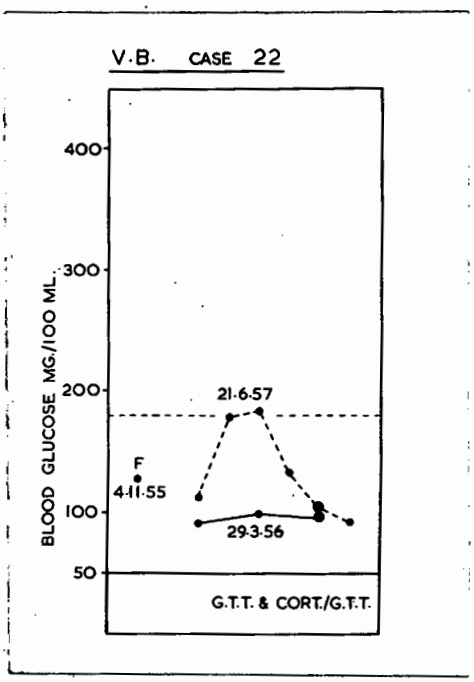
This patient was a very obese man and an excessive eater who had GOUT.

A glucose tolerance test showed severely hyperglycaemic levels (27.3.56). With diet and weight loss, a glucose tolerance test on 9.2.59 was within near normal limits. A cortisone/glucose tolerance test showed moderate enhancement at this stage (a peak value of 260 mg. at one hour).

With further loss of weight the glucose tolerance test on 18.7.60 showed completely normal fasting and low normal 2 hour level but a high one hour level. His cortisone/glucose tolerance test now paradoxically showed a lower curve.


G.J.W. CASE 166
BLOOD GLUCOSE MG./100 ML.
400
300
200
100
50
1958
F • 26-3-56
CORT./G.T.T.

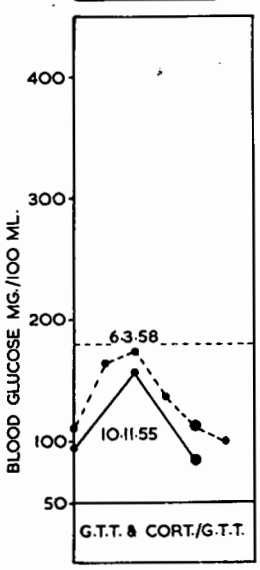

A.S. CASE 145
BLOOD GLUCOSE MG./100 ML.
400
300
200
100
50
20-6-57
F
24-11-55
29-5-56
G.T.T. & CORT/G.T.T.


V.B. CASE 22
BLOOD GLUCOSE MG./100 ML.
400
300
200
100
50
21-6-57
F
4-11-55
29-3-56
G.T.T. & CORT/G.T.T.

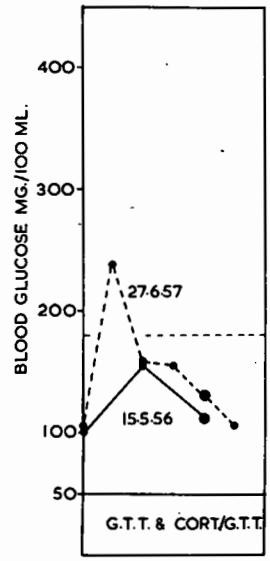
Cortisone has produced moderate enhancement in 3 patients: A.S. (Case 145), G.J.W. (Case 166) and V.B. (Case 22).

In A.S. and G.J.W. a diabetic type of curve is evolving.

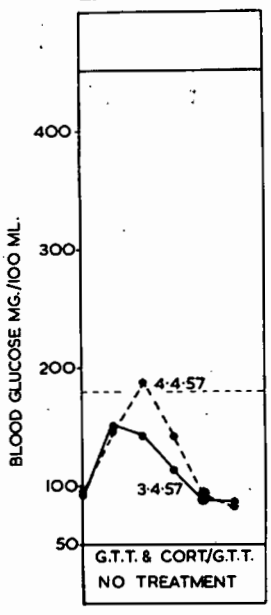
J.L. CASE 91



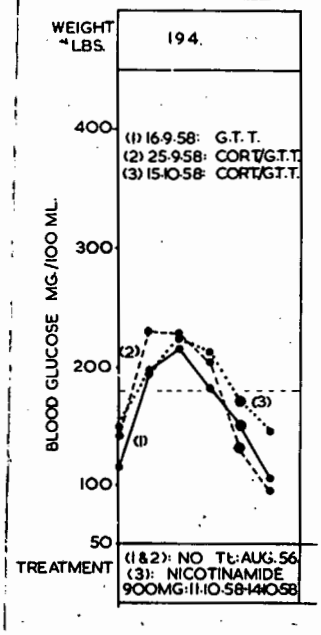
J. AD. CASE 7



H.N. CASE 111



G.W. CASE 161



Cortisone has produced only mild enhancement in the 2 patients J.L. (Case 91), and J.Ad. (Case 7).

H.N. (Case 111):

This patient was a young European man, aged 33 years, with uric acid calculi and hyperuricaemia but no symptoms of gout.

A cortisone/glucose tolerance test showed only mild enhancement over the standard glucose tolerance test.

Neither of the glucose tolerance tests was abnormal.

G.W. (Case 161):

This patient, a European man aged 50 years, had GOUT and was also a mild diabetic.

A cortisone/Glucose tolerance test (2) produced practically no enhancement over the normal glucose tolerance test.

Pre-treatment with nicotinamide for 4 days before the next cortisone enhanced test seemed to be responsible for slight enhancement in the glucose tolerance test. (3).

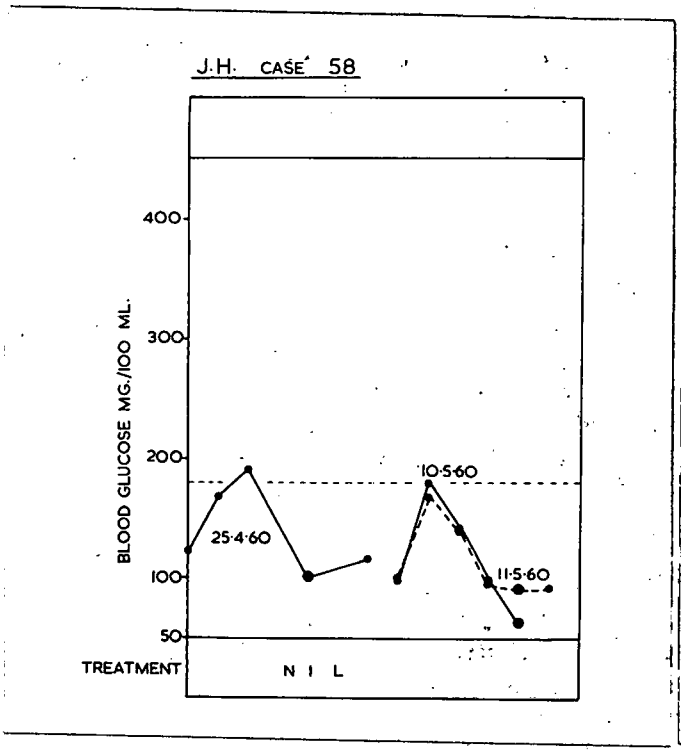
GROUP III.

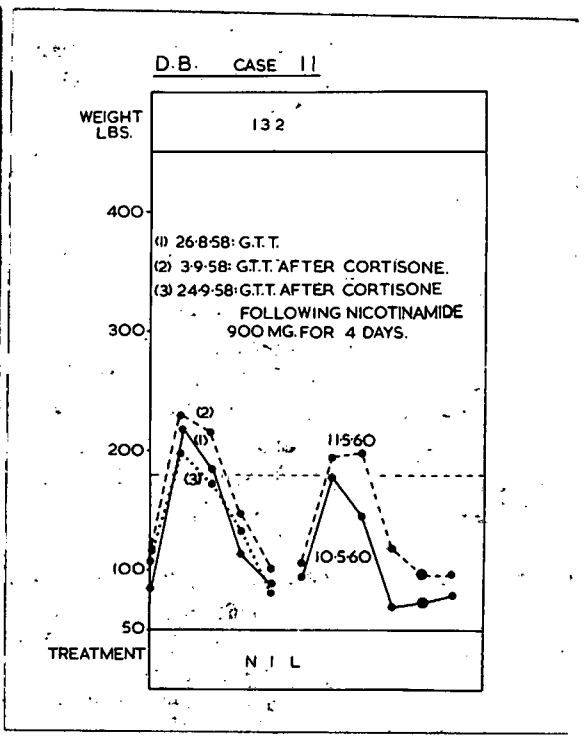
CORTISONE/GLUCOSE TOLERANCE TESTS IN PATIENTS NOT ON HYPOGLYCAEMIC AGENTS:

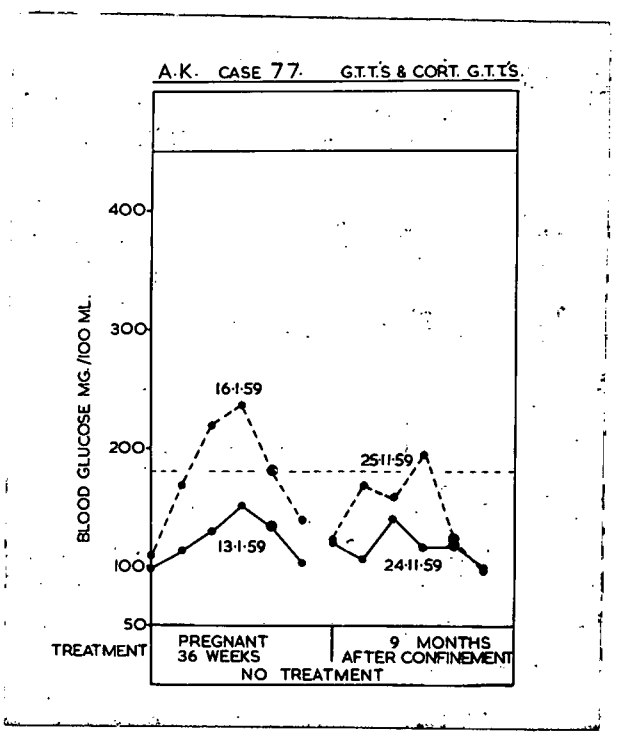
A: Patients with a NORMAL glucose tolerance test.

(before Cortisone/glucose tolerance test).

J.H.	Case 58
D.B.	Case 11
A.K.	Case 77
L.K.	Case 198


J.H. CASE 58
BLOOD GLUCOSE MG./100 ML.
400
300
200
100
50
25·4·60
10·5·60
11·5·60
TREATMENT
N I L


D.B. CASE 11
WEIGHT LBS.
132
400
300
200
100
50
(1) 26·8·58: G.T.T.
(2) 3·9·58: G.T.T. AFTER CORTISONE.
(3) 24·9·58: G.T.T. AFTER CORTISONE FOLLOWING NICOTINAMIDE 900 MG. FOR 4 DAYS.
(1)
(2)
(3)
11·5·60
10·5·60
TREATMENT
N I L


A.K. CASE 77. G.T.T.'S & CORT. G.T.T.'S.
BLOOD GLUCOSE MG./100 ML.
400
300
200
100
50
16·1·59
13·1·59
25·11·59
24·11·59
TREATMENT
PREGNANT 36 WEEKS
NO TREATMENT
9 MONTHS AFTER CONFINEMENT

J.H. (Case 58):

This young European man aged 18 years was referred in April 1960 because he had shown persistent glycosuria following a car accident 2 months previously.

D.B. (Case 11): a European man aged 32 years:

This man was referred to the diabetic clinic for glycosuria in 1958. The standard glucose tolerance test (1) was normal. Cortisone produced mild enhancement only (2). Pre-treatment with nicotinamide produced cortisone/glucose tolerance test (3) which was better than either of the preceding glucose tolerance tests.

The glucose tolerance test repeated 2 years later (10.5.60) was normal. The cortisone/glucose tolerance test showed a slightly enhanced but completely normal glucose tolerance test. These results were an almost exact reproduction of the findings in 1958.

In these 2 patients with renal glycosuria there was no enhancement in cortisone/glucose tolerance test.

L.K. (Case 198): Identical twin brother of P.K. (Case 74), one of the long term study cases (page 113).

	F	1 hr.		2 hr.	
G.T.T. (13.7.57):	103,	221,	157,	107,	89, 152
Cortisone/G.T.T. (27.7.57):	99,	204,	134,	84,	95, 95

No enhancement of glucose tolerance test by cortisone.

A.K. (Case 77): a young pregnant woman aged 28 years:

This patient had a strong family history of diabetes (her mother, father and brother were seen with diabetes).

(a) Considerable enhancement of cortisone/glucose tolerance test to a diabetic type of curve.

(b) Ten months later glucose tolerance test still normal. Cortisone/glucose tolerance test still shows considerable enhancement.

II

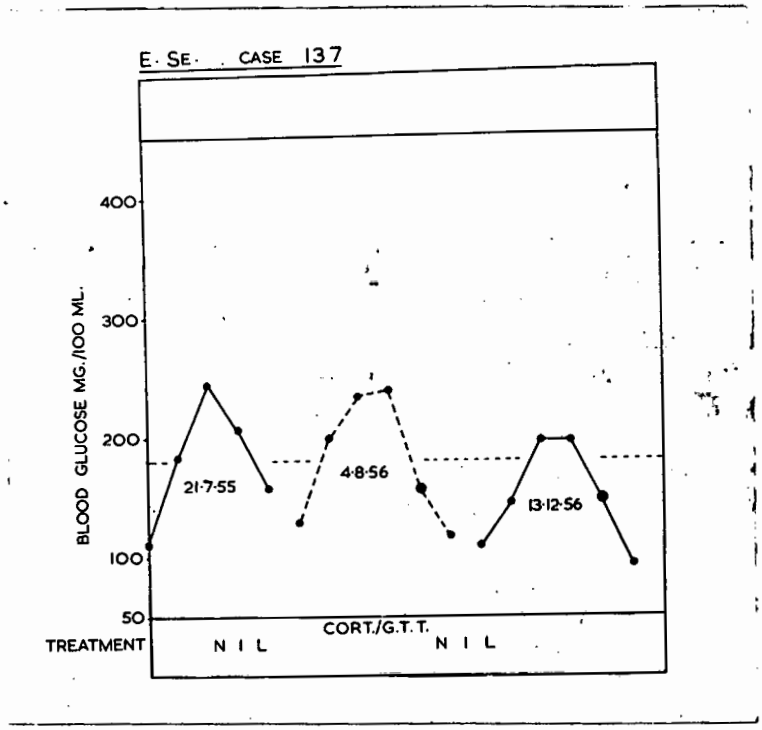
B. PATIENTS WITH DIABETES IN REMISSION (4).

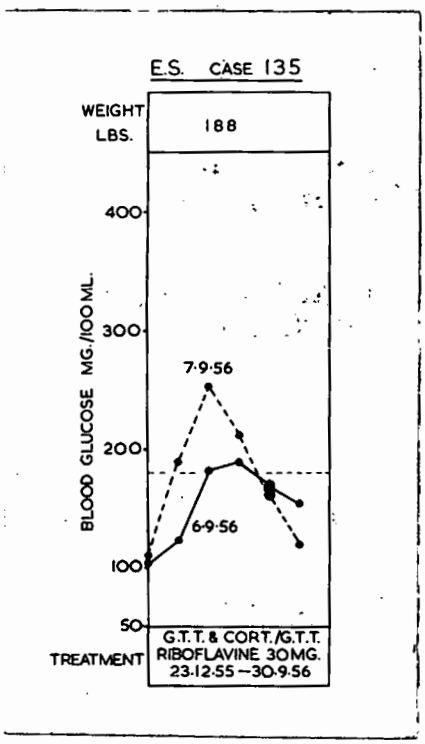
E.Se. Case 137

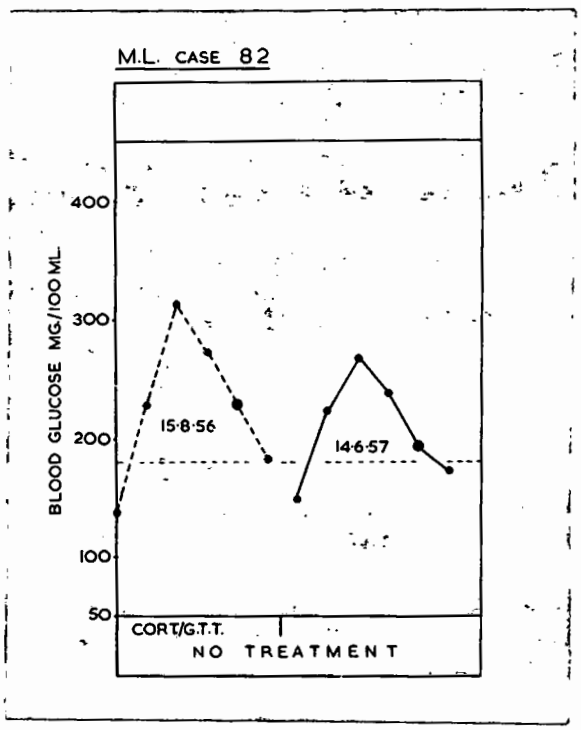
M.L. Case 82

E.S. Case 135

I.W. Case 162


E. SE. CASE 137
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
21·7·55
4·8·56
13·12·56
TREATMENT
NIL
CORT./G.T.T.
NIL


E.S. CASE 135
WEIGHT LBS.
188
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
7·9·56
6·9·56
TREATMENT
G.T.T. & CORT./G.T.T.
RIBOFLAVINE 30 MG.
23·12·55 — 30·9·56


M.L. CASE 82
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
15·8·56
14·6·57
CORT/G.T.T.
NO TREATMENT

E.Se. (Case 137):

This patient, a European man aged 55 years, was a mild diabetic in remission.

A cortisone/glucose tolerance test on 4.8.56 was practically the same as a standard glucose tolerance test done on 21.7.55.

A standard glucose tolerance test on 13.12.56 shows that the patient is in a phase of remission.

E.S. (Case 135):

This patient, an elderly European woman, had been treated with insulin prior to being seen at the diabetic clinic.

She was grossly overweight and subsequent glucose tolerance tests when off insulin were normal.

A cortisone/glucose tolerance test done at a time when the 2 hour level was elevated, showed moderate enhancement mainly of the peak one hour figure.

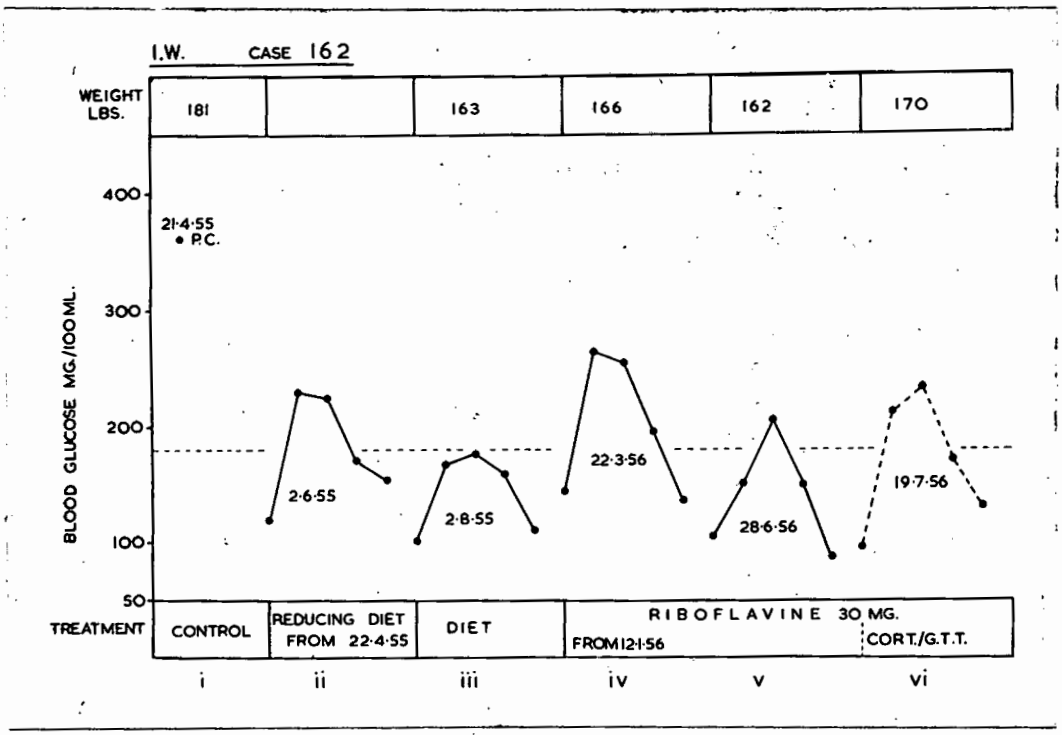
M.L. (Case 82):

This patient, a European man aged 53 years, has a brother who is diabetic.

This patient had an abnormal glucose tolerance test - an elevated 2 hour figure; his glucose tolerance test reverted to normal.

A cortisone/glucose tolerance test on 15.8.56 showed marked enhancement and an abnormal curve.

On 14.6.57 it is seen that a diabetic type of curve is developing.


I.W. CASE 162
WEIGHT LBS.
181
163
166
162
170
400
300
200
100
50
21·4·55 • P.C.
BLOOD GLUCOSE MG./100 ML.
2·6·55
2·8·55
22·3·56
28·6·56
19·7·56
TREATMENT
CONTROL
REDUCING DIET FROM 22·4·55
DIET
RIBOFLAVINE 30 MG. FROM 12·1·56
CORT./G.T.T.
i
ii
iii
iv
v
vi

I.W. (Case 162):

Mild enhancement by cortisone/glucose tolerance test while in a phase of remission (19.7.56).

II

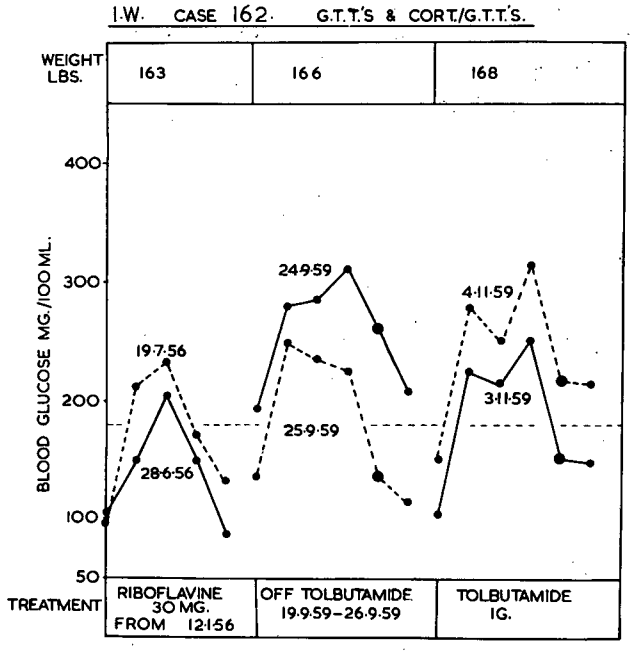
C. CORTISONE/GLUCOSE TOLERANCE TESTS IN DIABETICS NOT ON HYPOGLYCAEMIC AGENTS: (4).

I.W. (Case 162)

W.v.H. (Case 159)

W.R. (Case 126)

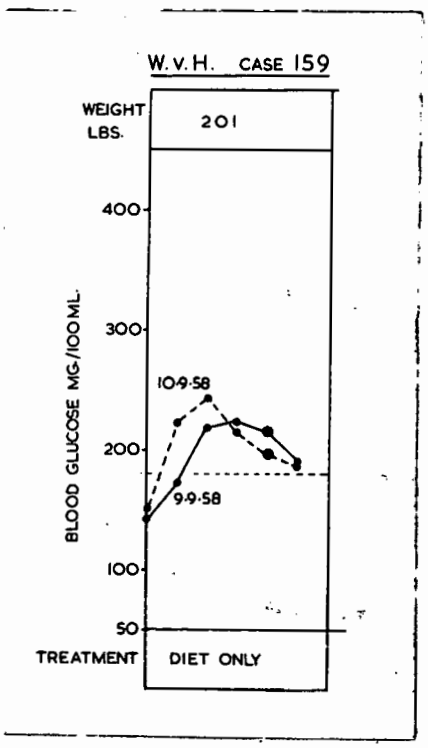
K.v.L (Case 87)

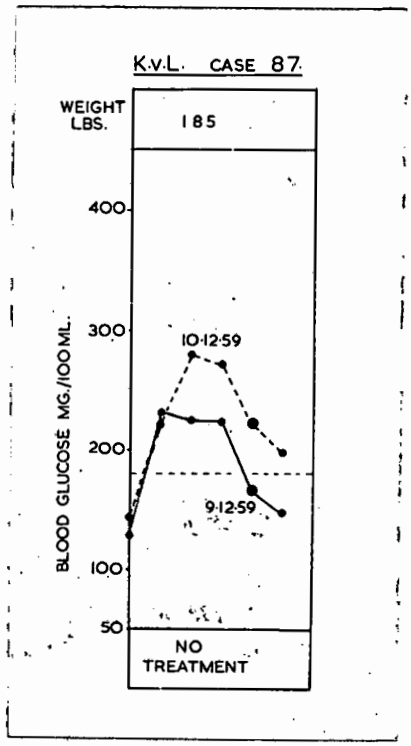

I.W. CASE 162. G.T.T.'S & CORT./G.T.T.'S.
WEIGHT LBS.
163
166
168
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
19·7·56
28·6·56
24·9·59
25·9·59
4·11·59
3·11·59
TREATMENT
RIBOFLAVINE 30 MG. FROM 12·1·56
OFF TOLBUTAMIDE 19·9·59–26·9·59
TOLBUTAMIDE 1G.

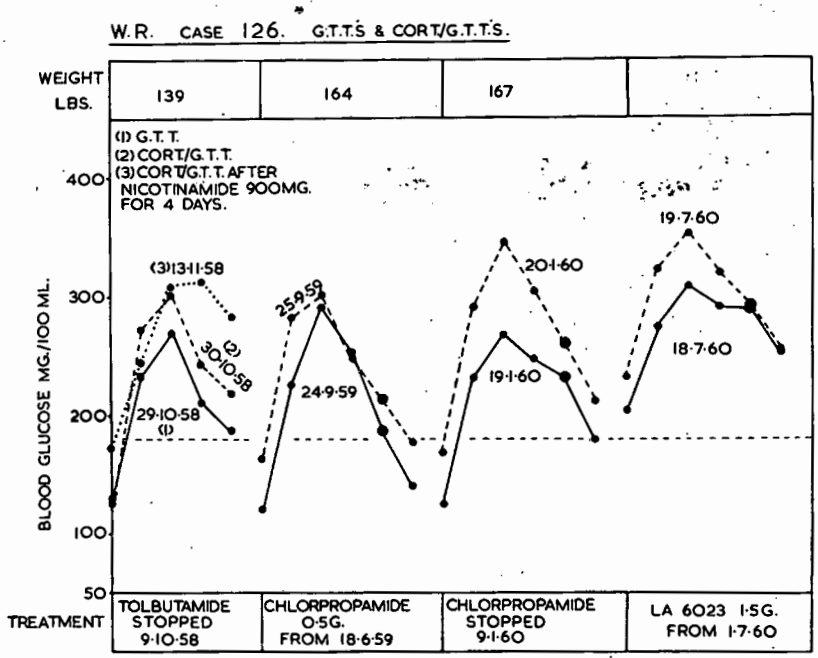
I.W. (Case 162):

After diabetes has relapsed this patient shows a paradoxical response to cortisone (i.e. glucose tolerance improvement): 25.9.59. although the peak of the curve is still high.

(It is to be noted that this response occurred when tolbutamide was stopped, in error, for one week).


W.V.H. CASE 159
WEIGHT LBS.
201
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
10·9·58
9·9·58
TREATMENT
DIET ONLY


K.V.L. CASE 87
WEIGHT LBS.
185
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
10·12·59
9·12·59
NO TREATMENT


W.R. CASE 126. G.T.T.S & CORT/G.T.T.S.
WEIGHT LBS.
139
164
167
(1) G.T.T.
(2) CORT/G.T.T.
(3) CORT/G.T.T. AFTER NICOTINAMIDE 900MG. FOR 4 DAYS.
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
(3) 13·11·58
(2) 30·10·58
29·10·58 (1)
25·9·59
24·9·59
20·1·60
19·1·60
19·7·60
18·7·60
TREATMENT
TOLBUTAMIDE STOPPED 9·10·58
CHLORPROPAMIDE 0·5G. FROM 18·6·59
CHLORPROPAMIDE STOPPED 9·1·60
LA 6023 1·5G. FROM 1·7·60

W.v.H. (Case 159):

This patient, a European man aged 49 years, was a mild diabetic.

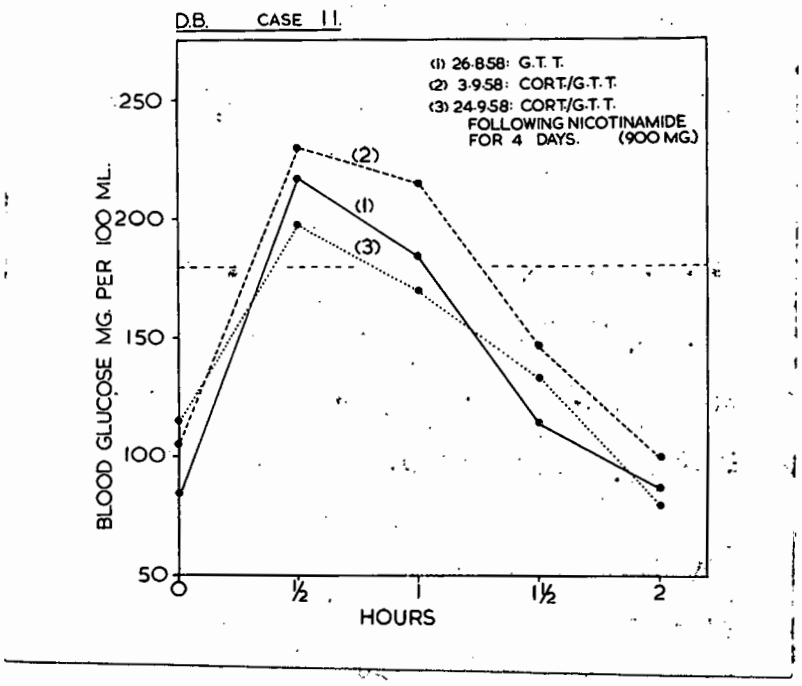
The cortisone/glucose tolerance test showed no enhancement, the 2 hour figure being lower than in the standard glucose tolerance test.

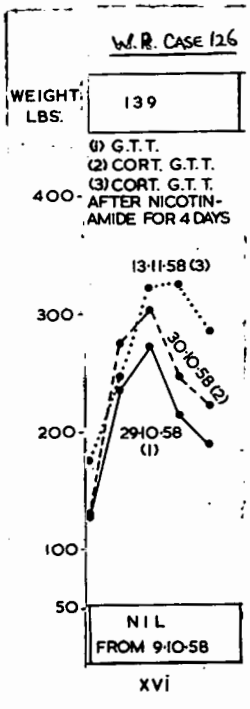
K.v.L. (Case 87):

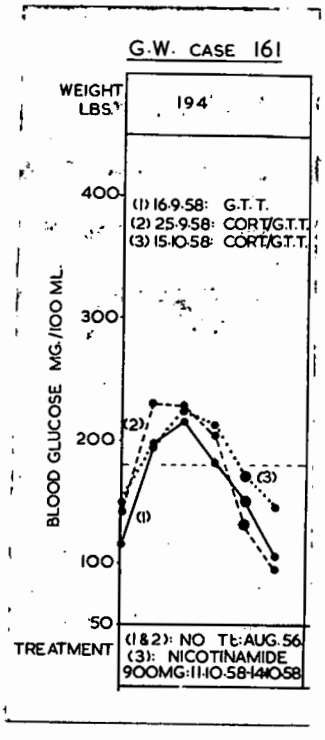
This patient, a European man aged 51 years, showed considerable enhancement of the latter half of the glucose tolerance test.

W.R. (Case 126):

Both diabetic curves show mild to moderate enhancement on cortisone: 30.10.58 and 20.1.60, when patient has discontinued hypoglycaemic agents.


D.B. CASE 11.
(1) 26-8-58: G.T.T.
(2) 3-9-58: CORT./G.T.T.
(3) 24-9-58: CORT./G.T.T. FOLLOWING NICOTINAMIDE FOR 4 DAYS. (900 MG.)
BLOOD GLUCOSE MG. PER 100 ML.
250
200
150
100
50
0
½
1
1½
2
HOURS
(1)
(2)
(3)


W.R. CASE 126
WEIGHT LBS.
139
(1) G.T.T.
(2) CORT. G.T.T.
(3) CORT. G.T.T. AFTER NICOTINAMIDE FOR 4 DAYS
400
300
200
100
50
13-11-58 (3)
30-10-58 (2)
29-10-58 (1)
NIL FROM 9-10-58
XVI


G.W. CASE 161
WEIGHT LBS.
194
(1) 16-9-58: G.T.T.
(2) 25-9-58: CORT/G.T.T.
(3) 15-10-58: CORT/G.T.T.
BLOOD GLUCOSE MG./100 ML.
400
300
200
100
50
(1)
(2)
(3)
TREATMENT
(1&2): NO TX: AUG. 56.
(3): NICOTINAMIDE 900MG: 11-10-58-14-10-58.

CORTISONE/GLUCOSE TOLERANCE TEST: PATIENTS NOT ON HYPOGLYCAEMIC AGENTS:

NICOTINAMIDE AND CORTISONE ENHANCEMENT OF THE GLUCOSE TOLERANCE TEST:

Nicotinamide prevents alloxan induced diabetes (Banerjee 1947, Lazarow et al 1950). Would prior administration of nicotinamide in large doses prevent cortisone enhancement of the glucose tolerance test ?

Patients studied (3):

D.B. (Case 11) had a normal glucose tolerance test.

G.W. (Case 161) was a diabetic in remission and had previously received large doses of nicotinamide.

W.R. (Case 126) was a diabetic who had also been treated with nicotinamide in the past.

These patients each had 3 glucose tolerance tests:

(1) Standard glucose tolerance test

(2) Cortisone/glucose tolerance test

(3) Cortisone/glucose tolerance test after receiving nicotinamide in doses of 900 mg. for 4 days.

The results were:

D.B. (Case 11): Curve (3) was better than (1) or (2).

G.W. (Case 161) and W.R. (Case 126): Curve (3) was worse than either (1) or (2).

DISCUSSION OF THE RESULTS IN PATIENTS NOT ON HYPOGLYCAEMIC AGENTS:

Cortisone/Glucose Tolerance Tests in Patients with Gout.

Of 11 gouty patients in whom the effect of cortisone was studied, 7 could have been considered to show cortisone enhancement to diabetes, or a diabetic type of curve.

Four showed mild enhancement only.

Cortisone/Glucose Tolerance Tests in other Patients not treated with Hypoglycaemic Agents: (12 Patients).

DISCUSSION OF RESULTS:

7 cortisone/glucose tolerance tests showed no (or only mild) enhancement of the glucose tolerance test in :-

2 cases of renal glycosuria:
J.H. (Case 58) and
D.B. (Case 11)

in :- 1 Pre-diabetic (?) man:

L.K. (Case 198) (Identical twin P.K. (Case 74) diabetic).

and in :-

4 patients with diabetes in remission:

E.Se. (Case 137)
I.W. (Case 162)
W.v.H. (Case 159)
G.W. (Case 161) (This patient had gout. He is included in this section as well because the cortisone test was done whilst his diabetes was in remission).

This was a surprising finding, as these 4 patients were known to have had an abnormality of glucose tolerance curve or a diabetic curve before.

If the cortisone/enhanced test is to be of value in predicting diabetes, it seems reasonable to expect a frankly diabetic curve in these cases.

Enhancement to a more abnormal form of curve was seen in 2 cases: E.S. (Case 135) and M.L. (Case 82).

In these 2 cases it may be said that the use of cortisone had confirmed the suspicion that these patients were tending to develop diabetes.

The glucose tolerance curve became more abnormal after cortisone in 2 diabetic patients: W.R. (Case 126) and K.v.L. (Case 87).

In one patient with a normal glucose tolerance test there was a considerable enhancement with cortisone:

A.K. (Case 77), a young pregnant woman with a strong family history of diabetes (Mother, Father and brother).

This is in keeping with reports on this type of case.

Nicotinamide failed to prevent cortisone enhancement of the glucose tolerance test in 2 patients who had previously had abnormal curves (G.W. and W.R.). In one patient, D.B. (Case 11) with a normal glucose tolerance test, prior treatment with nicotinamide resulted in a cortisone/glucose tolerance test which was better than the previous glucose tolerance tests.

A COMPARISON OF THE EFFECTS OF CORTISONE IN 11 GOUTY PATIENTS AND IN A GROUP CONSISTING OF 11 DIABETICS OR 'PRE-DIABETICS'.

It is of great interest to compare the results in the gouty group with a non-gouty group of 11 patients composed of:

Diabetics (known to have diabetic glucose tolerance tests): 2.

Previously known to have a diabetic or diabetic type of curve: 5.

Pregnant + strong family history of diabetes ('Pre-diabetic'):1.

Glycosuria: 2.

A 'Prediabetic ?' (identical twin a diabetic): 1.

Five of the 11 patients showed enhancement with cortisone.

7 of the 11 gouty patients showed cortisone enhancement.

This would suggest that the gouty group are at least as susceptible to the diabetogenic effect of cortisone as a strongly suspect diabetic or pre-diabetic group.

CONCLUSIONS:

These results would suggest that the gouty group may be unduly susceptible to the diabetogenic effect of cortisone.

II

D. CORTISONE/GLUCOSE TOLERANCE TESTS IN PATIENTS TREATED WITH PHARMACOLOGICAL HYPOGLYCAEMIC AGENTS:

(22)

No enhancement was shown in:-

O.P. Case 120
G.K. Case 76

Mild enhancement was shown in :-

W.R. Case 126
C.V. Case 158
J.F. Case 47
N.C. Case 32
P.L. Case 88
J.E. Case 42
M.D. Case 38
J.G. Case 52
J.R. Case 128

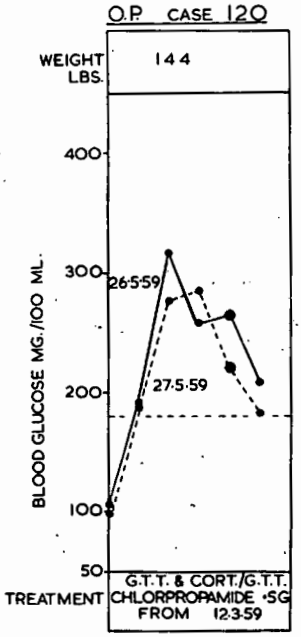
Moderate enhancement was shown in :-

I.W. Case 162
C.v.M. Case 160
A.d.S. Case 140
J.C. Case 31
G.S. Case 136

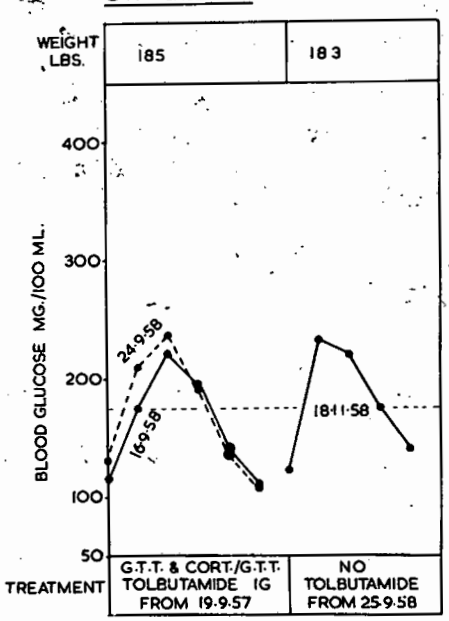
Marked enhancement was shown in :-

E.C. Case 29
G.H. Case 55
D.R. Case 127
M.P. Case 122
R.L. Case 79
A.F. Case 46

O.P. CASE 120



G.K. CASE 76



O.P. (Case 120):

This European woman aged 62 years, showed a good hypoglycaemic response to chlorpropamide, but a glucose tolerance test while still taking chlorpropamide was completely abnormal.

The cortisone/glucose tolerance test, if anything, was improved.

G.K. (Case 76):

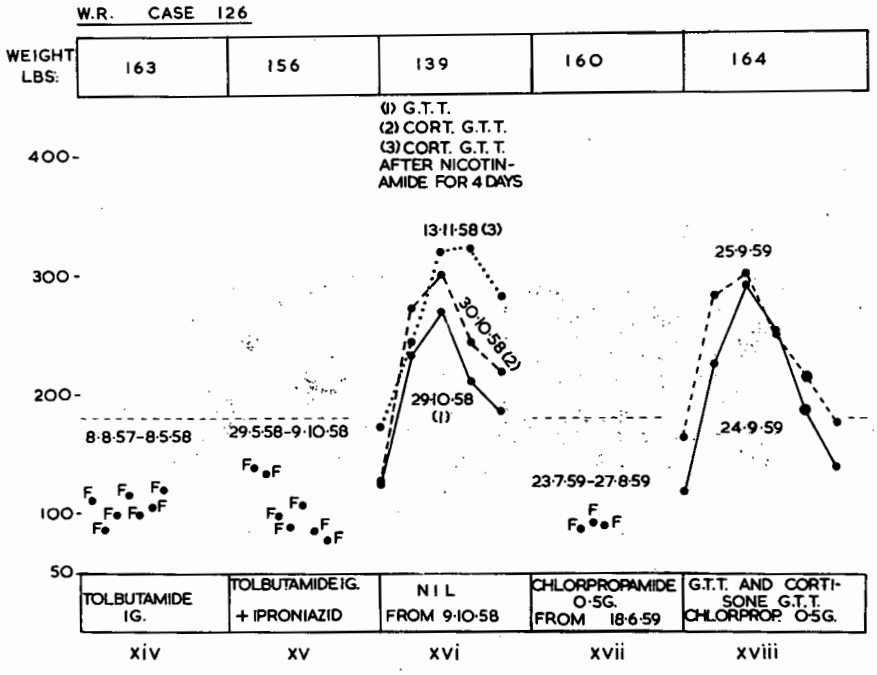
This European man aged 48 years, was a mild diabetic treated with tolbutamide since September 1957.

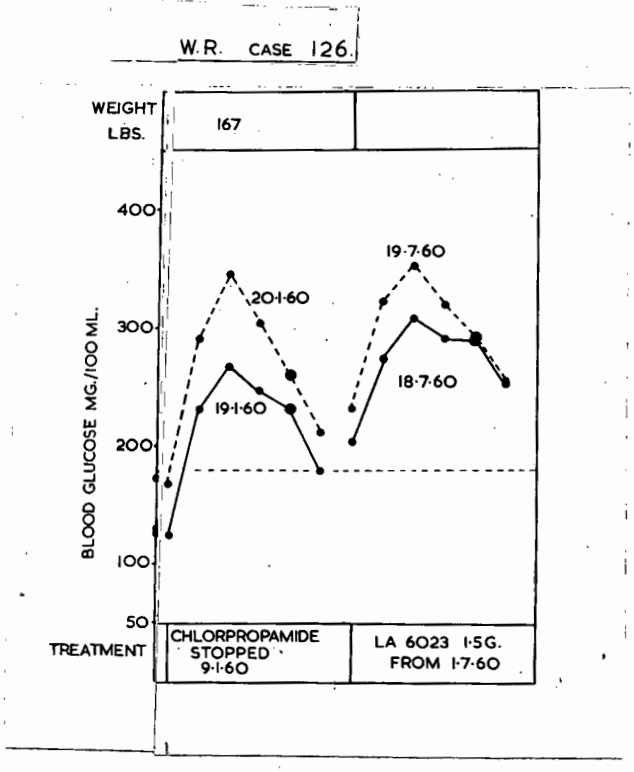
A cortisone/glucose tolerance test was almost identical to the standard glucose tolerance test - both these tests having been done while the patient was being treated with tolbutamide.

Tolbutamide was discontinued on 25.9.58 after his fasting glucose levels had been found to be consistently normal.

A standard glucose tolerance test done 2 months later was similar to those done while taking tolbutamide. This patient may have gone into a spontaneous remission.

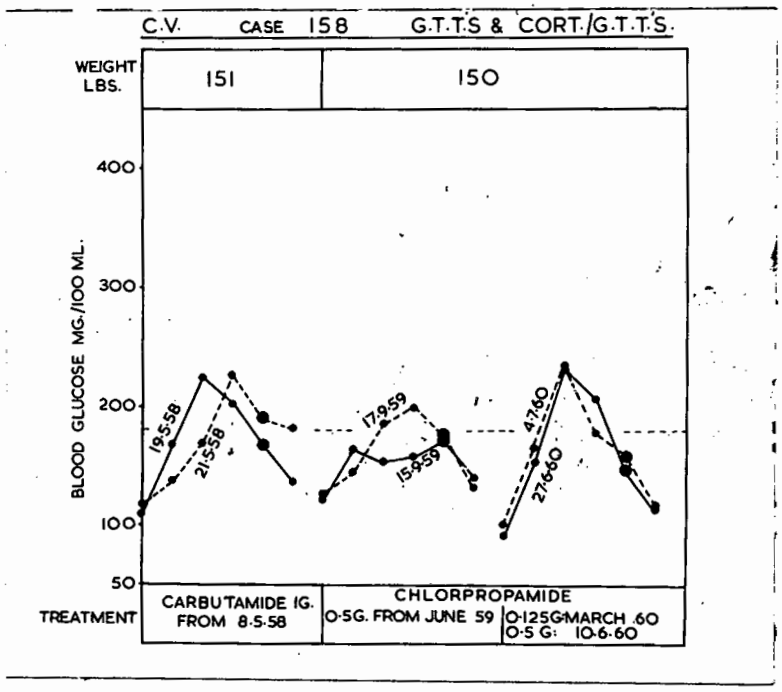
In January 1959, glycosuria had reappeared and the fasting glucose level (158 mg.) was suggestively diabetic.

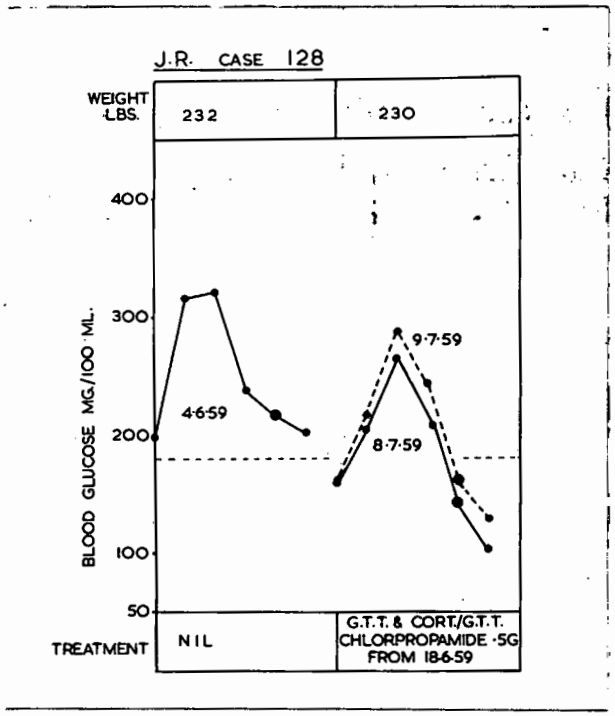

W.R. CASE 126
WEIGHT LBS:
163
156
139
160
164
(1) G.T.T.
(2) CORT. G.T.T.
(3) CORT. G.T.T. AFTER NICOTINAMIDE FOR 4 DAYS
400
300
200
100
50
13·11·58 (3)
30·10·58 (2)
29·10·58 (1)
25·9·59
24·9·59
8·8·57–8·5·58
29·5·58–9·10·58
23·7·59–27·8·59
TOLBUTAMIDE 1G.
TOLBUTAMIDE 1G. + IPRONIAZID
NIL FROM 9·10·58
CHLORPROPAMIDE 0·5G. FROM 18·6·59
G.T.T. AND CORTISONE G.T.T. CHLORPROP. 0·5G.
xiv
xv
xvi
xvii
xviii


W.R. CASE 126.
WEIGHT LBS.
167
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
20·1·60
19·1·60
19·7·60
18·7·60
TREATMENT
CHLORPROPAMIDE STOPPED 9·1·60
LA 6023 1·5G. FROM 1·7·60

W.R. (Case 126):

The cortisone/glucose tolerance test while the patient was being treated with the hypoglycaemic agents, chlorpropamide (xviii) and LA 6023 (xx), show only mild enhancement, but considerable enhancement is shown while this patient was treated with tolbutamide (xiii). (See page 114 SECTION V).


C.V. CASE 158 G.T.T.S & CORT./G.T.T.S.
WEIGHT LBS.
151
150
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
19·5·58
21·5·58
17·9·59
15·9·59
4·7·60
27·6·60
TREATMENT
CARBUTAMIDE 1G. FROM 8·5·58
CHLORPROPAMIDE
0·5G. FROM JUNE 59
0·125G MARCH 60
0·5 G: 10·6·60


J.R. CASE 128
WEIGHT LBS.
232
230
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
4·6·59
9·7·59
8·7·59
TREATMENT
NIL
G.T.T. & CORT./G.T.T. CHLORPROPAMIDE ·5G FROM 18·6·59

C.V. (Case 158):

This Coloured women aged 49 years was a mild diabetic and had been observed at the diabetic clinic since January 1955.

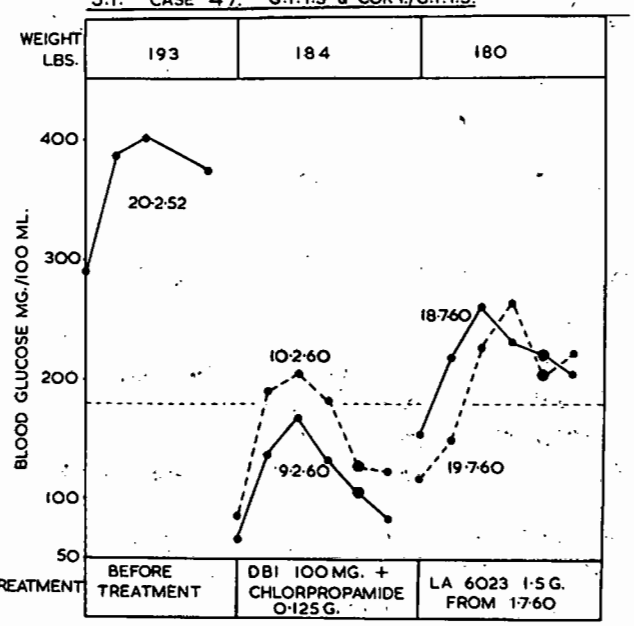
Cortisone/glucose tolerance tests showed only mild enhancement on carbutamide and no enhancement on chlorpropamide in September 1959 and January 1960.

J.R. (Case 128):

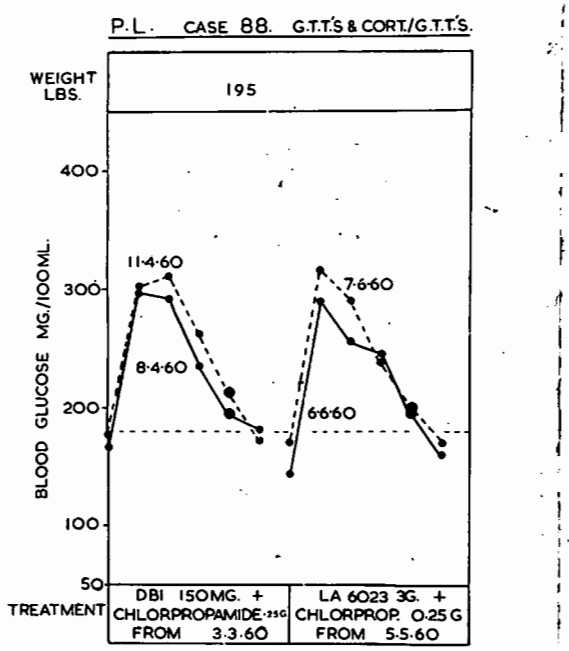
This patient was an obese elderly European woman.

The cortisone/glucose tolerance test while being treated with chlorpropamide showed practically no enhancement.

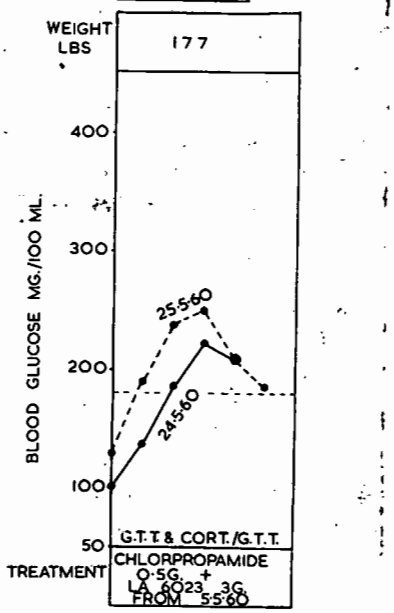
J.F. CASE 47. G.T.T.'S & CORT./G.T.T.'S.



P.L. CASE 88. G.T.T.'S & CORT./G.T.T.'S.



N.C. CASE 32



J.F. (Case 47), a European man aged 47 years:

This diabetic man had been observed over a period of 8 years.

The evaluation of the glucose tolerance tests is also discussed on pages 107 and 108.

The original diabetic curve (20.2.52) is inserted.

On 9.2.60 a complete remission in glucose tolerance test was recorded while the patient was being treated with a combination of phenethyldiguanide and chlorpropamide. The cortisone/glucose tolerance test shows mild enhancement, but is still normal.

A subsequent cortisone/glucose tolerance test while on dimethylbiguanide shows no enhancement over the standard glucose tolerance test.

P.L. (Case 88):

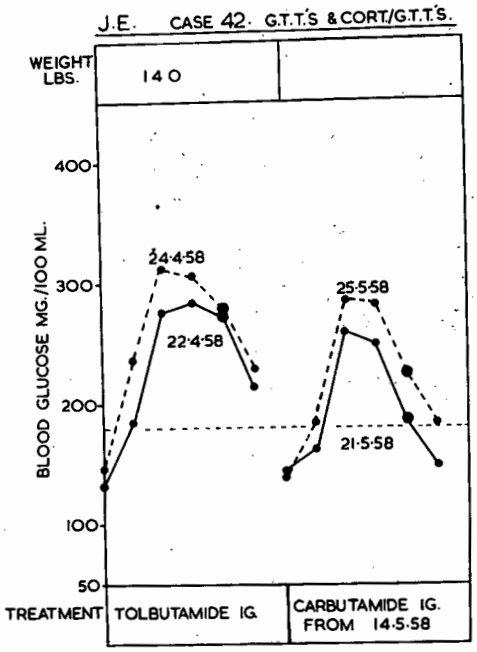
This diabetic patient, an elderly European man, was at one time poorly controlled on 60 - 80 units of insulin.

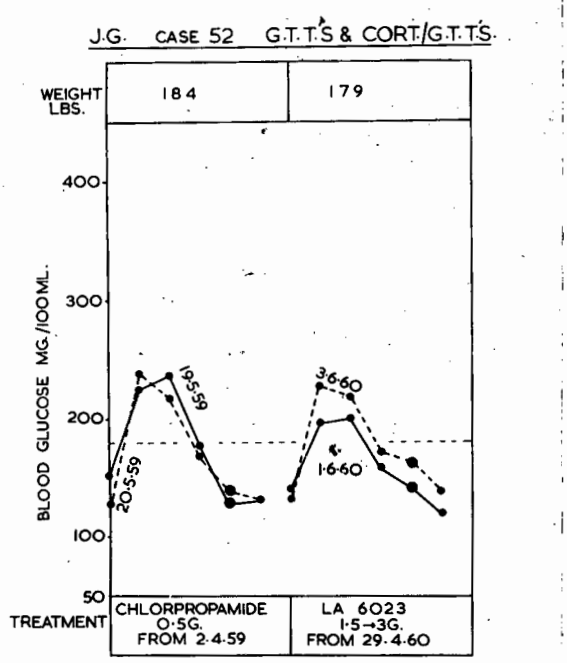
On DBI + chlorpropamide, and again on dimethylbiguanide + chlorpropamide he showed a good hypoglycaemic response but a definite diabetic curve. The cortisone/glucose tolerance tests showed practically no enhancement.

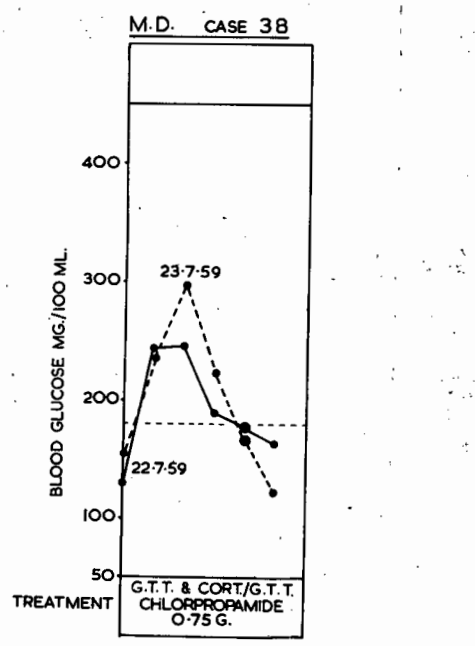
N.G. (Case 32):

This European man aged 35 years at onset of diabetes in 1948.

A cortisone/glucose tolerance test showed only mild enhancement over the standard glucose tolerance test while the patient was receiving the hypoglycaemic agents, chlorpropamide and dimethylbiguanide.


J.E. CASE 42. G.T.T.'S & CORT/G.T.T.'S.
WEIGHT LBS.
140
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
24·4·58
22·4·58
25·5·58
21·5·58
TREATMENT
TOLBUTAMIDE 1G.
CARBUTAMIDE 1G. FROM 14·5·58


J.G. CASE 52 G.T.T.'S & CORT/G.T.T.'S.
WEIGHT LBS.
184
179
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
20·5·59
19·5·59
3·6·60
1·6·60
TREATMENT
CHLORPROPAMIDE 0·5G. FROM 2·4·59
LA 6023 1·5→3G. FROM 29·4·60


M.D. CASE 38
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
23·7·59
22·7·59
TREATMENT
G.T.T. & CORT/G.T.T. CHLORPROPAMIDE 0·75G.

J.E. (Case 42): See also page 193.

This patient was a Coloured man aged 42 years.

He had GOUT and was of great interest in that corticosteroid therapy had induced diabetes.

The cortisone/glucose tolerance tests showed only mild to moderate enhancement while the patient was receiving tolbutamide or carbutamide.

J.G. (Case 52):

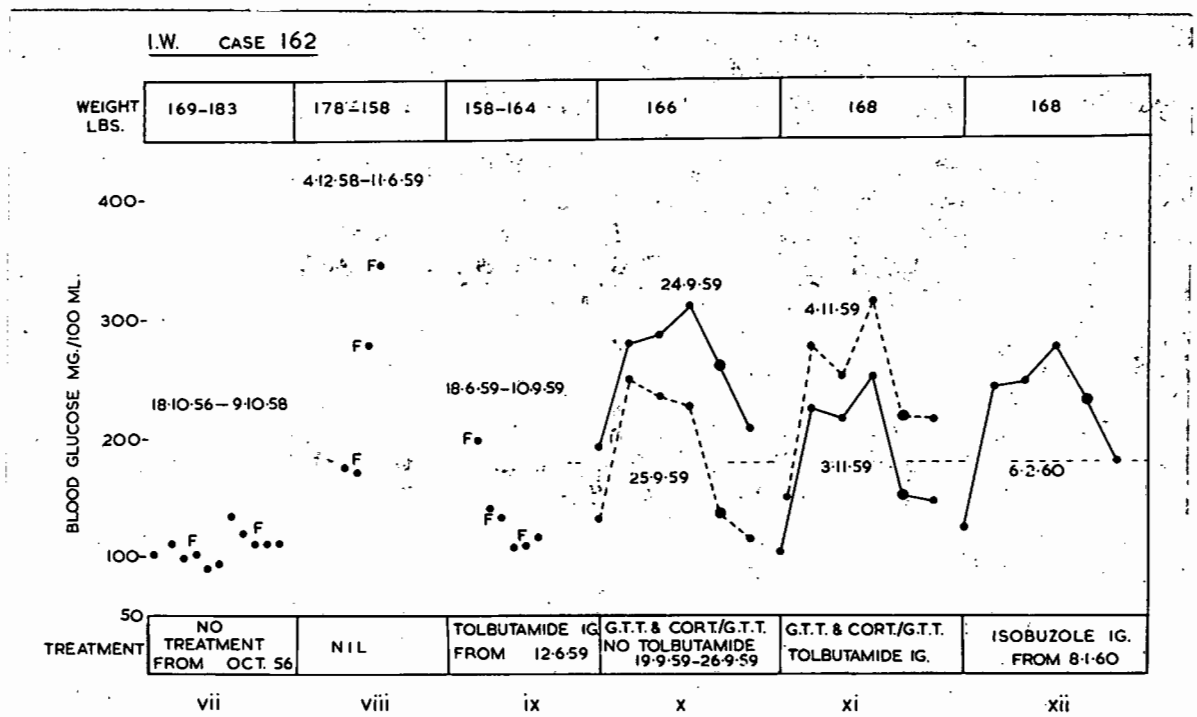
This patient was a European man aged 52 years.

The cortisone"glucose tolerance test showed no enhancement while on chlorpropamide, and mild enhancement only on dimethylbiguanide (LA 6023).

M.D. (Case 38):

This patient was a European man aged 42 years.

The cortisone/glucose tolerance test showed only mild enhancement over the previous glucose tolerance test.


I.W. CASE 162
WEIGHT LBS.
169–183
178–158
158–164
166
168
168
4·12·58–11·6·59
400-
300-
200-
100-
50
BLOOD GLUCOSE MG./100 ML.
18·10·56 – 9·10·58
18·6·59–10·9·59
24·9·59
4·11·59
25·9·59
3·11·59
6·2·60
F
TREATMENT
NO TREATMENT FROM OCT. 56
NIL
TOLBUTAMIDE IG. FROM 12·6·59
G.T.T. & CORT./G.T.T. NO TOLBUTAMIDE 19·9·59–26·9·59
G.T.T. & CORT./G.T.T. TOLBUTAMIDE IG.
ISOBUZOLE IG. FROM 8·1·60
vii
viii
ix
x
xi
xii

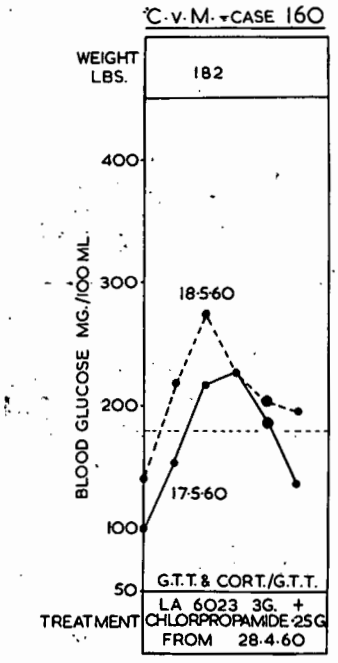
I.W. (Case 162):

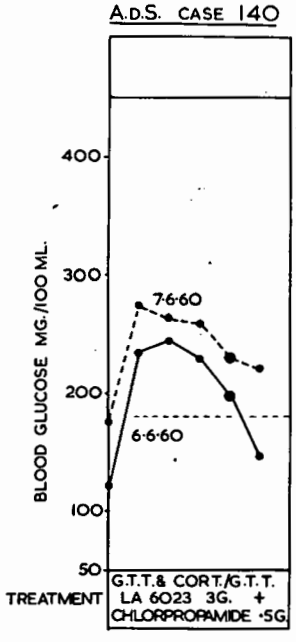
This patient was a European woman aged 58 years.

In December 1958 there was an exacerbation of the diabetes and the patient showed a very satisfactory hypoglycaemic response to tolbutamide.

This patient omitted taking tolbutamide in error for 5 days prior to the glucose tolerance test and the cortisone/glucose tolerance test on 24.9.59 and 25.9.59 respectively. The glucose tolerance test showed a severely abnormal diabetic curve on 24.9.59. Paradoxically the glucose tolerance test after cortisone showed improvement.

On Tolbutamide the glucose tolerance test was improved again and the cortisone/glucose tolerance test showed a moderate to marked enhancement.


C.V.M. CASE 160
WEIGHT LBS.
182
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
18.5.60
17.5.60
G.T.T. & CORT./G.T.T.
TREATMENT
LA 6023 3G. +
CHLORPROPAMIDE 25G.
FROM 28.4.60


A.D.S. CASE 140
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
7.6.60
6.6.60
G.T.T.& CORT./G.T.T.
TREATMENT
LA 6023 3G. +
CHLORPROPAMIDE .5G.

C.v.M. Case 160:

This patient, an elderly European man, was previously on insulin. He failed to respond to any of the following hypoglycaemic agents: Tolbutamide, chlorpropamide, metahexamide and isobuzole.

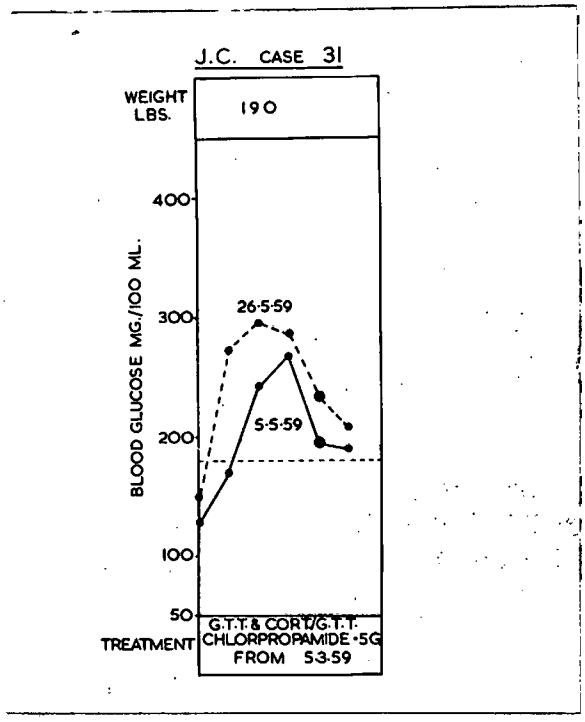
He showed an excellent response to a combination of 2 hypoglycaemic agents, dimethylbiguanide and chlorpropamide. There were low fasting blood glucose levels. The glucose tolerance test, too, was a moderately good one.

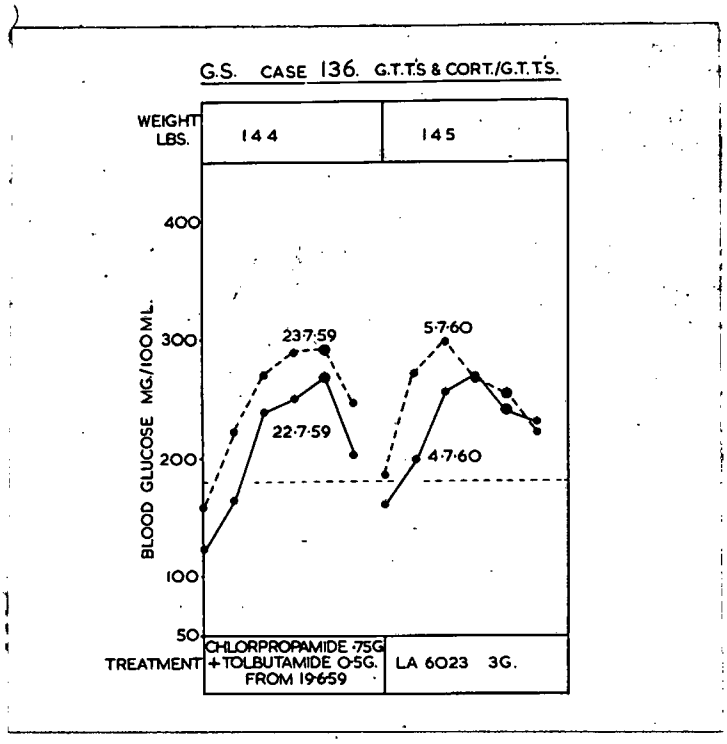
There was moderate enhancement with cortisone.

(Subsequent response to dimethylbiguanide alone was good).

A.d.S. Case 140.

This patient, a European man aged 52 years, had been on insulin. He failed to show any response to tolbutamide (Blood glucose 300 mg.). Response to metahexamide was unsatisfactory. On chlorpropamide he showed an initial response but failed to maintain this after 4 months. Isobuzole produced no response. Phenethyldiguanide 125 mg. produced little response, but when chlorpropamide was added there was a good hypoglycaemic response. On dimethylbiguanide + chlorpropamide this response was maintained. Even after glucose, the tolerance test did not show gross hyperglycaemia levels. Cortisone produced moderate enhancement.


J.C. CASE 31
WEIGHT LBS.
190
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
26·5·59
5·5·59
TREATMENT
G.T.T. & CORT./G.T.T.
CHLORPROPAMIDE ·5G
FROM 5·3·59


G.S. CASE 136. G.T.T.'S & CORT./G.T.T.'S.
WEIGHT LBS.
144
145
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
23·7·59
22·7·59
5·7·60
4·7·60
TREATMENT
CHLORPROPAMIDE ·75G
+TOLBUTAMIDE 0·5G.
FROM 19·6·59
LA 6023 3G.

J.C. (Case 31):

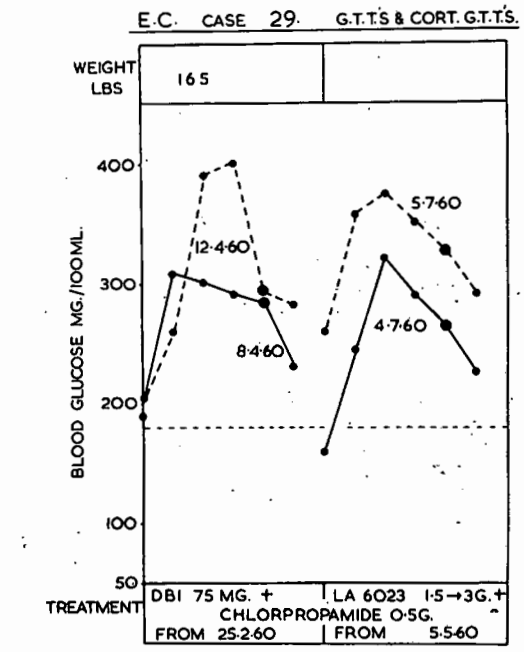
This patient was an elderly European woman. She was a mild diabetic seen since 1954; her diabetes showed an exacerbation in 1958.

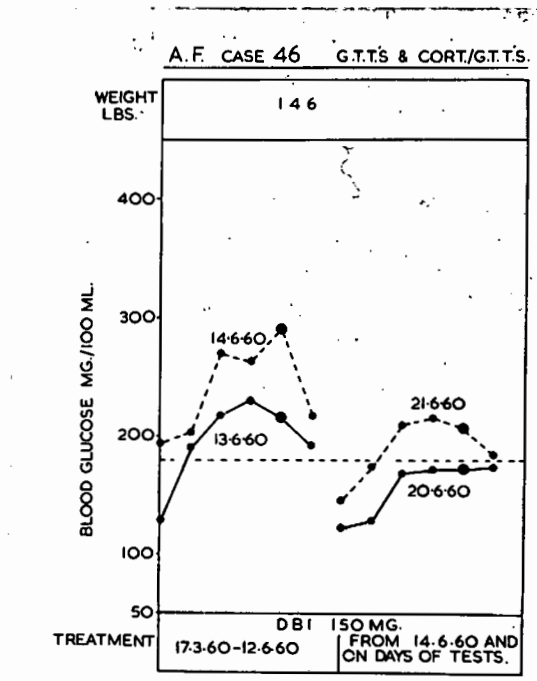
On chlorpropamide there was moderate enhancement as compared with the standard glucose tolerance test.

G.S. (Case 136):

This patient, a European woman aged 53 years, (1947) was followed up since the onset of diabetes in 1947.

She showed moderate enhancement on cortisone while taking chlorpropamide + tolbutamide and again when taking dimethylbiguanide (LA 6023).


E.C. CASE 29. G.T.T.'S & CORT. G.T.T.'S.
WEIGHT LBS
165
400
300
200
100
50
BLOOD GLUCOSE MG./100ML.
12·4·60
8·4·60
5·7·60
4·7·60
TREATMENT
DBI 75 MG. + CHLORPROPAMIDE 0·5G. FROM 25·2·60
LA 6023 1·5→3G.+ FROM 5·5·60


A.F. CASE 46 G.T.T.'S & CORT./G.T.T.'S.
WEIGHT LBS.
146
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
14·6·60
13·6·60
21·6·60
20·6·60
TREATMENT
DBI 150 MG.
17·3·60–12·6·60
FROM 14·6·60 AND ON DAYS OF TESTS.

E.C. (Case 29):

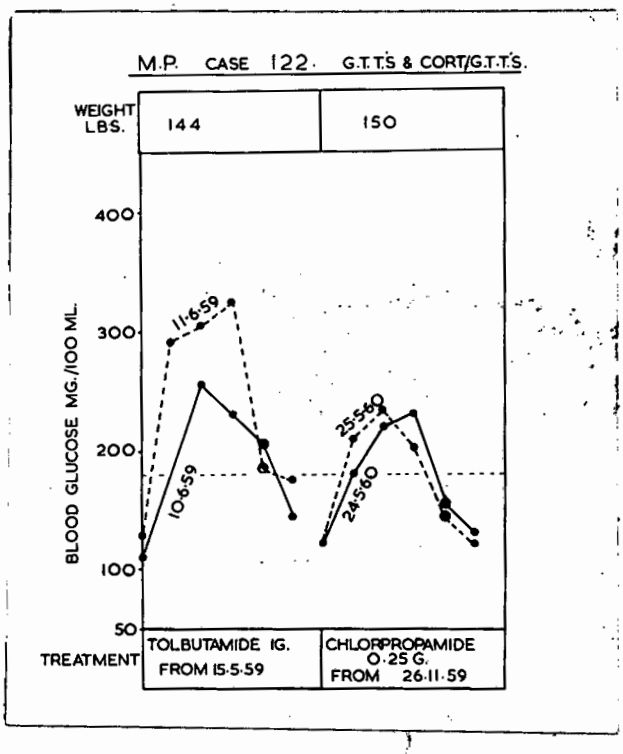
This patient, an elderly European woman, was a mild diabetic but poorly controlled on all hypoglycaemic agents which were tried. She was relatively insulin resistant too.

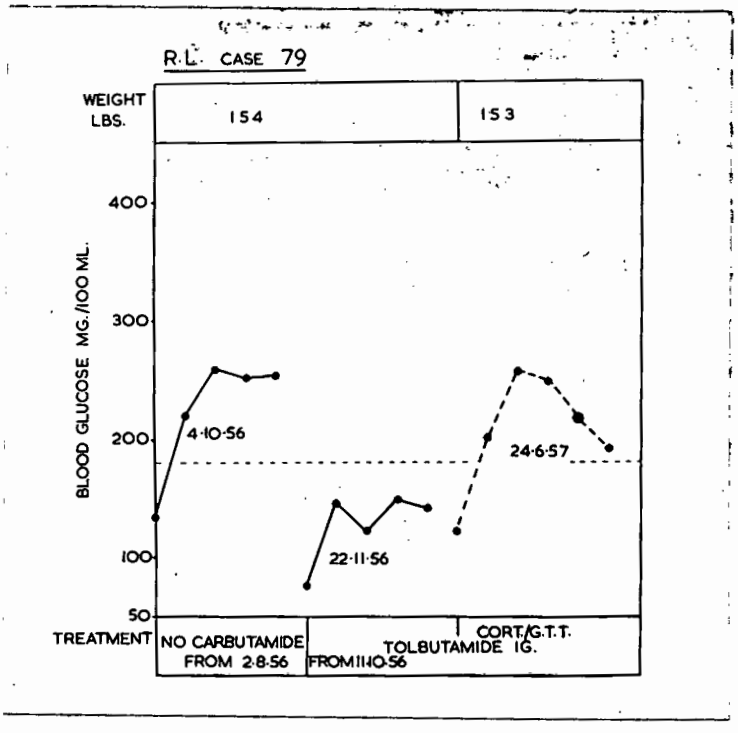
There was marked enhancement on cortisone while taking DBI + chlorpropamide and also while taking dimethylbiguanide (LA 6023) + chlorpropamide.

A.F. (Case 46):

This patient, an elderly Coloured woman, was well-controlled on phenethylbiguanide (DBI 150 mg.). A cortisone/glucose tolerance test on 14.6.60 showed considerable enhancement.

A week later the procedure was repeated exactly except that the patient took 50 mg. of DBI on the morning of the glucose tolerance test as well. Although the tests were at a lower level, there was still considerable enhancement following cortisone.


M.P. CASE 122. G.T.T.S & CORT/G.T.T.S.
WEIGHT LBS.
144
150
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
11·6·59
10·6·59
25·5·60
24·5·60
TREATMENT
TOLBUTAMIDE 1G. FROM 15·5·59
CHLORPROPAMIDE 0·25 G. FROM 26·11·59


R.L. CASE 79
WEIGHT LBS.
154
153
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
4·10·56
22·11·56
24·6·57
TREATMENT
NO CARBUTAMIDE FROM 2·8·56
TOLBUTAMIDE 1G. FROM 11·10·56
CORT/G.T.T.

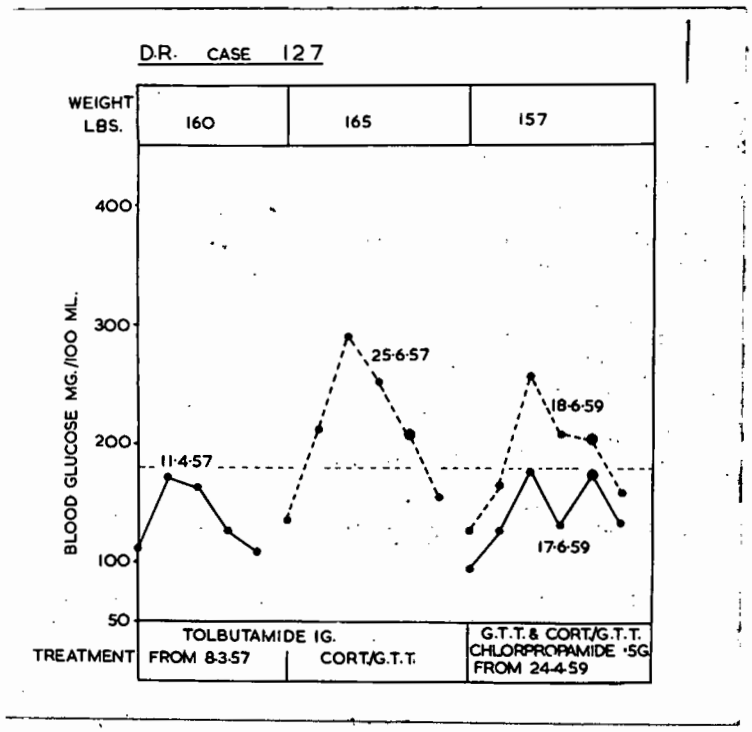
M.P. (Case 122):

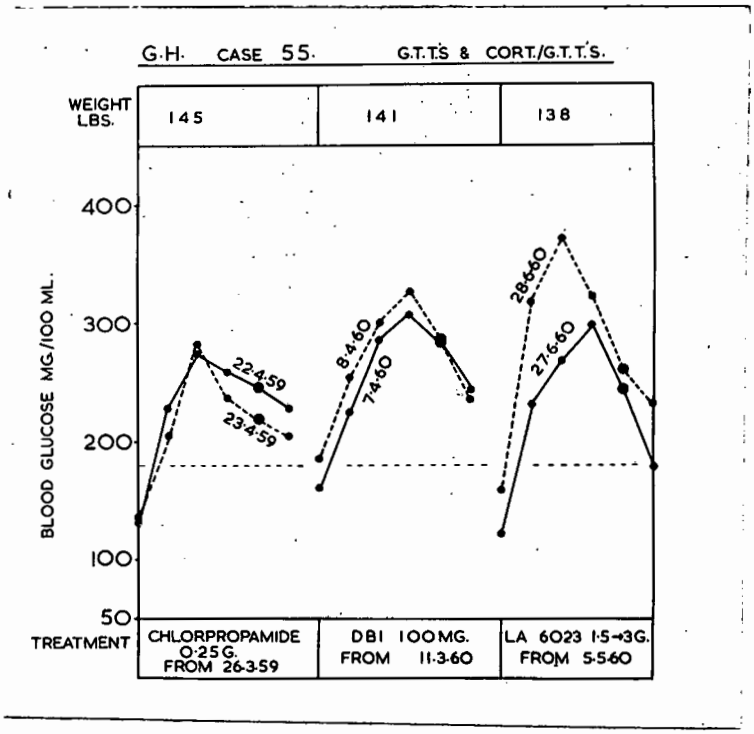
This patient, an elderly European woman, showed marked enhancement following cortisone while on tolbutamide. On chlorpropamide, however, there was no enhancement.

R.L. (Case 79):

This patient, an elderly European woman, showed a near normal glucose tolerance test while taking tolbutamide.

A cortisone/glucose tolerance test on 24.6.57 showed considerable enhancement.


D.R. CASE 127
WEIGHT LBS.
160
165
157
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
11-4-57
25-6-57
18-6-59
17-6-59
TREATMENT
TOLBUTAMIDE 1G. FROM 8-3-57
CORT./G.T.T.
G.T.T. & CORT./G.T.T. CHLORPROPAMIDE ·5G. FROM 24-4-59


G.H. CASE 55. G.T.T.S & CORT./G.T.T.S.
WEIGHT LBS.
145
141
138
400
300
200
100
50
BLOOD GLUCOSE MG./100 ML.
22-4-59
23-4-59
8-4-60
7-4-60
28-6-60
27-6-60
TREATMENT
CHLORPROPAMIDE 0·25G. FROM 26-3-59
DBI 100MG. FROM 11-3-60
LA 6023 1·5→3G. FROM 5-5-60

D.R. (Case 127):

The course of the diabetes of this patient was closely followed since onset in 1947, when she was aged 43 years.

There was a normal glucose tolerance test on tolbutamide on 11.4.57 but a cortisone/glucose tolerance test 2 months later (25.6.57) showed considerable enhancement. On 17.6.59 a glucose tolerance test while taking chlorpropamide was again practically normal (except for the rebound of the 2 hour figure).

A cortisone/glucose tolerance test on chlorpropamide showed considerable enhancement.

G.H. (Case 55), a European woman aged 55 years:

There was only mild enhancement while on chlorpropamide (April 1959), and on phenethylbiguanide (April 1960), but moderate to marked enhancement when on dimethylbiguanide (LA 6023) in June 1960.

ANALYSIS OF RESULTS: CORTISONE/GLUCOSE TOLERANCE TESTS IN PATIENTS ON PHARMACOLOGICAL AGENTS:

Patients on CHLORPROPAMIDE ALONE:

10 Patients: (11 tests)

No enhancement: 3 patients: (O.P., G.H., M.P.)

Mild enhancement: 5 patients (6 tests): (C.V. (2 tests), M.D., J.G., J.R., W.R.)

Moderate enhancement: 1 patient: (J.C.)

Marked enhancement: 1 patient: (D.R.)

Patients on CHLORPROPAMIDE +ANOTHER HYPOGLYCAEMIC AGENT:

7 Patients: (9 tests)

Mild enhancement: 3 patients (4 tests): (N.G., P.L. (2 tests), J.F.)

Moderate enhancement: 3 patients: (C.v.M., A.d.S., G.S.)

Marked enhancement: 1 patient (2 tests): (E.C.)

Patients on TOLBUTAMIDE ALONE: 7 patients:

No enhancement: 1 patient.
(G.K.)

Mild enhancement: 1 patient.
(J.E.)

Moderate enhancement: 1 patient.
(I.W.)

Marked enhancement: 4 patients
(D.R., M.P., R.L.; W.R. (xiii) See page 114 SECTION V).

Patients on TOLBUTAMIDE CHLORPROPAMIDE: 1 patient:

Moderate enhancement: 1 patient
(G.S.)

Patients on CARBUTAMIDE: 2 patients:

Mild enhancement: 2 patients.
(C.V., J.E.)

Patients on LA 6023 ALONE: 4.

No enhancement: 1 patient. (J.F.)

Mild enhancement: 1 patient (W.R.)

Moderate enhancement: 1 patient. (G.S.)

Marked enhancement: 1 patient (G.H.)

Patients on LA 6023 + CHLORPROPAMIDE: 5.

No enhancement: Nil.

Mild enhancement: 2 patients. (P.L., N.C.)

Moderate enhancement: 2 patients. (C.v.M., A.d.S.)

Marked enhancement: 1 patient (E.C.)

Patients on DBI ALONE: 1. (2 tests).

Marked enhancement: 1.
(A.F. 2 tests).

Patients on DBI + CHLORPROPAMIDE: 3.

Mild enhancement: 2.
(J.F., P.L.)

Marked enhancement: 1.
(E.C.)

CORTISONE ENHANCEMENT IN RELATION TO THE SUBSEQUENT COURSE OF DIABETES:

Patients with near normal glucose tolerance tests who showed no (or only mild) cortisone enhancement of the glucose tolerance test:

GROUP I.

Case	Name	Agent used	Comments.
76	G.K.	Tolbutamide	Improved G.T.T. persisted after tolbutamide discontinued.
158	C.V.	Chlorpropamide	Persistance of low fasting levels on small doses for 1 year; low fasting level after omitting chlorpropamide for 2 weeks.
128	J.R.	Chlorpropamide	Low fasting levels persisted for several months after discontinuing chlorpropamide.
38	M.D.	Chlorpropamide	G.T.T. 1 year after commencement of chlorpropamide shows further improvement towards normal. (Previously remission recorded after insulin discontinued).
52	J.G.	Chlorpropamide	Near normal G.T.T's and normal fasting levels on various agents - ? in remission.
122	M.P.	Chlorpropamide	Persistently low fasting levels on small dose of chlorpropamide.
47	J.F.	Chlorpropamide +DBI	Low fasting levels persisted for 5 months after stopping hypoglycaemic agents.

Patients with a near normal glucose tolerance test and who showed marked cortisone enhancement of glucose tolerance test.

GROUP II.

Case	Name	Agent used	Comments.
127	D.R.	Tolbutamide Chlorpropamide	G.T.T. abnormal++ after tolbutamide stopped.
122	M.P.	Tolbutamide	(No enhancement when treated with chlorpropamide).
79	E.L.	Tolbutamide	Stopping hypoglycaemic agent previously produced abnormal G.T.T.
126	W.R.	Tolbutamide (xiii) page 114	Previous and subsequent G.T.T's when tolbutamide stopped show G.T.T. abnormal+. (Mild enhancement with chlorpropamide although curve remains abnormal).
162	I.W.	Tolbutamide (4.11.59) (Low F and 2 hour level)	Previous G.T.T. abnormal+ (24.9.59).

DISCUSSION OF THE RESULTS OF CORTISONE/GLUCOSE TOLERANCE TESTS IN PATIENTS ON HYPOGLYCAEMIC AGENTS:

An analysis of the results shows that the least enhancement was produced by cortisone where the patients had been treated with chlorpropamide alone.

This effect was less well seen where chlorpropamide was used in conjunction with another hypoglycaemic agent to control the diabetes.

Thus 8 patients (of a total 10) who were treated with chlorpropamide alone showed either no (or mild) enhancement. In the tolbutamide treated group on the other hand, 5 patients (of a total 7) showed moderate to marked enhancement.

This difference in response was strikingly shown in the patient M.P. (Case 122): While treated with tolbutamide (1 G. daily) the cortisone enhancement of the glucose tolerance test was considerable, but on chlorpropamide (0.25 G.) the same patient showed no enhancement. A similar type of result with tolbutamide and chlorpropamide was seen in W.R. (Case 126).

Cortisone enhancement while patients were being treated with chlorpropamide was found to be less than with the other hypoglycaemic agents.

Possible explanations for this action (which was well exemplified in cases treated with both chlorpropamide and tolbutamide) are :-

1. The duration of action of chlorpropamide is longer. The half-life of chlorpropamide is 34.5 hours (Stowers et al 1959). The half-life of tolbutamide is only 2 - 5 hours.

In this connection, it is to be noted that in A.F. (Case 46) the tests were carried out in the usual way and were repeated after a preliminary dose of 50 mg. of DBI on the mornings of the second series of tests. The level of the glucose tolerance tests was lower in the second series but enhancement was still marked, i.e. in spite of the fact that concentration of the guanide in the patient's blood had influenced the level of the blood glucose, it did not significantly change the type of enhancement produced by cortisone.

2. Chlorpropamide has a more powerful hypoglycaemic effect.

Although chlorpropamide was found to be a powerful hypoglycaemic agent, this does not seem to be a likely explanation: Thus in D.R. (Case 127) in whom its hypoglycaemic effect was dramatic, cortisone enhancement was still considerable; in W.R. (Case 126), in whom the cortisone enhancement was only slight, chlorpropamide did not produce a striking improvement in the glucose tolerance test.

Thus the type of enhancement was not an index of hypoglycaemic effectiveness.

An analysis of the results of the type of cortisone enhancement of the glucose tolerance test seen in patients with near normal glucose tolerance tests showed that these fell into 2 groups (See GROUPS I and II pages 227 and 228).

I. No (or only mild) cortisone enhancement was seen in 7 patients (5 treated with chlorpropamide, 1 with chlorpropamide + DBI, and 1 with tolbutamide).

II. Marked enhancement was seen in 5 patients. (The 5 were treated with tolbutamide; one of these patients responded similarly when treated with chlorpropamide).

<u>The Subsequent course in relation to the Cortisone Response:</u>

I. In the patients who showed only slight enhancement: 1 maintained an improved glucose tolerance test after treatment was stopped (G.K. Case 76); another patient maintained the remission in fasting levels (J.R. Case 128). In all the other cases (except J.P. Case 47), the subsequent response to the hypoglycaemic agent remained excellent (or improved further) and it was very suggestive that <u>these patients too were in a phase of remission.</u>

II. In those who showed marked enhancement of the glucose tolerance test with cortisone:
(a) D.R. (Case 127) showed a severely abnormal glucose tolerance test when the hypoglycaemic agent was discontinued;

(b) R.L. (Case 79) had previously shown a grossly abnormal glucose tolerance test when carbutamide was omitted for a while;

(c) W.R. (Case 126) showed a considerably abnormal curve when tolbutamide was stopped.

(d) I.W. (Case 162) also showed a considerably abnormal curve when tolbutamide was stopped for 1 week (24.9.59).

An outcome of the findings in Group I and II is that the cortisone/glucose tolerance test in patients treated with hypoglycaemic agents might prove to be an index of what might occur if the hypoglycaemic agent were to be omitted.

Thus a previous or subsequent glucose tolerance test (<u>without treatment</u>) resembling the glucose tolerance test of cortisone + hypoglycaemic agent was seen in the following patients:

R.L.	Case 79
D.R.	Case 127
G.K.	Case 76
W.R.	Case 126
I.W.	Case 162

An inspection of individual results in the patients who showed only slight enhancement with cortisone seemed to suggest that of the remaining 6 patients, 5 were in a state of remission. Thus in 5 patients cortisone had reproduced the expected change in glucose tolerance test and in a further 5 there was suggestive evidence that it would.

It is tempting to speculate after an inspection of the results seen in Group I whether these patients were in a phase of remission when the cortisone/glucose tolerance test was done. The results seem suggestive that one patient on tolbutamide and 5 patients on chlorpropamide had gone into remission. Further study on this point is required.

(In this connection it is interesting to note that Granville-Grossman et al (1959) had reported that a glucose tolerance test with lower blood levels persisted for weeks or months after a 6 week course of chlorpropamide).

What was the significance of this finding which could be equated as follows ?

Glucose tolerance test (cortisone + hypoglycaemic agent)=Glucose tolerance test (without either).

This is a point of considerable interest in this section where we are investigating the influence of cortisone in patients who are being treated with hypoglycaemic agents.

The action of Cortisone in relation to Hypoglycaemic Agents:

Cortisone is generally believed to increase gluconeogenesis by the liver by resulting in an increase in liver transaminase activity. Increased liver transaminase activity has been demonstrated in animals as a result of cortisone administration (Brin et al 1956, Gavosto et al 1957).

This has also been confirmed by Rosen et al (1958) who suggest that the steroids exert their gluconeogenetic activity by virtue of their effect on liver-transaminase.

Patrick et al (1959) pointed out that various conditions - glucocorticoid administration, high protein diet and starvation - which are associated with

increased liver gluconeogenesis, are accompanied by an increase in transaminase activity.

It has been reported too that in alloxan diabetic rats there is a distinct increase in liver transaminase activity (Copenhauer et al 1951).

Patrick et al (1959) showed that in most of the cases of diabetes they investigated, the transaminase activity of the liver cell is reduced by treatment of the diabetic state - regardless of the type of diabetes and whether treatment was by diet alone or insulin as well.

Bernstein (1957) has demonstrated inhibition of alanine transaminase by the two sulphonylurea compounds carbutamide and tolbutamide and has suggested that these compounds exert their hypoglycaemic effect by inhibiting transamination in vivo. It is suggested that by inhibiting transamination, such compounds decrease the rate of neoglucogenesis and hence lower the blood sugar. Increased hepatic gluconeogenesis is the most readily demonstrated metabolic effect of the steroids and has been established in isolated liver

as well as in the intact animal and human organism (Thorn et al 1957).

Do the hypoglycaemic agents inhibit gluconeogenesis as has been suggested by Bornstein (1957) ?

Could the results found in this study of the opposing effects of hypoglycaemic agent and cortisone be used as evidence that the hypoglycaemic agents act, as suggested by Bornstein, by inhibition of alanine transaminase?

Where cortisone has failed to produce enhancement does this signify that the hypoglycaemic agent has produced its effect by countering the action of cortisone (i.e. by inhibiting hepatic gluconeogenesis or alanine transaminase activity) ? If the hypoglycaemic agent produces its effect in this way is it that severe enhancement is seen in some cases who are well controlled with the hypoglycaemic agent ?

This would suggest that in these cases at least, the hypoglycaemic effect is achieved by a mechanism other than by alanine transaminase inhibition.

CONCLUSION:

In the cases described in this section, the degree of cortisone enhancement may be an index of the subsequent course of the patient, but not of the hypoglycaemic effectiveness of the agents.

VIII.

DISCUSSION OF THE STUDY AS A WHOLE:

The action of insulin:

From the available evidence at the present time it seems that the suggestion made by Levine and his colleagues (1949 and 1950) that the key point in the action of insulin is on the permeability of the cells to glucose, is the correct one.

This suggestion has also been supported by the work of Park (1953) and by Drury et al (1952). Insulin accelerates the transfer of glucose from the blood or extracellular fluid into the fixed tissues of the body. Its principal site of action therefore, is the cell membrane.

There is now no real evidence to support the previously held view of an accelerating effect of insulin on the intracellular catabolism of glucose.

The work of Villee et al (1949) on the intracellular action of insulin in in vitro preparations, has not been supported by the results

of experiments on intact living animals where the rate of disposal of pyruvate and lactate did not seem to depend on the presence or absence of insulin (Flock et al 1938). More recent experimental work on completely diabetic animals (Ingle 1951) has demonstrated an increased utilisation of glucose by muscle during muscular exercise in the complete absence of insulin.

In discussing the mechanisms of insulin action, Stadie (1955) has indicated that the possible biochemical lesions in diabetes may be concerned with:

(1) the permeation of glucose through the cellular barriers to sites of enzymatic action,
(2) the activation of glucose by reaction with adenosine triphosphate to form glucose-6-phosphate,
(3) the production and storage of high-energy phosphate compounds such as ATP and creatine phosphate,
(4) the defects in the oxidative reactions particularly of derivatives of glucose.

Whereas the action of insulin on the cell

membrane seems well established, the suggested action on the hexokinase reaction (2) as well is still uncertain. It seems likely then, that after glucose has entered the cell it is not dependent on the action of insulin.

Inside the cell, glucose follows one of 3 main paths:

(i) Conversion into glycogen

(ii) Conversion into fat or protein

and (iii) Oxidation to CO_2 and H_2O.

Insulin in relation to Diabetes in man:

The present evidence for the existence of 2 main types of diabetes in man is considerable, and probably generally accepted.

Two clinical types of diabetics have long been recognised:

1. The young diabetic who rapidly loses weight and becomes ketotic without insulin: the so-called Juvenile type or 'Growth-onset' type. (This type occurs at any age, but mainly in the young.)

2. The 'Maturity-onset' type of diabetic: obese and of an older age group who can generally be managed without insulin.

According to their mode of response to insulin the 2 types have also sometimes been classified as the insulin sensitive group (the juvenile type) or the insulin resistant group (Maturity-onset type).

Pathologists had noted that in a large percentage of diabetics they were unable to detect any morphological changes in the islets of the pancreas at autopsy. Warren (1938) reported that 26% of the autopsies in his series of diabetics revealed essentially normal islets. Wrenshall et al (1952) found that whereas the growth-onset type of diabetics have practically no insulin in the pancreas, the insulin-content of the pancreas of the maturity-onset diabetics was approximately half that of non-diabetics.

The final evidence in support of the clinical subdivision came with the report by

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Bornstein and Lawrence (1951) that there was no available insulin in the plasma of the juvenile type but that the plasma of the maturity-onset diabetics contains available insulin (roughly 70% of normal controls). The 2 groups can therefore be broadly divided into:

(a) Diabetics with insulin deficiency and

(b) Diabetics-without-insulin-deficiency.

From the available evidence it might be deduced that an insulin lack is probably not the factor responsible for the maturity-onset type of diabetic.

From this, it would appear that while diabetes due to insulin deficiency will be corrected by the administration of insulin, diabetes-without-insulin-deficiency will not be fully corrected by the administration of insulin alone.

The metabolic lesion in this type of diabetes seems to occur in the intracellular metabolism of glucose. Is it due to an interference with the enzyme systems (i.e. the enzymes or coenzymes) which

are concerned with activities of intermediary metabolism such as oxidation-reduction, cleavage, group transfer and removal or addition of water, phosphate, CO_2 and ammonia? Is such an interference independent of hormonal control?

The intracellular metabolism of glucose is dependent on the integrity of various enzyme-coenzyme systems. In SECTION III of this thesis the importance of the coenzymes DPN and TPN in intermediary metabolism was discussed. Does the metabolic lesion in diabetes - the earliest deviation from normal - occur in these coenzymes?

The Metabolic Lesion in Diabetes:

A defect in the coenzymes would produce a widespread derangement of carbohydrate metabolism and of the interconnected protein and fat metabolism as is apparent after the consideration of its multiple functions in intermediary metabolism previously discussed (SECTION III page 26).

That a block in intermediary metabolism can produce widespread effects, from a disturbance of function to death of cells, is seen in sodium

fluoroacetate ('SFA') poisoning. Thus in sodium fluoroacetate poisoning (the toxic principle of the South African plant, 'gifblaar'), Peters was able to demonstrate that fluoroacetic acid was transformed to fluorocitrate and this jammed the oxidation of citrate leading to abnormal accumulation of citrate (Peters 1954, Liebecq and Peters 1949).

In 'SFA' poisoned rats diabetes was noted (Engel et al 1954). The hyperglycaemia and ketonaemia of the 'SFA' poisoned rats was interpreted as representing diabetes mellitus secondary to the metabolic effect of 'SFA' on the tissues in general, or to a more specific effect of 'SFA' on insulin production by the beta cells of the pancreas. The metabolism of both carbohydrate and fat within the cell is 'jammed' at the citric acid stage and metabolism is slowed or stopped.

This is an excellent example of a <u>purely biochemical lesion</u> in the cell producing a widespread disruption of cellular metabolism. Can diabetes be similarly produced by an interference at the

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enzyme-coenzyme-substrate level?

DPN is of vital importance in carbohydrate metabolism. Does the metabolic lesion in diabetes occur at this point?

Disturbances of DPN (See also SECTION III pages 37-39):

DPN may be interfered with in various ways. Nicotinamide is its most active component. It has been shown that a variety of analogues of nicotinamide i.e. anti-metabolites can replace nicotinamide in the molecule of DPN (Woolley 1945). INH is one such anti-metabolite of nicotinamide (Zatman et al 1954 (a) and (b)) and there have been reports of aggravation of diabetes and a disturbance of carbohydrate metabolism in non-diabetic tuberculous patients treated with INH (Luntz et al 1953). Whether a mechanism similar to this occurs naturally is still problematical. If such a mechanism were shown to operate naturally, it would be of great interest.

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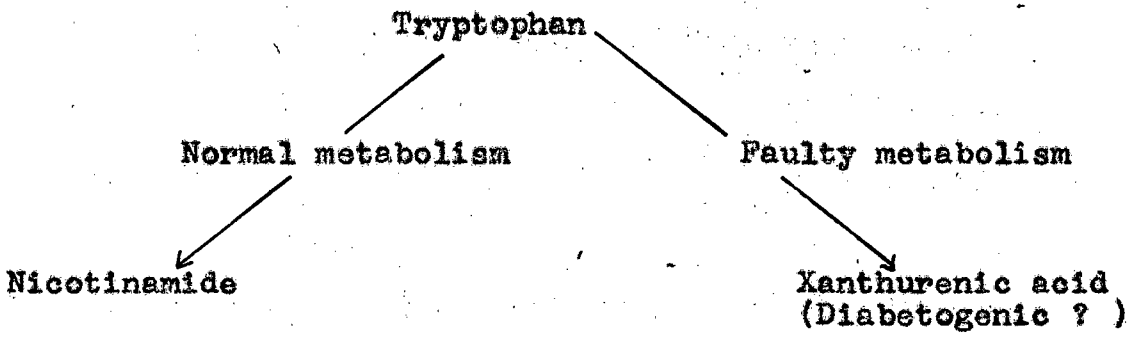
Substances related to nicotinamide which are known to occur in metabolism in man:

In man, nicotinamide is formed from tryptophan.

In SECTION III it was stated that xanthurenic acid can be formed from tryptophan. Its formation can be diagrammatically shown as follows:



This may prove to be a product of great interest in studies of diabetes. Kotake (1955) has summarised a series of experiments carried out by him and his associates which indicate that xanthurenic acid caused diabetes in rats and that it may be a factor which is operative in man as well.

Tryptophan metabolism in relation to nicotinamide and Xanthurenic acid:

Animal experiments indicate that tryptophan

appeared to be more important than nicotinamide in maintaining liver pyridine nucleotides even though nicotinamide is present in these nucleotides (Williams et al 1950 and 1951).

Pyridoxine has been shown to be necessary for the conversion of tryptophan to tissue pyridine nucleotides (Kring et al 1952) and for the conversion of tryptophan to nicotinic acid (Sarett 1950, Sarett et al 1950). When there is a pyridoxine deficiency xanthurenic acid is formed instead of nicotinic acid.

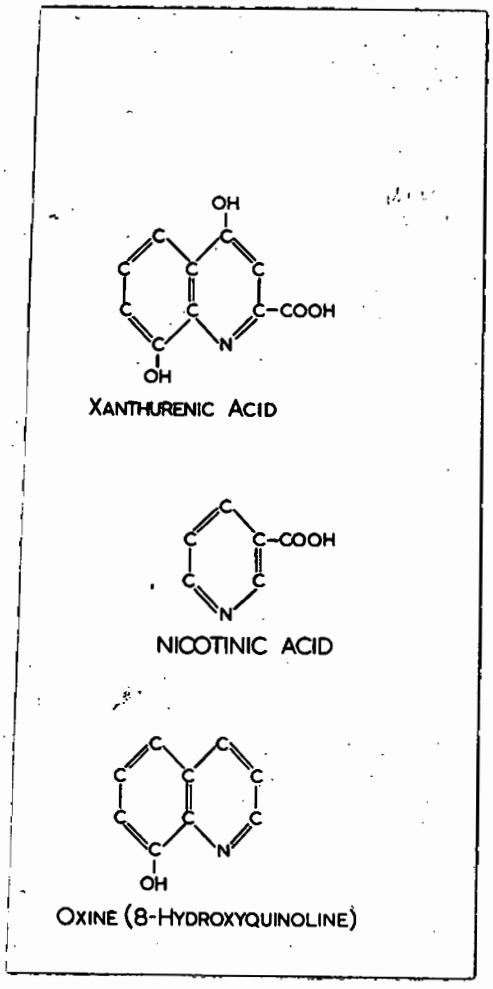
An increase in xanthurenic acid excretion was found after high doses of INH when tryptophan was administered (Biehl et al 1954 (a) and (b)). (Compare the finding of Luntz et al (1953) of an aggravation of carbohydrate tolerance when INH was given to tuberculous patients).

Xanthurenic acid has been found to be present in the urine of diabetic patients in greater quantities than in normal man (Rosen et al 1955).

Xanthurenic acid has a structure similar

to oxine (8-hydroxyquinoline) which has been shown to be diabetogenic in rats (Kadota 1950).

The structural formulae of oxine, xanthurenic acid and nicotinic acid are shown:



Are the substances, xanthurenic acid and oxine, diabetogenic by virtue of an action which interferes with nicotinamide in DPN, i.e. are these substances anti-metabolites of nicotinamide?

Kadota had attributed the diabetogenic effect of oxine to its chelating action; but subsequently (Kadota 1951) he has found that several related products did not produce diabetes in spite of the fact that they were equally or more effective as chelating agents.

The chelating action does not seem to be the likely explanation, therefore, and we are left with the previous suggestion that xanthurenic acid and products similar to it may be diabetogenic by virtue of a possible anti-metabolic action in relation to nicotinamide.

It has been pointed out that a low concentration of a critical enzyme or coenzyme in the beta cells may be responsible for the production of diabetes (Lazarow 1949). It has been shown (in the production of diabetes) that the interference of cellular metabolism need not occur only in the beta cells, e.g. SFA diabetes (also, in view of the fact that the diabetes of maturity onset is not dependent on insulin deficiency are we perhaps not overstressing the part played by pancreatic destruction when considering the diabetogenic activity of a substance?)

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The question for consideration here is whether a low concentration, or a qualitative or quantitative alteration, of the coenzymes DPN and TPN are responsible for the production of diabetes?

An anti-metabolite could bring about such an alteration in the coenzymes and it is very tempting to postulate that substances like xanthurenic acid and related diabetogenic products act in this way. Up to the present time there has been no evidence that this actually occurs.

It has already been stated in SECTION III that nicotinamide has been reported to prevent alloxan induced diabetes in animal experiments (Lazarow et al 1950 and Banerjee 1947).

In view of the important role of nicotinamide in the coenzymes DPN and TPN, it was decided to test the effect of nicotinamide administration in large doses over a long period to patients with diabetes. (In man the concentration of DPN and TPN can be increased by the ingestion of large amounts of nicotinamide (Axelrod et al 1940, Kohn et al 1938, Handler et al 1943).

Blood glucose levels and glucose tolerance tests were used as the index of progress in these cases. It was found (see SECTION IV) that several (20) of the nicotinamide treated group showed improvement and in some of these patients a remarkable improvement in glucose tolerance tests was noted to normal or near normal; in the majority of the treated diabetics (28), however, no change was recorded.

It is difficult to assess the part played by nicotinamide in producing such complete remissions as seen in some of the cases of the study. There is a dearth of such long term studies of diabetes in the literature; but remissions in diabetes are recorded. These reported cases of remission have not been studied as comprehensively (with records of glucose tolerance tests before and after remission occurred). It is possible that if there were reports of similar long term studies, remissions similar to those demonstrated in this thesis may be recorded in the natural course of the disease. At present there is suggestive evidence only that nicotinamide may have played a part in producing the completeness of the remissions seen.

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It seemed possible that nicotinamide may have favourably influenced the course of the diabetes in some of the diabetic patients of the study; but it must be pointed out that a failure of response to nicotinamide administration does not rule out the possibility of the existence of a mechanism of production of diabetes dependent on interference with the coenzymes DPN and TPN, e.g. if irreversible intracellular changes have already occurred as a result of the changes produced. In this connection it may be pointed out that there is evidence of a change in diabetic response (to treatment) with the passage of time, e.g.

(1) Remissions have been noted to occur in diabetes (of recent onset) shortly after the commencement of treatment with insulin - i.e. the insulin requirement may decrease for a while.

(2) Remissions in diabetes can be induced by weight loss - if these patients have a relapse in diabetes after regaining weight a second attempt at inducing a remission by weight loss will not succeed. This was pointed out to me by Professor Linder (1954) and

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since then I have been able to confirm this in patients observed at the diabetic clinic.

This latter type of response was seen in other instances as well. Remissions seen in the nicotinamide treated patients lasted for a variable time (in some for years) and were then followed by a relapse of diabetes when there was a failure of response to nicotinamide treatment. These same patients in whom there was this relapse of diabetes, when treated with tolbutamide, showed an excellent remission - in some to a normal glucose tolerance test. After the passage of a variable time, this response was followed by a relapse in the diabetes once again (or the recurrence of grossly abnormal carbohydrate tolerance) in spite of continued tolbutamide administration (secondary tolbutamide failure).

At this point it might have been thought that these patients had developed a more severe type of diabetes (e.g. the juvenile type), yet clinically, they were still behaving in the same way as the maturity onset diabetics and this was confirmed by a

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good hypoglycaemic response to another sulphonylurea drug, chlorpropamide.

Riboflavine in Diabetes:

A point worthy of mention was the incidental observation that in the patients who received riboflavine (15 - 45 mg.) over a long period of time, there seemed to be some elevation of the fasting blood glucose levels and of the glucose tolerance test. Thus, riboflavine may have seemed to behave as a diabetogenic agent in these patients. It is of interest that some workers should have suggested that in the metabolic breakdown of riboflavine, alloxan may be formed (Banerjee et al 1945).

Potassium Salts in Diabetic Patients:

The observations on the effect of the administration of potassium salts (300 m.Eq. daily) were continued for up to 2 months. It was found that potassium produced a uniform elevation of the fasting blood glucose level in these diabetic patients.

Pharmacological Hypoglycaemic Agents in Diabetes:

The most striking outcome of the long term study on these patients was the demonstration of remissions in glucose tolerance test to normal or near normal after administration of these agents.

The changes noted in glucose tolerance tests:

This study showed that there were gross fluctuations in glucose tolerance tests under the influence of various agents. Patients who had been shown to have severe abnormalities in glucose tolerance test were shown to remit to the extent of having a normal glucose tolerance test. In the same patient the form of the curve was shown to vary considerably from time to time. This could best be seen by an examination of the illustrations in the individual cases.

It was possible to classify the patients who showed a good fasting hypoglycaemic response into 2 types:

(1) those who had a normal or almost normal glucose tolerance curve during treatment,

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(2) those who had a low normal, a normal, or near normal fasting level but <u>considerable elevation of the rest of the glucose tolerance curve.</u>

This long term study of fluctuations in glucose tolerance tests during diabetes showed that the previously held view that there was merely a general lowering of the curve after treatment could not be applied to the results seen in the patients of the study.

Although 2 cases in the first group may have demonstrated this effect by merely a general lowering of the curve, the majority showed a change in form of the curve, e.g. low fasting and 2 hour levels were often demonstrated in the glucose tolerance tests.

<u>The Mechanism of Action of the Hypoglycaemic Agents:</u>

This is still not understood. Various suggestions have been made for the mode of action of sulphonylureas. Loubatieres had suggested a stimulation of insulin secretion. Pancreatectomised animals showed

no fall in blood sugar following IPTD but partially pancreatectomised animals did show this response (Loubatieres 1944 and 1946). Mirsky (1956) postulated that they acted as 'insulinase inhibitors', i.e. the action of insulin was enhanced by inhibition of its destruction.

These are the views most generally held at present, i.e. the sulphonylureas act by increasing the amount, or the effectiveness, of insulin.

It seems likely that their effect is independent of insulin. The diabetics who are benefited by the sulphonylureas, have been shown to have plasma insulin; the sulphonylureas do not enhance the action of administered insulin in the juvenile type. It seems far more likely that their action is on the intracellular metabolism of glucose, i.e. beyond the insulin level.

In this study the biguanides were shown to be effective in a group of diabetics who were not benefited by a trial of all the sulphonylurea drugs.

These were all of the maturity onset. With the exception of one, whose commencement was under 40 years, all were elderly diabetics. Some of them, however, were being controlled with insulin prior to the institution of the biguanide therapy.

It was found too, that in a few of the younger diabetics, who had severe juvenile type diabetes (established for some years) and who required large doses of insulin, the biguanides improved diabetic control on a smaller dose of insulin. This effect was never seen in established diabetes of the juvenile type with the sulphonylurea drugs. The biguanides achieve their effect in a different way from the sulphonylureas.

DBI lowers the blood sugar in alloxan - diabetic (Ungar et al 1957), and hepatectomised (Nielsen et al 1958) animals, the degree of response being greater in the intact animal.

The latter workers suggest that DBI decreases gluconeogenesis, and that this may be one way in which it achieves its effect.

Both DBI and guanidine appear partially to inhibit, within the tricarboxylic acid cycle, the energy transfer dependent upon the coupling of oxidation with phosphorylation (Hollunger 1955).

Regarding the mechanism of action of the hypoglycaemic agents: it was hoped that interesting information might be obtained from a study of the cortisone enhanced glucose tolerance test particularly in the patients who had shown a good hypoglycaemic response to a pharmacological agent. It was suggested by Bornstein (1957) that the hypoglycaemic agents produced their effect by an inhibition of alanine transaminase, i.e. that they inhibited hepatic neoglucogenesis.

Would they inhibit this action of cortisone (see page 223) if cortisone were given? It was found that some of the cases who showed an excellent response to the hypoglycaemic agent (e.g. with a normal glucose tolerance curve) showed marked enhancement of the glucose tolerance curve when cortisone was given as well. In these cases it seemed unlikely that there

was an inhibition of neoglucogenesis by the hypoglycaemic agent.

The use of cortisone in these cases did reveal an interesting point. It was found that the cortisone test enabled a prediction of the further course of diabetes were the hypoglycaemic agent to be omitted. The response seen could be equated thus: G.T.T. (Cortisone + Hypoglycaemic agent) = G.T.T. (without either).
In those patients in whom a good remission in diabetes was seen (e.g. a normal glucose tolerance test) and no enhancement was produced by cortisone, was it possible to predict that the diabetes was in remission? The evidence was suggestive but more observations would have to be made.

It could be speculated whether the hypoglycaemic agent had in fact achieved its effect <u>in these cases</u> by an inhibition of hepatic neoglucogenesis.

<u>Carbohydrate tolerance in Gout:</u>

In a study of carbohydrate tolerance in

gout it was found that there was a high incidence of abnormality of glucose tolerance. 12% of the cases showed a frankly diabetic curve.

This study on gout was undertaken to see whether a product of intermediary metabolism - of normal or faulty metabolism - might play a part in the pathogenesis of diabetes.

In discussing the significance of the high incidence of abnormal carbohydrate tolerance in gout in SECTION VI, it was suggested that this finding was related to the faulty metabolism in gout itself. (Herman 1958). This would imply that naturally occurring substances might interfere with intermediary metabolism of carbohydrate in man.

The Adrenal Cortical Steroids and Diabetes:

The effect of the cortico-steroids on carbohydrate metabolism has been extensively studied.

Cortisone is now known to have a diabetogenic action in man by virtue of its action on hepatic neoglucogenesis. It has become an important

research tool in the discovery of potential and latent diabetes. Its effect in producing enhancement of the glucose tolerance test in diabetes has been extensively studied by Fajans and Conn (1954) and this type of work has been carried out in various centres now.

In this study the influence of cortisone on the glucose tolerance test of gouty patients has been investigated. The results have suggested that the gouty patients are at least as susceptible to the diabetogenic effects of cortisone as are a group of patients who were selected because they were considered to be latent diabetics or who were known to have had a diabetic curve or an abnormal curve before.

This could be cited as additional support for the suggestion that some inherent defect of carbohydrate metabolism exists in gout.

A surprising finding was the failure of cortisone to produce significant enhancement in more of the patients who were previously known to have had

an enhanced curve. If these patients were merely in a latent phase of diabetes (during their remissions) it was to be suspected that cortisone would provoke a manifestly diabetic curve.

Although nicotinamide had been shown in animal experiments to prevent alloxan induced diabetes, the administration of nicotinamide failed to prevent cortisone enhancement in 2 patients (one who had a diabetic curve and the other who was in a state of remission). In one patient though, with a normal curve, the cortisone/glucose tolerance curve following nicotinamide was better than the 2 preceding curves (i.e. a preceding standard glucose tolerance test and cortisone enhanced glucose tolerance test).

B

A UNIFYING CONCEPT

A UNIFYING CONCEPT:

My study of diabetes mellitus over the years has proved fascinating. In the beginning certain questions were posed and yet more have arisen as the study has progressed.

There are still many unsolved problems in diabetes. Some of them are connected with the most fundamental aspects of the disease, e.g. we still do not know where the metabolic lesion in diabetes lies; we do not understand fully the mechanism of action of insulin in diabetes; what was the significance of von Noorden's (1903) provocative, but universally confirmed, finding of the beneficial influence of the oatmeal diet which was destroyed by the addition of protein foods ?

There seems to be little doubt that the composition of the diet, particularly with reference to its protein content, may influence the development of diabetes in man (Minkowski 1892, Allen 1913, Marks and Young 1939).

What factors in man lead to the production of diabetes ? Alloxan is the best known diabetogenic agent. Does a substance resembling alloxan occur as an intermediary in metabolism in man. Loubatieres (1954) has done interesting work on this aspect but the final answer is not yet known.

Xanthurenic acid too has been reported to be diabetogenic. This substance is related to nicotinamide and both are derived from the same parent substance tryptophan.

In my studies I have sought those factors occurring in the errors of metabolism which may influence the development of diabetes.

I was struck by the many interesting correlations in the 2 most studied metabolic disturbances, gout and diabetes. The experimental evidence in animals made me go on to a study of the interconnections of these conditions in man as well.

The production of the 2 metabolic disturbances, gout and diabetes by the same agent, alloxan, in the pigeon is of fascinating relevance: Was this to presage a common underlying mechanism of production of the 2 disturbances ?

There are other features which these 2 disturbances of metabolism also share: obesity, hypercholesterolaemia, atherosclerosis, nephropathy, etc. [It is interesting to compare the incidence of these associated metabolic disturbances with that found in the South African Bantu people in whom several studies have shown the strikingly low incidence of diabetes mellitus (Politzer et al 1960). A low incidence of diabetes, low incidence of gout and of atherosclerosis. Their serum cholesterol is low and there is a low serum uric acid (Mibashan 1959)].

The high incidence of diabetes and abnormal carbohydrate tolerance in gout found in my study may be considered a further link in the association of these 2 metabolic disturbances.

The cortisone enhanced test in a group of gouty patients in this study suggested that the gouty patients

may be unduly susceptible to the diabetogenic effects of cortisone. This point requires further investigation.

The administration of A.C.T.H. causes an upheaval of purine metabolism and it has been suggested by Conn (1948) that a purine metabolite exerts an alloxan-like effect and is responsible for reducing the intracellular availability of free sulphydryl groups and this leads to the development of diabetes. Both glutathione (Conn et al 1949) and nicotinamide have been shown to afford protection against alloxan-induced diabetes in animals.

Do alloxan-like substances exert their influence by an effect on nicotinamide (Racker 1955) and glutathione ?

Nucleoproteins may serve as a reservoir of readily available material for use as coenzymes (Soodak 1955). Will it be shown that the adenine component of the coenzymes may be disturbed in the same way as the nicotinamide moiety can (Woolley 1945) ?

Is there an interconnecting link between these disturbances? Will it be shown e.g. that there is some faulty diversion in protein metabolism (e.g. at the Krebs urea cycle - a meeting point of carbohydrate, protein, and purine metabolism -) towards increased production of pyrimidine (or associated alloxan-like substances) ?

SUMMARY:

In this thesis I have pointed out the very interesting association of the two metabolic disturbances, gout and diabetes mellitus.

Cortisone has been used as a means of further investigating this association and also for studying its effect on the action of the hypoglycaemic agents in diabetes.

Physiological and pharmacological hypoglycaemic agents have been investigated.

CONCLUSIONS:

The most significant outcome of the Study:

1. In the study of the influence of nicotinamide on the glucose tolerance test, it was seen that patients who had grossly abnormal glucose tolerance curves developed glucose tolerance tests which had reverted to normal. This remission in diabetes lasted in some cases for a period of years.

2. Patients treated with the pharmacological agents showed considerable fluctuations in their glucose tolerance curves. Glucose tolerance curves during treatment differed from those before and after treatment. Some patients developed a normal curve.

3. A considerable proportion of the patients with gout showed diabetic glucose tolerance curves, or other abnormalities of the glucose tolerance curve.

4. Patients with gout were found to be more susceptible to cortisone enhancement of the curve than a comparable group.

5. Cortisone enhancement of the glucose tolerance curve was less pronounced with chlorpropamide than with any of the other hypoglycaemic agents used.

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