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"The Glucose and Cholesterol of the Blood in Diphtheria."

By

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

Schwentkner and Noel (1930)[1], who investigated the carbohydrate metabolism of clinical cases of diphtheria, observed a definite rise in the blood sugar concentration during the early stages of the disease. They also found that the blood sugar, following upon this initial increase, tended to fall progressively to a hypoglycaemic level in those cases in which the intoxication was very severe. The changes in the concentration of the blood sugar were associated with a definite decrease in the tolerance of their patients for glucose, a high maximum concentration with resultant glycosuria and an abnormally slow decline being the characteristic anomalies of the blood sugar curves obtained. Schwentkner and Noel attach to the theory of disturbed carbohydrate metabolism the pathological significance that there result, in consequence, nutritional changes in vital tissues, such as that of the cardiovascular system; whereupon they seek to explain the occurrence of the clinical phenomena for which diphtheria is noted.

Contributions to the study of carbohydrate metabolism in this disease are not new: Lereboullet,[2] (1922) showed that,

in a considerable proportion of cases of severe diphtheria, a definite hypoglycaemia was present, and that, in mild and moderately severe cases, the blood sugar was unaltered. Hector (3) (1926) first drew attention to the abnormally slow decline of the blood sugar curve in diphtheria, and noted, also, the low concentration of the fasting blood sugar in severe cases. This observer was of the opinion that the metabolic disorder passed off with the stage of intoxication, though Elkeles and Heiman (4) (1927) believed that a similar type of blood sugar curve persisted for a long time after clinical recovery.

Various theories have been advanced in explanation of the disorders found, the chief of which attribute to diphtheria the distinction of being an intoxication frequently complicated by a metabolic syndrome. Thus the theory of "diminished glycogenesis" suggests the affinity of the toxin for the islet tissue of the pancreas, whereas the theory of "increased glycogenolysis" would implicate the thyroid and adrenal glands in a specific stimulation of the toxin.

While it is possible that a diabetic or other syndrome may explain the abnormalities encountered, it seems reasonable to attribute to the toxin a more widespread effect

in which the tissue concerned with carbohydrate metabolism share, with those of the body generally, the adverse consequences of toxaemia. In this connection it is interesting to note that Josephs (5) (1927), who found an increase in the nitrogen excretion of diphtheria dogs, was of the opinion that protein is broken down by the action of the toxin. This observer noticed that the excretion of creatin paralleled the severity of the intoxication. He pointed out that the increased nitrogen of the urine was, therefore, probably derived mainly from muscle tissue, that of the heart being conjectured by him to have contributed its quota thereto.

Recent evidence, too, suggests that not only may carbohydrate be subject to abnormal reactions in diphtheria but, exemplifying the tissue lipoids, cholesterol also. Lereboullet (6) (1928) and his collaborators have shown that the cholesterol content of the blood is lowered in severe diphtheria, and that in rapidly fatal cases the fall may be considerable. Hypercholesterolaemia was noticed by them to be particularly frequent during the stage of diphtheritic paralysis. The value of cholesterol in the economy of the organism is unquestioned, and its occurrence in the white matter of the nervous system is, doubtless,

of more than casual circumstance. This consideration may add significance to these findings in view of the tendency to paralysis in the disease.

The investigation of which this thesis treats was undertaken, in a series of cases of diphtheria, with the following objects:

i. To determine the extent and duration of any abnormality which might be demonstrated to occur in the tolerance of the subjects for glucose.

ii. To study the changes, if any, in the concentration of the glucose and of the cholesterol of the blooddurine the disease.

iii. To note the relationship of any abnormal findings to the classical complications of the disease.

iv. To compare the results obtained with those of other workers.

The work involved in the investigation was carried out at Belvidere Hospital, Glasgow, between October 1st, 1932 and October 8th, 1933. I am indebted to Dr. Thomas Archibald, Physician Superintendent of that institution, for many facilities extended to me. I am particularly grateful to him for making it possible for me to obtain all of the apparatus and reagents required.

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CHAPTER I.

The Physiology of Carbohydrate Metabolism.

In this section there are outlined certain considerations which are relevant to the subject, and which form a necessary basis for many of the terms used and hypotheses quoted later in the work.

THE PHYSIOLOGY OF CARBOHYDRATE METABOLISM.

I. DIGESTION AND ABSORPTION.

(i) Digestion. From the moment of ingestion until absorption takes place the digestive influences acting upon carbohydrate are of the nature of ferments. These ferments enter the gastro-intestinal tract in the secretions of the saliva, the pancreatic juice and the succus entericus. For optimum activity they discriminate between degrees of acidity and alkalinity of the medium in which they act.

The first of these digestive influences is the Ptyalin of the saliva. The effect of Ptyalin is most pronounced in a feebly acid medium, though it may also proceed to a lesser extent in one which is alkaline or even neutral. A necessary preliminary to its effectiveness upon starch is that the containing envelope of cellulose must first of all be burst. From this it follows that its action is greatest upon the cooked starches. Ptyalin digestion continues only up to the point when the reaction of the gastric contents becomes excessively acid. Under its influence starch passes through the stage of erythro-dextrin and is converted chiefly into achro-dextrin, though to some extent also into maltose.

Whatever the stage of conversion reached in the stomach, however, all forms of starch are rapidly and completely transformed into maltose by the action of amylase of the pancreatic juice. Its action is favoured by the presence of bile salts and takes place in an alkaline medium.

Acted upon by three ferments of the succus entericus, cane sugar or saccharose is converted into glucose and laevulose, maltose into glucose, and lactose into glucose and galactose. These three ferments are respectively Invertase, Maltase and Lactase, and they have in common the function of reducing sugars to the condition of monosaccharides, which are the end products of carbohydrate digestion. The chief of these monosaccharides is undoubtedly glucose.

(ii) Absorption. The monosaccharides are absorbed into the portal vein and are carried to the liver. Laevulose and Galactose may there be converted into glucose, most of the glucose being transformed into Glycogen and stored in the liver as such. Some glucose passes through the liver into the systemic circulation, a phenomenon which may be demonstrated to occur by means of a blood sugar curve.

II. THE SUGAR OF THE BLOOD.

(i) In the fasting Subject. In the normal subject in the fasting state the concentration of sugar in the blood, expressed as a percentage, is found to lie somewhere between 80 and 100 milligrammes. This is spoken of as the fasting blood sugar or glycaemia. Whilst variations within these limits may occur physiologically, there are certain pathological states in which the fasting blood sugar level is abnormally high or low, the terms used to signify these conditions being respectively Hyperglycaemia and Hypoglycaemia.

(ii) After the ingestion of Glucose. When the blood sugar is investigated in man at short intervals after the ingestion of 25-50 grams of glucose, very constant results are obtained, which when plotted on a graph with percentages of sugar as ordinate against the corresponding time intervals as abscissa, constitute a blood sugar curve or glucose tolerance test. For this purpose specimens of blood are withdrawn at half-hourly intervals after the administration of a solution of glucose. Half-an-hour after the ingestion of the glucose, the blood sugar concentration is

found to rise from the fasting level of 80-100 milligrams per cent. to 140-170 milligrams per cent. During the next hour the blood sugar falls steadily to its original level, as the tissues remove glucose for energy purposes or for storage as glycogen.(1)

III. THE FACTORS CONCERNED IN THE PRODUCTION OF THE NORMAL BLOOD SUGAR CURVE.

(i) Historical. At one time it was believed that the blood sugar concentration remained at a practically constant level and that even a large carbohydrate meal produced no increase in the amount of sugar circulating in the blood. It was thought that the liver prevented any rise in the blood sugar concentration and that if hyperglycaemia resulted through the liver failing in its functions the excess of sugar would be excreted immediately in the urine.

In 1911, however, Baudouin(2) found that there was a slight increase in the blood sugar one hour after a meal, an observation that was confirmed by Frank(3) and also by Reicher and Stein.(4) Two years later, Jacobson(5) showed that the rise in blood sugar occurred much earlier than one hour after a meal, and might even be present within

five minutes. A maximum concentration was usually reached in from 15-30 minutes after the administration of glucose and in seven of Jacobson's cases a return to the normal level had occurred by the end of an hour. These observations have been confirmed by McLean (6) and others.

(ii) Theories. The rapid rise in the blood sugar concentration which occurs immediately after the ingestion of glucose is an expression of the fact that absorption is taking place and is doing so at a rate slightly in excess of that of storage and utilization.

The fall which occurs in the normal curve soon after the maximum concentration has been reached is less easily explained. It might be due to:-

a) The cessation of absorption.
b) The excretion of sugar in the urine.
c) The increased oxidation of sugar.
d) The rate of storage exceeding the rate of absorption.

That the first cannot be held to explain the matter is obvious by instancing the fact that in the diabetic the blood sugar often continues to rise after the elapse of an interval, when, in the normal, it has commenced to fall. The second possible explanation is untenable, since glycosuria does not develop in the course of a

normal glucose tolerance test. With regard to the third, there is reason to believe that the absorbed sugar is in part burned up at once. It is well known that both heat production and the respiratory quotient rise immediately after a carbohydrate meal. Gephard and Du Bois[7], who studied this, showed that the rise and fall in the respiratory quotient occurred in 1½-2 hours, during which time the metabolism of their subjects closely approached the basal. Under the circumstances of this experiment it is hardly possible that the amounts of sugar administered (30-60 grams) could be completely used up. It would represent the utilization of 123-246 calories from carbohydrate alone, an occurrence the more unlikely since metabolism was at basal rate.

Johannson[8] has furthermore shown that, after the ingestion of 200 grams. of glucose the carbon dioxide output remains raised for as long as six hours before returning to the fasting level. And the blood sugar has long since returned to normal.

Although, therefore, increased oxidation may be responsible for the immediate consumption of some of the ingested glucose, it cannot be held to be the whole story with regard to its disposal. The fall of the normal blood sugar curve which occurs soon after the maximum has

been reached, must be assumed therefore to be due to storage and utilization occurring at a rate slightly in excess of that of absorption.

Physiologists therefore assume the fall in the blood sugar curve to be due to the intervention of a storage mechanism, the activity of which is so great that it masks the later stages of absorption. The storage mechanism is absent or deficient in the diabetic, so that by comparing a diabetic with a normal curve, the lag in the former represents absorption and the decline in the latter storage. The contrast is all the more marked when it is remembered that in the diabetic the development of glycosuria may render less marked the expression of the rising tide of blood sugar concentration.

A striking phenomenon in the curve of the healthy subject is that, even if the ingestion of glucose is pushed to the limits of digestive tolerance, it is rarely possible to produce a demonstrable glycosuria. (9)

IV. THE STORAGE OF CARBOHYDRATE.

The question of the storage of carbohydrate is a complex one. The liver and the muscles are the great sugar storehouses of the body and condensation of sugar

occurs in these tissues in the form of Glycogen.

(i) The Liver and Glycogen. Glycogen is always present in the liver of well fed animals. It may be deposited in the liver, as McLeod (10) has pointed out, by two processes.

(a) The first of these is achieved by the condensation of glucose and other hexose monosaccharides carried to the viscus by the blood. It seems probable that the presence of insulin is necessary for this reaction, "since glycogen is stored in the liver of depancreatised dogs, following the administration of carbohydrate and insulin, and since the respiratory quotient under these circumstances rises markedly." (11) Joslin.

This formation of glycogen is spoken of as glycogenesis or the condensation of glucose and other hexose monosaccharides as glycogen.

(b) The second process by which glycogen may be stored in the liver is that of gluconeogenesis, or the new formation from protein of sugar which becomes deposited in the liver as glycogen during starvation. This takes place in the normal subject and is the mechanism by which the blood sugar is maintained at its normal level in the starving subject, and at an abnormally high level in the diabetic. The phenomenon has been observed

by others.[12] McLeod[13] speaks of this new formation of glycogen as an internal secretion of the liver by reason of which the glycogen of the liver should be regarded dynamically and not, as heretofore, statically. Under the latter conception glycogen is a mere store of the excess of carbohydrate. Dynamically it assumes the properties of an elastic reserve. The liver glycogen has been investigated experimentally under different circumstances.

During starvation, the amount of glycogen in the liver at first shows a diminution and later an increase.

When the attempt by starvation to exhaust the liver of its glycogen is augmented by muscular exercise, it is not found to be more successful.[14] Hershey and Orr, who used the combination of starvation and muscular exercise on the white rat, were unable to induce any greater reduction in liver glycogen than could be achieved by starvation alone.

It is thus clear that the liver plays an enormous part in regulating the normal blood sugar level. It is not only a storehouse of glycogen derived from carbohydrate, but its functions are greater still since it also elaborates sugar from other foodstuffs, particularly from the non-nitrogenous fraction of many of the amino-acids. Sugar formation from protein is checked by insulin.

If the liver glycogen is exhausted as a result of starvation the blood sugar is found to remain at its normal level till near the end, although sugar is continuously being withdrawn from the blood to supply the needs of the tissues. Obviously sugar is being made from other sources. This fresh sugar might be formed in the tissues generally, or exclusively in the liver. The fact that removal of the liver produces hypoglycaemia proves that the fresh sugar is formed solely in the liver. The hyperglycaemia of diabetes is dependent on the presence of the liver, since the absence of insulin minimises the formation of sugar from glycogen but allows the formation of sugar from protein to proceed unabated. The fasting diabetic with exhausted liver glycogen also shows a pronounced hyperglycaemia. It would appear therefore that the blood sugar of the diabetic is largely made in the liver from protein. Owing to the loss of the controlling influence of insulin the liver in the diabetic is elaborating sugar extravagantly without regard to the ability of the body to utilize it.

Pollak (15) and Marcowitz (16) injected adrenalin repeatedly into animals after the glycogen of the liver had been reduced to a minimum by means of fasting and strychnine convulsions. Each injection was followed by hyperglycaemia, and after the injections had been repeated

many times during several days the liver was found to contain considerable amounts of glycogen. From this experiment it would appear that adrenaline stimulates the internal secretion of glycogen in the fasting animal. This conception endows adrenaline with a reversible effect, since it is generally regarded to hasten the breakdown of glycogen, when given to animals with large glycogen stores in the liver. In short, adrenaline causes glycogen to be deposited in the liver when none is there and to be broken down and mobilised as sugar under conditions of emergency, when abundance is already present.

Liver glycogen may thus be diminished by a fall in the blood sugar in which case its mobilisation is compensatory. It may also be diminished by increased demands upon it, as for example, by starvation, by exposure to cold, by muscular exercise, and by the hypoglycaemia which results from the abuse of insulin.

Insulin exhibits similar reversible effects. When it is given without food to fasting white rats, it first of all causes the glycogen content of the liver to become reduced. Later, if a convulsive dose has not been given, this decrease is followed by an increase (McLeod).

(ii) Muscle Glycogen. The formation of muscle glycogen seems to be dependent on the sugar of the blood which may either be derived from the breakdown of glycogen of the liver or from glucose absorbed into the blood stream. In support of the transmutation of liver glycogen and its resynthesis in the muscle, there is the evidence of a fall in muscle glycogen when the liver is removed experimentally. The formation of glycogen in the muscles from the sugar of the circulating blood would appear to be dependent upon the presence of insulin. Best, Hoet and Marks[17] have shown that when glucose is added to the blood of the eviscerated preparation, no glycogen is formed in the muscles unless when insulin is injected along with the sugar. Choi[18] has further demonstrated that glycogen is formed in the muscles of non-eviscerated animals only when the pancreas is intact and not when it has been removed some hours before hepatectomy.

The glycogen store of the muscles becomes reduced when they contract. Manché[19] and Chandelon[20] by causing paralysis in the muscles of one leg while the opposite leg remained more or less active, compared the amount of glycogen in the muscles of each, and showed that glycogen becomes depleted during muscular activity, and that the

glycogen of one set of resting muscles cannot be drafted by the circulation to provide glycogen for an active set, even although the demands of the latter may be urgent.

V. THE ROLE OF INSULIN IN CARBOHYDRATE METABOLISM.

It may be assumed, therefore, that just as the prolongation of the blood sugar curve in diabetes is due to a deficiency in the internal secretion of the pancreas, so the rapid fall in the blood sugar curve in the normal is due to the integrity of the pancreas and its hormone.

The modus operandi of insulin has not yet been fully established. It is probable that it acts chiefly in the liver and in the muscles, that its action is both synthetic and oxidative in character, and leads to the formation of glycogen together with hexose phosphate and the intermediate sugars from glucose, and also to an oxidation of the latter.

That all the tissues, however, may be acted upon by insulin has been demonstrated by Bücher and Gräfe (21) who have demonstrated a rise in the oxygen consumption and respiratory quotient of thin slices of different tissues in an oxygenated Ringer's solution containing glucose, when insulin is added to it.

VI. INSULIN AND THE ISLETS OF LANGERHANS.

1. Historical. More than a decade has elapsed since Banting and Best demonstrated that the specific anti-diabetic hormone could be successfully isolated from the pancreas.

Minkowski and von Mering (30) had already shown that the extirpation of the pancreas in dogs produced a condition closely resembling diabetes mellitus. Minkowski also produced evidence that if a portion of the excised gland was transplanted below the skin diabetes and glycosuria did not develop. If the graft was subsequently removed, however, a fatal issue resulted from diabetic coma.

Laguesse (31) ligated the pancreatic ducts with resulting atrophy of the externally secreting glandular tissue. Glycosuria did not develop, the thin strip of connective tissue which remained presumably retaining the ability to elaborate the unknown factor. If this remnant of tissue was removed, diabetes and glycosuria resulted.

This experimental work established the dual nature of the pancreatic function. It became evident that the specific anti-diabetic properties of the pancreas were affected through the medium of an internal secretion. Opie (31) was the first to suggest that the islet tissue of Langer-

hans was concerned with the production of this internal secretion, a view that has gained universal acceptance in modern times.

The search for the anti-diabetic hormone culminated in the discovery of Banting and Best (32), who isolated from the pancreas a substance which they called insulin. Unlike pancreatic substances hitherto prepared, which had been abandoned owing to the severe local reaction following upon injection, they found that insulin was suitable for parenteral administration. When injected subcutaneously it lowered the blood and urinary sugar of depancreatised animals.

(ii) Islets of Langerhans. Scattered between the externally secreting alveoli of the pancreas are small groups of epithelial cells which have no connection with the secretory ducts of the alveoli. These islets have an abundant blood supply and contain two different kinds of cell distinguishable by the reaction of their granules to intra vitam staining with neutral red. The alpha granules are fixed in alcoholic solution while the beta granules are fixed in watery solution. In diabetes mellitus in man gross macroscopic changes in the pancreas are not usually found post mortem, but if the pancreas is

examined microscopically shortly after death, it is said that oedematous changes are found in the beta cells of the islets. (21).

(iii) Preparation of insulin. Insulin is prepared from the mammalian pancreas. The glands are removed as quickly as possible after the death of the animal and are rapidly frozen to preserve the active principle from the effects of autolysis which would otherwise set in. As required the glands are removed from cold storage and processed by mincing in an alcoholic solvent. The alcoholic extract is evaporated to small bulk in vacuo at 45°C., when the fat separates out and can be removed. The percentage of alcohol is increased to about 80 to remove the bulk of the inactive protein. The resulting clear solution is concentrated at low temperature by vacuum distillation, the concentrate containing the insulin in an impure condition. Various other methods of obtaining the crude insulin have been described. The above is an account of the fractional precipitation method introduced by Collip. (33)

The insulin is then purified. This may be done either by (1) the picrate method or (2) precipitation at a given hydrogen ion concentration of the solvent. By the former method picric acid precipitates the insulin as insulin-picrate.

This is separated from the total precipitate of picrates by means of acetone in which the insulin picrate is alone soluble. By the latter method the insulin, obtained in crude form by fractional precipitation in various solvents, is precipitated within a given pH range - 5 to 5.7 - of the solvent.

(iv) Properties of Insulin. Insulin in its usual form, the hydrochloride, is a white powder, non-deliquescent but readily soluble in water. Crystalline insulin was first prepared by Abel in 1926.(34) Examination of the pure crystalline hormone shows it to be a protein of high molecular weight. It has a nitrogen content of 15.4% and a sulphur content of 3.2%.(35)

The purified insulin is dissolved in distilled water and the solution is passed through filter candles into sterile containers. The insulin solution is then adjusted to the various strengths required for clinical use. The insulin must be administered by injection. When it is administered by the mouth it is rendered ineffective owing to the action of proteolytic enzymes and to the non-permeability of the intestinal mucosa to so large a molecule.

VII. THE EFFECT OF THE ADRENAL, PITUITARY AND THYROID GLANDS UPON CARBOHYDRATE METABOLISM.

Reference has already been made to the effect of adrenalin in the transformations of glucose and glycogen. Adrenalin is the internal secretion of the adrenal medulla. This portion of the gland is composed of irregularly arranged cells, some of polyhedral shape and others of indefinite outline. The cells of the medulla, when stained with chromic acid, take on a dark brown coloration which has caused this tissue to be referred to as 'chromaphil' tissue. Large blood spaces pervade the substance of the medulla, and connector fibres of the splanchnic nerve can be traced into it to terminate around excitor cells, When the medullary substance is fixed with osmic acid, black granules can be seen which are supposed to represent the adrenalin store of the gland. After exposure of a small animal to cold, the granules are said to disappear, suggesting that, by such exposure, the gland has been stimulated to the point of exhaustion. (37)

With regard to its effect upon carbohydrate metabolism it may be said that adrenalin stimulates the conversion of glycogen into glucose in the liver. The glucose is

then poured into the circulating blood, the blood sugar rises and glycosuria will develop if the renal threshold is exceeded. If, however, no glycogen is present in the liver, adrenalin would seem to stimulate its deposition there, and, in the starving subject and the diabetic, the formation of sugar from protein also. Stimulation of the secretion of adrenalin occurs in various emergency states of which hypoglycaemia is one. The onset of the latter affects the central nervous system and impulses pass out along the sympathetic nerves to the liver and to the adrenal medulla. These impulses have as their object the mobilization of glycogen as glucose and the transference of the latter into the blood stream, to render normal the blood sugar concentration. (36) Cannon found that, at a certain critical level of blood sugar concentration, adrenalin is secreted to reinforce the nervous messages which pass to the liver. If the nerves to the adrenals are severed the hypo-glycaemia produced by insulin is more profound and more slowly recovered from than is the case in the intact animal. If the sympathetic nerves to the adrenals and to the liver are paralysed by ergotoxin, no mobilization of liver glycogen occurs. It has long been known that there is an increase

of blood sugar if the splanchnic nerves are stimulated, or if the floor of the fourth ventricle is punctured: but these results only occur if the suprerenal glands are intact.

Certain observations suggest that the pituitary gland is related to carbohydrate metabolism. Stimulation of the pituitary gives rise to glycosuria, and so, also, may the injection of pituitrin. In the condition known as acromegaly, in which the metabolic rate is often raised, glycosuria and decreased sugar tolerance are common and death may occur in diabetic coma. The condition is usually relieved by insulin. It may be due to over-secretion of pituitrin which antagonises insulin and so gives rise to a relative insulin deficiency.

If the secretion of thyroxin is abnormally increased, as in Graves' disease, the blood sugar becomes raised and glycosuria may actually occur. This effect also, is dependent upon the integrity of the medulla of the suprerenal glands.

It seems probable, therefore, that the adrenal medulla, the pituitary and thyroid glands antagonise insulin or control its action.

VIII. THE RENAL THRESHOLD.

(i) Glucose as a Threshold substance.

Threshold substances are those which are of value to the economy of the organism and are reabsorbed from the glomerular filtrate of the kidney into the circulation so as to maintain appropriate levels in the blood stream.

Richards and Wearn (22) obtained the glomerular filtrate of the frog by microscopic puncture of a Bowman's capsule with a micro-pipette made of quartz and measuring 10-20 μ in diameter. The filtrate was examined for sugar. In the normal state none could be detected either in the blood or in the glomerular filtrate. Glucose was then injected subcutaneously.

From the results obtained it was concluded that sugar must be absorbed in its passage down the tubules. If the concentration of sugar in the blood rose above a certain critical level, however, the excess was got rid of in the urine.

(ii) The Renal Threshold for sugar.

By the threshold of the kidney for sugar, therefore, we mean the percentage level above which an amount of sugar, recognisable by clinical tests, appears in the urine. The accuracy of this statement is dependent

on the assumption that dextrose is absent from the urine of normal subjects.[23] Benedict and Osterberg found that dextrose is constantly present in amounts up to 0.1 per cent in the urine of normal subjects. If this view is held, there is no such thing as a renal threshold for sugar: the latter must therefore be defined as "the critical point in blood sugar concentration, below which the sugars of the blood and of the urine run parallel, above which a large excess of sugar escapes into the urine."[11]

(iii) Variations in the renal threshold. It is a fact of common knowledge that in diabetes the concentration of sugar in the blood may be at a higher level than the normal renal threshold value, and yet no glycosuria results. Urine analysis for sugar should not therefore be taken as proof to imply that the concentration of sugar in the blood is normal. Such a condition is due to what has been called a "high renal threshold".

Just as the kidney threshold may be abnormally high, there is a clinical condition in which it is abnormally low. This condition, which is known as "renal glycosuria", was described in 1896 by Klemperer.[24] It is recognisable in a blood sugar curve by the low point of maximum concentration of sugar in the blood and the presence of demonstrable sugar in the urine.

IX. THE EFFECTS OF DIFFERENT SUGARS UPON THE BLOOD SUGAR CURVE.

The blood sugar curves obtained after the ingestion of glucose, maltose, galactose and cane sugar resemble each other. Lactose gives a slower and rather more prolonged rise. When laevulose is given, however, in moderate doses, no appreciable rise in the blood sugar concentration is demonstrable in healthy subjects. It would appear that laevulose is normally dealt with in the liver and should this organ be deficient either by reason of diabetes, toxaemia or other organic disease, laevulose will then give a blood sugar curve closely resembling that obtained with the first-mentioned sugars. This inability of laevulose to affect the blood sugar in health has caused it to be used as a test for hepatic efficiency.

X. THE DIETARY FACTORS THAT INFLUENCE THE TOLERANCE FOR GLUCOSE.

In any investigation into the blood sugar concentration it is necessary to have due regard to the previous dietary of the subjects investigated, and to draw conclusions with reserve.

It would appear that another factor enters into the formation of the normal blood sugar curve, namely the stimu-

lation, by the absorbed sugar, of the production of sufficient insulin to cause the disappearance of the excess of blood sugar within two to two and a half hours. This effect has been suggested by Sweeney[25], Lawrence[26], and others[27][28][29].

Sweeney has shown that persons who have been fed on rich carbohydrate diets for two days prior to the performance of a test for glucose tolerance have shown a marked increase in tolerance. On the other hand, persons who have been starved or fed on exclusive fat and protein diets have shown a definitely decreased tolerance for glucose.

The following possibilities suggest themselves as explanations of the foregoing phenomena.

(1) That there is an increased oxidation of glucose in those who have had an antecedent diet consisting mainly of carbohydrate, whilst in those from whose previous diet carbohydrate has been excluded, oxidative processes are decreased.

(2) That there is increased excretion of sugar through the kidneys in those of the carbohydrate group.

(3) That, stimulated by carbohydrate feeding, there is an increase in the efficiency of the Islets of Langerhans to produce insulin. When the Islet tissue is then stimulated by the glucose ingested during a glucose tolerance test, the maximum response which has become the rule, results in

a speedier removal of the excess of the glucose from the blood. The reverse obtains in those cases from whom carbohydrate has been withheld.

It is difficult to explain the foregoing phenomena in any way except by the action of endogenous insulin. If increased or decreased oxidation of the dextrose was the cause, one would have to account for the effect of the antecedent diets on this process. A reason is not clear why antecedent diets rich in sugars should cause a more rapid combustion of dextrose than diets consisting of fat or protein. The only other explanation apparent would be that there is a more rapid elimination of the excess sugar through the kidneys. This however cannot be held to be the explanation, because there is no evidence that those who had been fed on carbohydrate subsequently developed a glycosuria.

To explain these results, therefore, it is assumed that when carbohydrate in the diet is the rule, there is a more active stimulation of the production of insulin which results in a quicker removal of the excess glucose from the blood. In other words, it gives rise to a state of increased sugar tolerance. Conversely when exclusion of carbohydrate from the diet obtains, a state of decreased sugar tolerance exists.

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CHAPTER II.

The Metabolism of Cholesterol.

The sources of Cholesterol and its distribution in the body are here considered. A brief account is given of the variations in the cholesterol content of the blood in health and disease. What is known of the factors which govern its metabolism is alluded to.

THE METABOLISM OF CHOLESTEROL.

Cholesterol was first isolated in the middle of the 18th century. It is only within comparatively recent times, however, that attempts have been made to understand the principles which govern its distribution in the body in health and in disease.

Although much progress has been made in recent years with regard to the changes that carbohydrate and protein undergo in the chemical transformations within the organism, our knowledge of cholesterol remains comparatively meagre.

(i) Distribution of Cholesterol in the Body. Cholesterol is usually found together with lecithin, and is probably a constituent of all cell membranes. It is found in the red cells and in the plasma of the blood, and large amounts are present in the ovaries, in the suprarenal cortex and in the white matter of the central nervous system. The cholesterol derived from cellular disintegration in the body is said to be retained, and not excreted.

Cholesterol exists in the body in two forms, (a) a

free cholesterol, and (b), in combination with higher fatty acids, as ester of cholesterol or cholesteride. These two forms are not equally distributed in the tissues. In the brain and in the red blood corpuscles free cholesterol only is present, whereas in all other tissues, including the blood plasma, the cholesterol is present in both forms, the ester generally in somehwat greater quantity than the free form.

(ii) Sources of Cholesterol in the Food. The chief sources of cholesterol in the food are fat, cream, butter, yolk of eggs, brain, liver and kidney. When ingested in the food it is largely absorbed into the blood. Some of it is excreted in the bile, and of this, a proportion may be eliminated in the faeces, after being reduced by intestinal bacteria to coprosterol. The remainder is absorbed into the blood once more together with the bile salts.

(iii) Cholesterol of the Blood. Fat exists in the blood in various forms, (1) mainly as neutral fat, (2) as lecithine, (3) as free cholesterol, and (4) as cholesterol combined with fatty acid (cholerteride). The systemic blood fat begins to rise in from

one to two hours after a meal, and reaches a maximum in about six hours. The change is due mainly to neutral fat, being the result of an increase in the fatty acid compounds of the blood. This increase in neutral fat occurs both in plasma and corpuscles. A smaller increase in the lecithin of the blood occurs mainly in the red cells.

The amount of free cholesterol circulating in the blood after a meal may increase slightly, depending on the amount present in the food. There may also be a very slight increase in the amount of cholesteride, probably as a result of the blood cholesterol uniting with the absorbed fat.(1)

Active absorption of fat may occur without the concentration in the blood being appreciably altered. Samson Wright(2) records that 60 grammes of butter were given to eight normal men. In one case the blood fat fell, in one it remained unchanged, and in six it rose. The fat is probably removed from the blood by the liver, the tissues generally, and the fat depots.

(iv) The adrenal Cortex and Cholesterol Metabolism.

The following observations, as yet incompletely understood, suggest that the cortex of the adrenal gland may

be associated with the metabolism of cholesterol.[3] (1) The cortex has a higher lipoid content than any other organ or tissue in the body. (2) It undergoes enlargement during pregnancy, at which time the blood cholesterol has been found to undergo an increase. (3) Diets rich in cholesterol increase the lipoid content of the cortex. (4) Animals which have been fed on cholesterol prior to double adrenalectomy survive the operation for a longer period. (5) After extirpation of both adrenals the blood cholesterol is said to rise.

(v) The Physiological and Pathological Variations in the Blood Cholesterol.

The normal level for total blood cholesterol is stated variously by different observers using different methods of estimation. The values recorded are discussed on pages 89 - 93. Generally, it is taken to lie within the range of 150 and 200 milligrams per cent. While the blood cholesterol is found to vary in different subjects in health, it is remarkably constant for any particular individual. An increase in the blood cholesterol, or hypercholesterolaemia occurs physiologically during pregnancy, the increase in this case being due to a rise in the esters of cholesterol.[4]

It usually returns to normal in the first or second week of the puerperium. The blood fat is also increased during starvation.[1]

Pathologically an increase in the blood cholesterol occurs in subacute parenchymatous nephritis, in which condition it is often associated with an increase in the cholesterol ester content of the kidney.[5][6] The increase in the blood cholesterol is due to both free and ester forms. Hypercholesterolaemia has also been said to occur in cholelithiasis and obstructive jaundice,[7] and in myxcedema and diabetes.[8]

In both diabetes and starvation, fat from the depots is called upon to supply the needs of the body. The fat is transported to the liver, there to be desaturated and converted into lecithine-like bodies which the tissues can utilize. The blood lecithine and the blood cholesterol consequently rise.

A decrease in the blood cholesterol or hypocholesterolaemia, is said to occur physiologically during menstruation[8] though this finding has been contradicted by other observers.[9] Hypocholesterolaemia has been reported to occur pathologically in epilepsy,[10][11][12] and also during the febrile

stage of many illnesses due to infection. (8) It is believed to occur at the height of the fever only.

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CHAPTER III.

The Nature of the Influence of Toxaemia upon Carbohydrate Metabolism.

In this Chapter the literature of the experimental aspect of the subject is reviewed and the theories extended in explanation of the disorders are outlined.

The Nature of the Influence of Toxaemia on Carbohydrate Metabolism.

That toxaemia may have disastrous effects upon the carbohydrate metabolism of the diabetic is a fact that has gained wide clinical acceptance in modern times. It has its expression in the fear with which intercurrent infections in this type of patient are regarded.

The observation of this phenomenon has its counterpart in the realisation that toxaemia may also produce a state of diminished sugar tolerance in those who are not the subjects of diabetes. Experimentally it is possible to produce an almost analogous condition in laboratory animals, and such experiments have been the basis of the various theories which are held to explain the condition of diminished sugar tolerance, resulting from toxaemia, in man.

The pathology, both of the experimental disease in animals and of the actual disease in man, affords abundant evidence that the toxin of diphtheria has a marked effect upon the various tissues concerned with carbohydrate metabolism - the liver, the pancreas and the ductless glands. For this reason and also because the toxaemia

which it produces is capable of fairly accurate measurement in respect of dosage, diphtheria toxin lends itself to, and has been widely used in, comparative experimental studies aimed at determining the influence of toxaemia on carbohydrate metabolism. In consideration of its known effects the diphtheria toxin has also been applied, conversely, to the elucidation of physiological problems pertaining to normal carbohydrate metabolism.

To explain disordered carbohydrate metabolism in the presence of toxaemia the following theories have been advanced by different workers on the subject.

I. Toxaemia interferes with the production of endogenous insulin and causes diminished glycogenesis.

II. Toxaemia causes a stimulation of the thyroid and adrenal glands and brings about increased glycogenolysis.

III. Toxins actually destroy, inactivate or inhibit insulin in a manner similar to that by which the latter is broken down by pancreatic trypsin.

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(1)

I. Sweeney and Lackey tested the tolerance of glucose of rabbits suffering from varying degrees of toxaemia produced by subcutaneous injection of a dose of diphtheria toxin such that death occurred in from 5-7 days. This

dose was found to amount to .0075 - .01 c.c.m. of the particular toxin used, the minimum lethal dose of which equalled .03 c.c.m.

All the animals used, including the controls, were starved during the experiments in order to eliminate effects due to diet. On the day preceding the administration of glucose all food was removed from the animals cages water alone being allowed. On the following day each animal was given 5 grams. of glucose in 25 c.c.ms. of water, by means of a stomach tube. Samples of blood were drawn from the marginal vein of the ear, and the blood sugar was estimated before, and 30, 60, 90, and 120 minutes after, the administration of the glucose. The tests were repeated daily until the animals died in order to observe the effect of a toxaemia of increasing duration upon the tolerance for glucose. Non-toxic rabbits were used as controls and were treated in an exactly similar manner, being observed over periods equal, in duration, to those by which the experimental animals survived the administration of toxin.

Only three toxic rabbits were used the results obtained being so marked and so uniform that additional

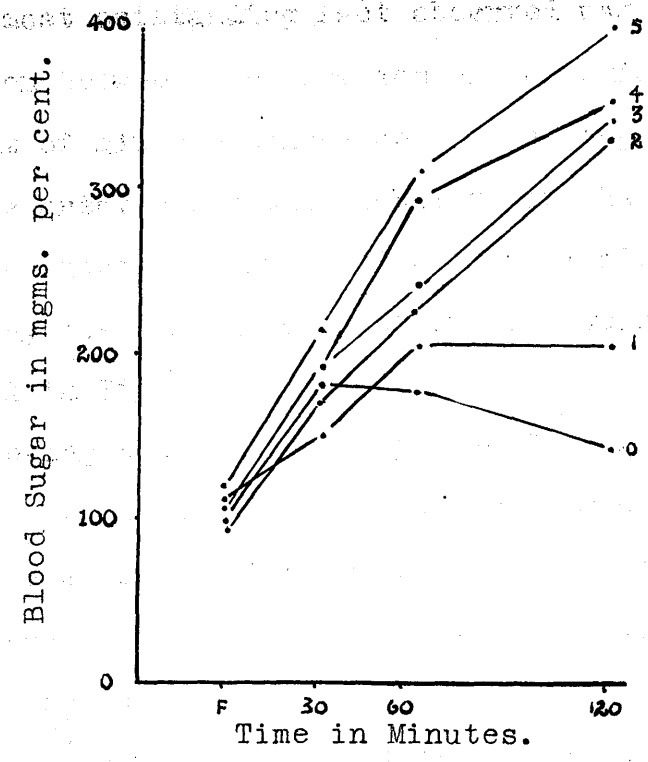

Fig. I. Daily curves showing the tolerance for dextrose of an experimental rabbit following sub--cutaneous injection of 0.0075 c.c. of diphtheria toxin. The numbers at the end of each curve indicate the duration of the toxaemia in days. (After Sweeney.)

observations were considered unnecessary. Sweeney and Lackey found that rabbits poisoned thus by diphtheria toxin suffered a markedly decreased tolerance for glucose.

The most outstanding fact observed was the positive association between the duration of toxaemia and the impairment of glucose tolerance. The longer the toxaemia lasted the greater was the inability of the animals to remove the excess of glucose from the blood. The results obtained by them in the case of one of their animals are reproduced in Fig.I

Believing that the principle action of insulin is one of glycogenesis, these workers suggest that the most probable explanation of decreased sugar tolerance in the presence of toxaemia is a disturbance in the action or in the production of insulin.

Sweeney (2) pursuing this suggestion further, repeated the work quoted and observed the effect of injected insulin. Rabbits were again used, the procedure followed being identical with that adopted in the previous experiments. Fifteen minutes after the administration of glucose two units of insulin were injected subcutaneously. Four rabbits were used, one as a control. Of the three

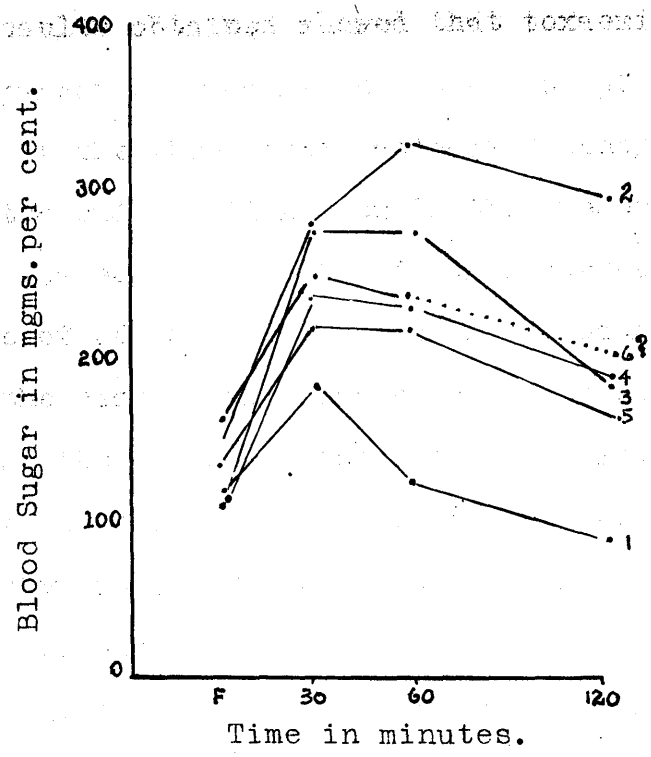

Fig. II. Daily curves showing the tolerance of an experimental rabbit for dextrose. The animal received 0.00075 c.c. of diphtheria toxin. Two units of insulin were given subcutaneously each day fifteen minutes after the administration of the dextrose. The figures at the end of each curve represent the number of days of fasting and toxaemia. (After Sweeney.)

experimental animals each rendered toxic with .0075 ccms of the particular toxin used, one lived for six, one for seven and one for eight days.

The results obtained showed that toxaemia does not cause an appreciable change in the action of injected insulin. In the three toxic animals Sweeney found a constant "two unit" action even in the presence of an increasing toxaemia. The blood sugar curves obtained in the case of one of the rabbits is reproduced in Fig. II.

From the results of these experiments Sweeney assumed that the effect of toxaemia upon glucose tolerance was principally that of an impairment of the ability to store carbohydrate. Believing the storage of carbohydrate to be brought about by endogenous insulin, he suggested that the effect of toxaemia was, directly to depress the production of insulin, since the action of injected insulin was affected little, if at all, by toxaemia. Since insulin brings about the storage in the liver of glucose as glycogen, Sweeney concluded that the abnormality of carbohydrate metabolism during toxaemia was due to diminished glycogenesis.

The view may be held that the inefficacy of insulin

in diabetics suffering from infections and toxaemia, is due to a temporary relapse of an inherently damaged pancreas. In normal subjects, disordered carbohydrate metabolism, under similar conditions and in a similar manner, may be due to the temporary manifestation of a subclinical disorder, latent during health. If the former were true the condition would not be expected to improve so rapidly as it does when the causative factor ceases to act. In the second instance it is unlikely that so many subjects have latent pancreatic defects. Without presupposing, in either case, the existence or aggravation of a pancreatic lesion, most observers do not accept the view that infection so seriously damages the pancreas as to impair its elaboration of insulin.

II. A more likely explanation is that infection and toxaemia produce a metabolic condition which will not respond to endogenous insulin in the usual way.

Lawrence and Buckley (3) found that a similar insulin resistant condition could be produced in normal rabbits after the injection of different infective and toxaemic agents. The most definite results obtained by them were achieved with diphtheria toxin. Observing the blood

sugar response before and after the injection of this toxin they found it possible to produce in normal animals a condition in which the blood sugar was spontaneously raised and in which the power to reduce blood sugar was greatly diminished and sometimes absent.

The effect of a small dose of insulin upon the blood sugar was observed. Toxin was then given .004 c.c.m. being most successful in ensuring the death of the rabbits in 4 - 7 days. The effect of a similar dose of insulin was observed daily till the animals died.

They found (1) a great tendency for the fasting blood sugar to vary, from time to time, between 90 and 150 mgms. per cent. Their rabbits refused all food after the second or third day. Since by this time the glycogen store of the liver and muscles is reduced to the point of exhaustion, they regard the variations in the fasting blood sugar as due to variations in the rate of production of sugar from endogenous sources such as protein and, possibly, fat. When the blood sugar is high, either an excessive production of sugar is taking place from these substances (gluconeogenesis) or mobilization of what glycogen has been stored from this new sugar is

suddenly taking place. It is probable that new formed sugar from other substances passes through the stage of glycogen, because a liver that has been deprived of glycogen by starvation or strychnine convulsions gradually recovers a certain amount of glycogen as the starvation proceeds. This has been referred to on page ? where it was noted that adrenaline has a reversible effect - causing deposition of glycogen in the liver when none is there and bringing about its mobilization as sugar when abundance is present.

Variations in metabolic activity by causing varying rates of sugar utilization will bring about fluctuation in the blood sugar level. Lawrence and Buckley's animals, however, crouched at the bottom of their cages all day. The variations in the fasting blood sugar concentration would appear to be due therefore to a periodicity of adrenal thyroid function, antagonising insulin at all times but in varying degree. Overactivity of this function would result in increased gluconeogenesis maximum depression of the insulin effect and a relatively high blood sugar concentration. Exhaustion of the adrenals, or paralyses of their function, on the other hand would lead to suppression of gluconeogenesis,

minimum depression of the insulin effect and a relatively low blood sugar concentration.

(2) Lawrence and Buckley also observed a prelethal rise in blood sugar in those rabbits whose death was prolonged until the 7th day, whereas in those animals where death followed within a day or two of the injection of toxin the blood sugar remained low. Since ergotoxine prevents the mobilization of sugar from the liver by sympathetic impulses and adrenalin, and so prevents the prelethal rise in blood sugar, they conclude that the latter is due to terminal glycogenolysis from the liver, brought about, probably, by the final reaction of the adrenals to falling temperature, with which they correlate the condition, and by approaching dissolution and death. Cramer (page 18) has shown that when an animal is exposed to cold, great depletion and final exhaustion of the adrenal gland occurs.

In those animals in which death occurred early and was associated with a low blood sugar, it is conjectured that the adrenal was paralysed from the commencement by the large dose of toxin used.

(3) In the case of nearly all of the animals used,

blood sugar curves, carried out after the injection of diphtheria toxin, revealed a diminution or failure of the hypoglycaemic action of insulin. This was most obvious when the febrile reaction wore off and when the "fixed" or chronic effect of the toxin was fully extablished. When the fasting level was low, insulin action was least.

The reversible effect of insulin has already been noted on page 11 . It forms glycogen in the muscles and liver when sugar is plentiful. When given without food to fasting animals insulin causes the glycogen store of the liver to become reduced. It also checks the new formation of sugar from protein and perhaps from fat also. In the normal animals insulin tends to lower the blood sugar, after carbohydrate ingestion. If it fails to do so in the toxaemic animal, the high blood sugar which results may be due to an overactivity of the adrenals, which causes glycogen mobilization if glycogen is available, or gluconeogenesis if the contrary condition obtains. In short the actions of adrenalin and insulin are opposite and, in this case, unequal, the balance being in favour of the former. Insulin, according to another conception, is anabolic and adrenalin is katabolic. The result depends

upon whether insulin can lower the blood sugar at all, or is, in varying degree, antagonised in this respect by the contrary mechanism. If this view of the disturbance of carbohydrate metabolism is accepted the abnormality would seem to result from increased glycogenolysis in which thyroid-adrenal stimulation, by the toxic agent, is the causative factor.

III. Karelitz (4) and his co-workers observed a girl aged 6 years who displayed peculiar reactions to insulin. On a constant diet and with a standard dose of insulin this child displayed at one time an insulin resistance and at another a hypoglycaemic response. The suggestion was made that the patient had a substance in her blood which annulled or inhibited insulin action during the resistant phases, though no pathological basis was found to explain the phenomenon.

The question arose whether the blood plasma of normal people might not, also, inactivate insulin in vitro and whether a similar, though more pronounced, effect occurred in diabetes. In the event of this proving to be the case, they thought that an explanation might be given to

the fact that diabetes becomes worse during infections. and after injuries or operations. Any hypothetical substance which might be held to have this effect in vitro might reasonably be conjectured to have an exalted action during spontaneously acquired diseases and intoxications in vivo.

As judged by the effect of the insulin upon the blood sugar of rabbits, they found that normal blood plasma inhibited insulin in vitro, and that this inactivation was quantitiative and governed by the time during which the reagents were incubated. Thus 1, 2 and 3 c.c. of serum had no effect upon 3 units of insulin but 4 and 5 c.c. showed definite inhibition. Complete neutralisation of the insulin occurred when this amount was incubated with 10 or 15 c.c. of serum.

It was their impression that the inhibitor was probably, of the nature of an enzyme, and since blood cells, particularly leucocytes, were likely to contain it in greater degree, they investigated the phenomenon when these were used.

5 c.c. of blood cells gave reactions similar to 10 c.c. of plasma, but no consistent reaction was obtained unless

the blood cells were first laked. When this was done, it was found that 2 c.c. of cells consistently caused a greater neutralisation than 10 c.c. of plasma or 5 c.c. of unlaked cells. As little as .5 c.c. of laked cells caused a definite inhibition.

The authors conclude that the inhibitory substance is mainly intracellular. They carried out similar experiments using various samples of blood plasma and cells, and found that diabetic blood is more inhibitory than normal blood. The blood of patients with infection affected insulin in a similar manner and to the same degree as diabetic blood. Blood from a child in the first day of an attack of serum sickness, which occurred on the 10th day after an injection of diphtheria antitoxin, showed marked insulin inactivation which was, of course, very much less than that found during the period of toxaemia. Since leucocytosis accompanies various infections, an enquiry was made as to whether white blood cells had a greater inhibitory effect than a mixture of white and red cells together. The blood of a case of myeloid leukaemia giving a count of 900,000 whites and 900,000 reds, was used. The leukaemic blood showed a greater inactivating power than did normal blood. Insulin resistance was also

noticed in rabbits after the injection of typhoid vaccine, but was inconstant.

These observations were limited to in vitro experiments. The explanation of the phenomenon is entirely conjectural. Karelitz, Cohen and Leader quote Epstein and Rosenthal to the effect that trypsin, under conditions of surmised increased permeability of the pancreatic capillaries, may pass into the blood stream with resultant inactivation of the internal secretion.(5) Collip suggested that insulin requires a complement for its action, while Lundsgaard(6) and others(7) have attempted to show that a co-ferment is necessary for the effective action of insulin upon carbohydrate metabolism.

It is conceivable that, when the cells are injured as they are during infection and intoxication, an abnormal state exists enabling a ferment to act upon insulin.

Lawrence and McCance(8), however, hold the view that insulin resistance is not due to sepsis or toxaemia but to the accompanying bodily changes. In support of this contention they described an unusual case of septicaemia caused by the staphylococcus aureus. The insulin require-

ments, after an initial increase, became pregressively less as the sepsis grew worse, the reduction coinciding with a falling temperature and a failure of reactive power.

They regard a successful termination of infective processes as being due to the activity of the thyroid and adrenal glands. If a patient's reaction fails, as in their case, it indicates that thyroid-adrenal exhaustion has come about, whereby the recognised antagonism of these glands is removed, with resultant over-action of insulin. In this way the insulin requirements became less as the sepsis grew worse and reaction failed.

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C H A P T E R IV

The Clinical and Laboratory Methods Employed.

The Clinical and Laboratory Methods Employed.

1. Administration of Glucose. The tests for glucose tolerance were carried out after a fasting period of not less than 12 hours' duration. Oral administration of a solution of glucose in water was the method adopted in preference to glucose by the intravenous route. The collapsed state of the superficial veins and the fact that the subjects of the investigation were mainly children in whom the veins are small were obvious disadvantages of the latter method. Intravenous technique, in addition, requires time and deliberation and for these it was deemed unsuitable for the investigation in hand. Advantages of the method are accuracy of dosage and absence of vomiting following administration. Vomiting, whether of cardiac origin or due to acidosis, is a common occurrence during the course of diphtheria. When it occurred during the glucose tolerance tests it was the means whereby many cases were lost for the purposes of the investigation. The balance of the factors concerned favoured administration of glucose by the mouth, and this was the procedure followed throughout. The glucose was given on an empty stomach. Pure medicinal glucose was used and it was dis-

solved in water in the proportion of 4 grams glucose to 1 fluid ounce of water.

2. Withdrawal of Blood. Capillary blood from the pulp of the finger was used for the estimation of blood sugar and blood sholesterol. Success in blood sugar work depends very much upon the technique evolved for obtaining blood specimens. The following is an account of the technique which was found to give the best results.

A set of flat surgical needles of the Hagedorn type was used. These were kept sharp on a small carborundum hone. A blunt needle, invariably, gives poor results. The finger nails were trimmed short and the hand was thoroughly cleaned by scrubbing with soap and warm water. This has the further effect of increasing the circulation through the part. Since specimens are required at intervals during 2-2½ hours (required for tolerance tests) the hand and wrist were enclosed in a clean towel applied after the manner of a gauntlet. Shortly before the withdrawal of each specimen of blood the hand was immersed in a basin of warm water which, in conjunction with light friction of the forearm, aided the flushing of the part with blood. No procedures were adopted which might cause passive conges-

tion of the fingers and thereby interfere with the accuracy of the results. In particular squeezing of the punctures in order to obtain more blood must be avoided. It was found unnecessary with the present technique.

The second finger was usually chosen. With the palmar surface facing upwards the finger was held, at the first interphalangeal joint, between the thumb and first finger of the clinician's left hand. The patient's hand rested on the edge of the bed. A deliberate, forceful thrust was made into the pulp of the finger, after sterilisation with ether. A newly-sharpened needle was used for each case, and was held between the second finger and thumb of the operator's right hand. The blood pipette could then be held in readiness, pencil-wise, between the first and second fingers. The blood was allowed to run into the pipette which was held with a slight inclination downwards, air bubbles being carefully avoided. It was found better to aim at the precise amount of blood required rather than to rely on adjusting the blood column in the pipette when too much blood has been withdrawn. This takes time, allows clotting and, as often as not, results in "pulling" the column below the required mark. Precision saves time, prevents clotting, is more accurate

and is easily accomplished with practice. When too much blood was allowed to enter the pipette it was found to be the best procedure to coax the column down by capillary attraction on the smooth skin at the edge of the operator's hand. Gauze is too absorbent for this purpose. The outside of the point of the pipette is best cleaned of adhering blood with a small piece of moist silk. It was considered sufficient reward for the elaboration that this method gave good results. In no case did a septic finger result from the puncture.

3. Estimation of Blood Sugar. A colorimetric method was favoured because of the advantages which it offers in making accurate blood sugar determinations. It is particularly suited to investigations in children because of the small quantity of blood required, and for clinicians it has the appeal of rapidity when a wide survey of the blood sugar is contemplated.

Various techniques are available for the micro-estimation of blood sugar. The method used was that of Folin and Wu, as adapted by Wallis for .1 c.c. of blood. The method is described by Harrison (1) on whose description the following account is based. With the exception of the stock glucose solution the reagents required are the

same as in the original method of Folin and Wu. The proteins are precipitated from the blood and the blood sugar is estimated colorimetrically in the filtrate.

PRINCIPLE: The proteins are precipitated with Tungstic Acid which is formed by the interaction of sodium tungstate and sulphuric acid. The protein free filtrate is treated with an alkaline cupric tartrate solution under standard conditions. It is then treated with a solution of phosphomolybdic acid which is reduced in proportion to the amount of cuprous salt and, therefore, in proportion to the quantity of sugar present. The compound formed by the reduction of the phosphomolybdic acid is blue and the intensity of colour is compared in a colorimeter with that of a standard solution of pure glucose treated in a similar manner.

APPARATUS: Set of flat Hagedorn needles.
.1 c.c. blood pipettes.
2 c.c. reagent pipettes (4).
1 c.c. reagent pipettes (3).
Pyrex centrifuge tubes.
Small pointed stirring rod.
Filter papers (7 cm. Whatman No.41).
Folin sugar tubes.
Small filter funnels.

The Folin sugar tubes are constricted in their lower third into a stem, which terminates in a bulb holding a fraction less than 4 c.c. of fluid. The 4 c.c. mark is

placed on the stem just above the bulb, the tube itself being marked off at 12.5 c.c.

REAGENTS.

1. 10% sodium tungstate ($Na_2WO_4.2H_2O$))
2. 2/3N. sulphuric acid.) As in
3. Folin and Wu alkaline copper reagent.) original
4. Phosphomolybdic acid reagent.) method
5. Stock glucose solution, .1%
6. Standard glucose solution, .005%

PREPARATION of REAGENTS.

1. Stock sugar solutions. These solutions are made in a saturated solution of benzoic acid in water (solubility 1:400). A saturated solution of benzoic acid is prepared by adding 2.5 gm. to 1000 c.c. of boiling water and allowing to cool. This gives a 0.25% solution of benzoic acid. 0.1 gm. of pure dry glucose is dissolved in 100 cc. of the saturated benzoic acid solution. This solution keeps indefinitely and the standard glucose solutions are prepared freshly from it for each series of estimations.

2. Standard glucose solution. 5 c.c. of stock glucose solution are diluted in 100 c.c. saturated benzoic acid solution in a 100 c.c. volumetric flask. This gives a standard .005% solution of which 1 c.c. equals .05 mg. of glucose. Fresh standard solutions do not keep and should, therefore, be prepared immediately before use.

3. Folin and Wu's Alkaline Copper Reagent. 40 g. of anhydrous sodium carbonate are dissolved in 400 c.c. of water, and the resulting solution is transferred to a litre flask. 7.5 g. of tartaric acid are added, and when this has dissolved, 4.5 g. of crystalline copper sulphate are added. After thorough shaking, the substances dissolve and the volume is made up to a litre.

4. Molybdic Acid Solution. 35 g. of molybdic acid and 5 g. of sodium tungstate are added to a litre beaker, together with 200 c.c. of 10% NaOH and 200 c.c. of water. The contents of the beaker are then boiled for half an hour or so to remove the ammonia from the molybdic acid. After cooling, the solution is transferred to a 500 c.c. measuring flask, and diluted to about 350 c.c. 125 c.c. of 85% phosphoric acid are then added and the volume is made up to 500 c.c.

5. $\frac{2}{3}$ N. Sulphuric Acid Solution. (20 c.c. H_2SO_4 in 500 c.c. H_2O). The acid used was standardised and had a factor = .667N.

TECHNIQUE:-

i. Mix in a graduated pyrex centrifuge tube the following:

3.5 c.c. distilled water
.1 c.c. blood
.2 c.c. 10% sodium tungstate
.2 c.c. N. sulphuric acid.

Allow to stand for 10 minutes by which time the protein precipitate will have clumped. Centrifugalisation should result in a crystal-clear supernatant fluid. This is filtered through a small washed filter paper (Whatman, No.41, 7 cm.).

ii. Into a Folin sugar tube pipette -

2 c.c. blood filtrate
2 c.c. alkaline copper solution.

Into 2 more Folin sugar tubes, A and B, pipette -

A.	B.
2 c.c. .005% glucose	1 c.c. distilled water
2 c.c. alkaline copper solution.	1 c.c. blood filtrate
	2 c.c. alkaline copper sol.

These are the standard solutions. A is the Strong Standard = .1 mg. glucose, and B is the Weak Standard = .05 mg. glucose.

The tubes are then placed in a boiling water bath for exactly 6 minutes. They are then allowed to cool for 1 or 2 minutes only. If cooling is prolonged or if the tubes are shaken, there is a risk of oxidation of the cuprous oxide by the atmosphere.

To each tube is added 2 c.c. phosphomolybdic acid. Distilled water is run in from a burette to the 12.5 mark and the contents are mixed by inversion.

The unknown is then compared in the colorimeter with the Standard which most closely matches it in colour.

iii. Calculation. The unknown U is placed in the left-hand cup and set at 40. The standard S is placed in the right-hand cup and the rack on that side is adjusted till the colours match.

Standard A: The standard contains 2 c.c. of 0.005% glucose.

100 c.c. of standard solution = 5 mgm. glucose.

1 c.c. " " " = $\frac{5}{100}$ " "

2 c.c. " " " = $\frac{5 \times 2}{100}$ " "

= 0.1 " "

Standard B: The standard contains 1 c.c. of 0.005% glucose.

100 c.c. of standard solution = 5 mgm. glucose.

1 c.c. " " " = .05 " "

Let S be the reading of the standard, U the reading of the unknown, and let X be the amount of sugar in mgm. in the 2 c.c. blood filtrate taken.

Then for standard A,

$$X \times U = 0.1 \times S$$

$$X = \frac{0.1 \times S}{U} \text{ mgm. glucose}$$

But,
4 c.c. blood filtrate are derived from 0.1 c.c. blood

∴ 2 c.c. " " " " " 0.05 c.c. "

∴ 0.05 c.c. blood contains $\frac{0.1 \times S}{U}$ mgm. glucose

∴ 1 c.c. " " $\frac{0.1 \times S}{.05 \times U}$ " "

∴ 100 c.c. " " $\frac{0.1 \times S \times 100}{.05 \times U}$ " "

$$= \frac{S}{U} \times 200 \text{ " "}$$

For standard B,

$$X \times U = .05 \times S$$

$$X = \frac{.05 \times S}{U}$$

But,
4 c.c. blood filtrate are derived from 0.1 c.c. blood.

∴ 2 c.c. " " " " " 0.05 c.c. "

∴ 0.05 c.c. blood contains $\frac{0.05 \times S}{U}$

∴ 1 c.c. " " $\frac{0.05 \times S}{0.05 \times U}$

∴ 100 c.c. " " $\frac{0.05 \times S \times 100}{0.05 \times U}$

$$= \frac{S}{U} \times 100$$

If the unknown U is set at 40,

Then with standard A,

100 c.c. blood contain $\frac{S}{U}$ x 200 mgm glucose

$= \frac{S}{40}$ x 200 " "

$= \underline{\underline{S \times 5}}$ " "

And with standard B,

100 c.c. blood contain $\frac{S}{U}$ x 100 mgm. glucose

$= \frac{S}{40}$ x 100 " "

$= \underline{\underline{S \times 2.5}}$ " "

Abbreviated Method of Calculation:

With standard A blood sugar $= \frac{S}{40} \times 0.1 \times 2000 = S \times 5$ mgm.%

" " B " " $= \frac{S}{40} \times 0.05 \times 2000 = S \times 2.5$ " "

iv. Observations. The blood was collected in .1 c.c. blood pipettes of which several were kept ready for use. A series of pyrex centrifuge tubes was carried in a wooden test tube rack holding 12 tubes. Before the blood was drawn 3.5 c.c. of distilled water was pipetted into the first tube. The blood was then discharged from the blood pipette directly into the distilled water, the pipette being washed thoroughly with the latter. If the blood was

discharged into the depths of the water by gentle tapping against the side of the tube, a sufficient quantity of clear supernatant fluid was obtainable to ensure accuracy in washing the pipette. The tungstate solution and the sulphuric acid were then added, protein precipitation and estimation being carried out forthwith. It was found convenient to use a small blunt pointed glass stirring rod to effect complete admixture of the reagents.

The pipettes must be kept scrupulously clean. After each experiment the pipettes were flushed several times in a hot mixture of sulphuric acid and potassium bichromate contained in a test tube. They were then washed in distilled water, alcohol and ether. The pipettes were then blown dry using gentle heat and a rubber air bulb with tube.

Accuracy in the measurement of the reagents is essential. Although graduated pyrex centrifuge tubes were used it is important to note that, although they may read accurately over the whole scale, they may read inaccurately at the intervening levels. Those used were selected, after checking, but it must be pointed out that in no case were micro-measurements made in any other way than by means of specially procured pipettes. At the very most, graduated tubes serve only as a check upon one's measurements in the

early stages of the investigation, before accuracy has become a habit.

The reagents used must be carefully and accurately prepared.* The $\frac{2}{3}$N sulphuric acid used had a normality factor of .667.

Accurate measurement of the reagents used is equally essential. The pipettes used were specially procured** and these were labelled, by means of "tags" of adhesive tape, with the names of the solutions they were intended to measure. Each pipette, therefore, was kept for but one purpose.

The procedure of withdrawing the blood directly into the pipette was adhered to throughout. At first the blood was collected into small glass combustion tubes measuring 4 x 1 cm., into which had been placed previously a small pinch of finely powdered potassium oxalate with the object of preventing clotting. The procedure was abandoned in favour of the method described, as the oxalate

* The reagents used were supplied by Messrs The British Drug Houses Ltd., Graham Street, City Road, London N.1.

** The blood sugar and reagent pipettes were supplied by Messrs Griffin & Tatlock, Scientific Instrument Makers, 45 Renfrew Street, Glasgow C.2. The pyrex centrifuge tubes and Folin sugar tubes were supplied by Messrs McCulloch, Brothers & Wilson, Scientific Glassblowers, 46a West Princes Street, Glasgow C.4.

was found to interfere with protein precipitation. Various procedures have been formulated to prevent this effect of the oxalate but none showed any advantage, after trial, over the simpler method used.

In view of the possibility of glycolysis estimations were carried out at once. In any series of experiments, the results of which are to be compared, uniformity in the time taken by the various steps involved is essential. The time during which the sugar tubes remain in the water bath, and cool on being removed from it, are important in this respect.

4. The Estimation of Blood Cholesterol. In this investigation the cholesterol of whole blood was investigated. The only absolute method of estimating cholesterol is the gravimetric method of Windaus, which involves the precipitation of cholesterol in combination with digitonin. The method is costly and tedious and it has, moreover, the disqualification of requiring larger quantities of blood than are practicable in clinical work.

In order to carry out the necessarily large number of cholesterol estimations required a micro-method was desirable such as could be carried out expeditiously and with a

small quantity of material.

In 1924 Leiboff[2] described a method of estimating the total blood cholesterol, which required only .25 c.cm. of blood. The method employed in this work is the Leiboff method as modified by Dutton.[2] The principle in both the original and the modified method is essentially the same, involving the extraction of cholesterol from a blood impregnated filter disc by means of chloroform distillation. In the original method it is difficult to prevent water from forming within the extraction tube by condensation of steam from the water bath in which distillation is carried out. This disadvantage has been overcome in Dutton's method.

The method has a further obvious advantage in the fact that the estimation is carried out in the same tube as that used for extraction, an arrangement which secures conservation of the cholesterol and aids accuracy. In the method of Myers and Wardell[4] one cubic centimetre of blood is absorbed in plaster of Paris. The mixture is dried, pulverised and transferred to a filter paper extraction thimble. In this manoeuvre loss is liable to be sustained in the transfer of the material from the mortar to the extraction apparatus, with consequent inaccuracy of the amount recorded.

The Micro-Estimation of Blood Cholesterol by the Leiboff Method as modified by Dutton.

APPARATUS:

Set of tubes with condensers.
Ether extracted $\frac{3}{4}$" filter discs.
Water bath and micro-burner.
Blood pipettes .25 c.c.
Reagent pipette 2 c.c.
Reagent pipette .1 c.c.
Rubber tubing.

THE METHOD: The apparatus consists of a tube 6" long and 1" in diameter; it is constricted at the lower end and terminates in a bulb after the manner of the Folin sugar tube. The bulb contains slightly less than 5 c.cms., this level being marked on the stem just above the bulb. The filter disc absorbs a measured quantity of blood which is thereafter dried to free it from moisture. The filter discs are of such a size that when one is placed within the tube, it rests horizontally on the shoulder of the tube at the upper end of the constriction. Suspended in the upper part of the tube is a simple condenser. When heated, chloroform vapour rises upwards, and to facilitate its

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Reagents: .08% stock solution of cholesterol in chloroform.
Acetic anhydride.
Concentrated sulphuric acid.
Pure chloroform.

passage two small crescents may be nibbled from opposite edges of the filter disc. The chloroform vapour condenses and a constant drip pours from the lower end of the condenser upon the blood saturated filter disc. The cholesterol is extracted from the blood and is carried down into the bulb by the stream.

TECHNIQUE: The blood specimen may be collected from a finger prick straight into the 0.25 c.cm. pipette; it is discharged on to a filter-paper disc $\frac{3}{4}$ in. in diameter cut from Whatman filter paper 1/16 in. thick; the discs should be ether-extracted in bulk before use.

In order to get rid of water the disc with the absorbed blood is dried by gentle heating for half an hour at between 40°C and 50°C. A little less than 5 c.cm. pure dry chloroform is poured into the extraction tube and the dried impregnated filter-paper disc is dropped into the tube where it remains supported just above the constriction. The condenser is placed in position and the tube immersed to the level of the chloroform in a bath of boiling water. Extraction has been found to be complete in 20 minutes, but half an hour is usually allowed. The tube is removed from the bath, wiped dry, and the condenser and disc are removed; when the tube has cooled to room temperature,

chloroform is added exactly to the 5 c.cm. mark. Estimation is performed in the usual way making use of the Liebermann-Burchard reaction; 5 c.cm. of a standard solution of cholesterol containing 0.4 mg. cholesterol per 5 c.cm. is placed in a similar tube; to both standard and test are added 2 c.cm. acetic anhydride and 0.1 c.cm. concentrated sulphuric acid. Cork stoppers are inserted, the tubes are then inverted twice to mix well, cooled for half a minute in cold water, and set aside in the dark for twenty minutes for the colour to develop. Comparison is made with the colorimeter, the standard being set at 10 or 15 depending on the intensity of colour of the unknown.

CALCULATION: The standard solution of cholesterol is prepared by diluting 10 c.c. of the stock solution to 100 c.c. with chloroform. 5 ccs. of the standard solution contain 0.4 mg. of cholesterol.

The colorimeter readings give one the amount of cholesterol contained in the unknown solution relative to that contained in the standard. This ratio is multiplied by the cholesterol content of the standard, i.e. 0.4 mg., the result expressing the absolute cholesterol content of the unknown, in milligrams. The amount of the blood used is 0.25 c.cm. To express the result as a percentage it is then

necessary to multiply by 400.

$$\frac{\text{Reading of Standard}}{\text{Reading of Unknown}} \times 0.4 \times 400 \text{ mgms. per cent.}$$

$$= \frac{S}{U} \times 160$$

ACCURACY of METHOD: The accuracy of the method is shown in Table , which shows a comparison of the modified method when compared with the original. Varying quantities of cholesterol were absorbed on to discs and extracted, the extract being compared with controls containing the same amounts of cholesterol. Comparative estimations by the methods of Bloor (5) and Wardell (4) are given on page 91 .

Table I.

Experiment No.	1	2	3	4
Amount of cholesterol:				
On disc	in.mg. 0.1	0.2	0.5	1.0
In control.	" 0.1	0.2	0.5	1.0
Colorimeter reading:				
Of control.	in.mm.15.0	15.0	15.0	10.0
Of extract (using Leiboff tube)	" 14.9	14.9	15.1	10.0
Of extract (using modified tube)	" 14.8	15.0	14.9	10.1

OBSERVATIONS: The Liebermann-Burchard reaction produces a blue-green coloration in the reagents due to acetylation by the acetic anhydride and condensation by the sulphuric

acid. The intensity of colour reaches a maximum after the elapse of a certain time which is quoted variously by different workers.[6] Grigaud advises reading after the reaction has been allowed to develop for half an hour. Autenreith and Fünk[7] advise a period of twenty minutes. They investigated the rate of development of the colour intensity in a standard solution of pure cholesterol. To this acetic anhydride and sulphuric acid were added, comparison being made with a standard green comparator after obtaining the Liebermann-Burchard reaction in the unknown.

In estimating the blood cholesterol by the modified Leiboff method, twenty minutes were allowed for the development of the reaction. Uniformity in respect of time is essential. After the addition of the reagents, the standard and the unknown solutions were placed in a dark room to prevent fading. This may be regarded as unnecessary by some, who hold that bright sunshine only is to be avoided. Since so much depends upon uniformity however and since light varies in intensity even in the shade, this procedure was found desirable.

A standard solution of cholesterol was used throughout for comparison with the unknown. A solution of naphthol green has been recommended for this purpose but such a sol-

ution has a yellow-green tint as compared with the blue-green of the Liebermann-Burchard reaction. Furthermore, when a standard solution of cholesterol is used inequalities, for example in the time allowed for the reaction to develop, are rendered trivial, since they are bilateral.

Another point to which attention must be drawn is the slight yellow tinge which appears in the unknown solution. It was found to vary in different blood specimens. Autenreith and Funk[7] believed it to be due to overheating during extraction, and made the recommendation that the water bath should be maintained at a temperature just sufficient to cause vaporisation of the chloroform. Although Dutton[2] suggests boiling in the water bath, it was found a better procedure to maintain the water at a temperature just sufficient to vaporise the chloroform, by means of a special burner.

The writer believes that the yellowish tinge in the unknown solution may be controlled by care during the drying of the blood. When this was done in an automatically regulated Hearson drying oven with the temperature set at 45° complete drying was effected in twenty minutes without undue "cooking" of the blood. In this way the yellow tinge was slight and was found to vary little, if at all, in successive specimens. The precautions which must be taken may be

summed up in the following: accuracy in the measurement of the reagents, uniformity in the time intervals allowed for drying, extraction and the development of the reaction, and uniformity in the rate at which these are achieved. Multiple estimations are therefore impracticable. It is not advisable to carry out more than two estimations with the one standard.

5. The Colorimeter. A Dubosq pattern colorimeter was used for the estimation of blood sugar and blood cholesterol. It consists of an eyepiece, two glass plungers of hexagonal section and two glass cups. Each cup is carried on a moveable stage and, by means of a rack screw, is capable of adjustment in a vertical direction. The position of the cups relative to the plungers, which are fixed, may thus be altered through a range of movement which is marked on vertical scales situated on the sides of the instrument. When the stages are raised the plungers dip into the cups, the scale being graduated to denote the extent to which they do so. When fully raised the distal end of each plunger comes in contact with the bottom of its respective cup, the reading of the corresponding scales being zero. If this is not so a correction must be made for the zero recorded.

The standard and the unknown solutions are placed to constant level in the cups. The latter are then raised, one being usually set to read at a certain mark on the scale. The other is adjusted by rack and pinion screw, the end point of the adjustment being that at which the colours match. Light is reflected from a substage reflector and, passing through the cups and plungers in a vertical direction, conveys to the eye a circular field of colour divided vertically into halves. The colour in each half of the field is contributed to by the homo-lateral solution so that, when accurate matching of the colours has been secured, the division of the field is dispersed, the whole presenting a uniform appearance. The colour effect is transmitted to the eyepiece by means of reflecting prisms.

In colour matching a fixed gaze must be avoided as this tends to tire the vision and make the appreciation of slight differences in shade difficult. Short sharp glances are better and a high degree of skill has been attained when several observations on the one specimen give identical readings. Three readings were usually taken. They were invariably found to be similar.

Daylight was used as the source of illumination when practicable. The mirror side of the reflector was found most suitable with daylight. When artificial light was

used the opaque side of the reflector was better. The source of illumination used under these circumstances was an enclosed electric light with an opaque violet-tinted window similar to the type used in microscopy.

For the estimation of cholesterol, cups with fused glass bottoms are essential as the acid-chloroform mixture destroys the cement used in the ordinary type of cup. Care must be taken to ensure that the mixture is not allowed to come in contact with the sockets of the plungers for the same reason.

6. Examination of Urine for abnormal chemical Constituents.

(a) Albumen: Serum albumen may be found in the urine and constitutes the condition known as "albumenuria". Before applying tests for albumen it is essential that the urine should be absolutely clear. This may be done by filtration, but if persistent turbidity, which is usually due to the presence of bacteria, remains, it may be necessary to centrifugalise the specimen. The test employed for the detection of albumen was the heat test, the method of applying it being as follows.

A thoroughly clean test tube is used. The urine is poured into it until about two-thirds full. The top inch of the column is heated to boiling in a bunsen flame, and

without shaking. The boiled portion of the column is compared with the unheated portion below, preferably against a dark background. If a turbidity appears in the former, it may be due to albumen or to the presence of earthy phosphates. A few drops of 33% acetic acid are then added. If the turbidity is due to earthy phosphates the specimen clears. If due to albumen the turbidity remains.

(b) Sugar: It would appear that glucose, dextrose or grape sugar may occur in the urine of normal persons, but in traces incapable of detection by the reagents generally used. If glucose is detected by these methods it may be held, generally, to be pathological, "glycosuria" being the name given to the condition. Glycosuria is a symptom of diabetes mellitus, but it may occur in other conditions. This has been referred to on page 22 . The tests employed for the detection of glucose were (1) Fehling's and (2) Benedict's. These tests depend upon the fact that glucose can become oxidised at the expense of certain metallic oxides, the oxidation occurring most readily at a temperature near boiling point, and in the presence of caustic alkali. Copper is the metal used in the tests. If a few drops of a dilute solution of sulphate of copper are added to a solution of caustic soda a blue precipitate forms. This precipitate is hydrated cupric oxide - $Cu.O.H_2O$. If the blue precipitate

is boiled it becomes black, due to the separation of cupric oxide CuO. In the presence of tartrate, however, the cupric hydrate, formed by the addition of the sulphate, goes into solution instead of being precipitated. A deep blue fluid is formed, which retains it's colour on boiling. If an oxidisable substance such as glucose is present, however, the blue cupric hydrate is reduced, on boiling, to cuprous hydrate $Cu_2.O.H_2O$, which is thrown down from the solution as a yellow precipitate. If creatinin is absent ? red cuprous oxide is precipitated instead. If a solution of glucose is made alkaline with caustic soda, and a few drops of cupric sulphate solution are added, the cupric hydrate is dissolved and a blue colour results. On raising this to the boiling point the glucose reduces the cupric hydrate and yellow cuprous hydrate or red cuprous oxide is precipitated.

(1) FEHLING'S TEST: The solutions* must be fresh. If not a deposit of cuprous oxide will follow on boiling. This possibility may be prevented by boiling a mixture of equal volumes of water and Fehling's solution for two minutes. If the solution remains clear it may be regarded as sufficiently fresh for use.

The urine must be free from albumen. If present it may be removed by heating and filtration. The result ob-

tained depends upon the amount of reducing substance present. To 1" of Fehling's solution in a test-tube a few drops of albumen-free urine are added. The mixture is then boiled. If any considerable quantity of glucose is present a yellow or red precipitate will appear. Should no precipitate form it may be that the quahtity of urine used was too small. Equal quantities of Fehling's solution and urine are then mixed - about 1" of each. The mixture is boiled for two minutes. If a red or yellow precipitate forms at once a moderate quantity of sugar is present, but if not, and, after standing, the precipitate is slight, only traces of sugar are present.

Substances other than glucose may also act as reducing agents. These constitute the fallacies of Fehling's test, and render it unsuitable for clinical work. Among normal constituents of the urine, fallacious results may result from the presence of uric acid, hippuric acid and creatinin. Lactose, glycuronic and glycosuric acids are the chief abnormal constituents. The products of certain drugs may also affect the result such as chloroform, chloral, salicylates, benzoic acid, carbolic acid and glycerin. Homogentisinic acid, which is present in the urine in alkaptonuria, reduces Fehling's solution, as also does formalin. If the patient is not receiving drugs and the urine has a high specific gravity,

dilution to a specific gravity of about 1015 followed by a reduction of Fehling's solution, immediately or on standing for 2 minutes, indicates the presence of glucose.

(2) BENEDICT'S TEST: Benedict's test overcomes most of the errors of Fehling's reaction, and is, therefore, much more accurate. It is equally simple to apply, and was used by the writer in addition to Fehling's for the detection of urinary glucose.

5 c.c. of the reagent* are placed in a clean test tube and 8 drops of urine are added. It is essential that these amounts be exactly measured. The contents of the tube are boiled over the flame for two minutes and are then allowed to cool. The technique described is rigid and does not allow of inaccuracy, since the quantities of urine and reagent used, and the time during which the mixture of these is heated, have given the test a high degree of specificity. If glucose is present, the reagent will change colour from clear blue to an opalescent green. If a large quantity of sugar is present the final colour will be an opaque red. Beaumont and Dodds (8) give a scheme of the intermediate reactions, on a quantitative basis, as follows:-

0.1% sugar - greenish opalescence; no red colour; no precipitate.

0.2% " - as above, but slight yellowish precipitate; fluid blue on standing.

0.3% sugar - green colour with slight orange precipitate; fluid blue on standing.

0.5% " - definite orange precipitate; fluid still blue on standing.

1.0% " - heavy orange-brown precipitate; still some blue colour in the fluid on standing.

2.0% " - bright red, heavy precipitate; blue colour of the fluid almost disappeared.

Benedict's reagent keeps better than Fehling's and is not affected by creatinin, uric acid, chloroform and simple aldehydes. It is reduced by glucose, laevulose, lactose, pentose and homogentisinic acid. A positive result for practical purposes, therefore, implies the existence of glycosuria.

* REAGENTS: The composition and the method of preparing the reagents is that given by Hutchison and Hunter.(9)

Fehling's solution:

A. Take 34.64 grm. pure sulphate of copper which has been powdered and pressed between bibulous paper; dissolve in 200 c.c. warm distilled water. Cool and make up to 500 c.c.

B. Dissolve 180 grm. crystallised Rochelle salt in 200 c.c. hot water; filter and add 70 grm. pure caustic soda or 100 grm. potash. Cool and make up to 500 c.c.

Equal volumes of A and B are mixed for use as required. The result is an alkaline solution of potassic cupric tartrate of which 1 c.c. is exactly reduced by 5 mgms. of pure glucose.

Benedict's Solution:

173 grm. crystalline sodium citrate and 100 grm. anhydrous sodium carbonate (or 200 grm. crystallised) are dissolved in 700 c.c. water. 17.3 grm. fine crystallised copper sulphate are dissolved in 100 c.c. water. The copper sulphate solution is poured into the former solution and the volume is made up to 1000 c.c.

(c) Acetone Bodies: Hydroxybutyric acid, aceto-acetic acid and acetone may all occur in the urine in the condition of ketosis. They show the following relationship:-

Hydroxybutyric acid - $CH_3.CH(OH)CH_2.COOH$

Aceto-acetic acid - $CH_3.CO : CH_2COOH$

Acetone - $CH_3.CO.CH_3$

Hydroxybutyric acid is formed first. It then becomes oxidised into aceto-acetic acid, which in turn yields acetone and CO_2 in accordance with the following formulae:-

$$CH_3.CH(OH)CH_2\ COOH + O = CH_3.CO.CH_2COOH + H_2O$$

$$CH_3.CO.CH_2COOH = CH_3.CO.CH_3 + CO_2$$

It is asserted that acetone is only formed after the urine is passed.

(1) Rothera's Test for Acetone and Aceto-Acetic Acid: This reaction is by far the most satisfactory test for ketosis. It is performed as follows: An excess of ammonium sulphate crystals is added to about 20 c.c. of urine in a test tube. The urine is saturated with the ammonium salt by shaking the test tube. 2 c.c. of strong ammonia are added and a few

drops of a dilute (5%) solution of freshly prepared sodium nitroprusside. The mixture is shaken and allowed to stand. The presence of acetone bodies will produce a colour ranging from mauve to deep purple. If Rothera's test is negative, acetone bodies are absent.

(2) Gerhardt's Test for Aceto-acetic Acid: If Rothera's test is positive the presence of aceto-acetic acid may be tested for by Gerhardt's ferric chloride test, which is applied in the following way.

To half a test tube of urine 10% ferric chloride solution is added until the precipitate of ferric phosphate has reached its full intensity and has wholly or partly redissolved. The specimen is then filtered. To the filtrate is added a few drops of ferric chloride solution. The presence of aceto-acetic acid is shown by a claret red coloration. A similar colour is produced by salicylic acid which may be present in the urine of patients who have taken aspirin, salol or other salicylates. This colour is not destroyed by boiling whereas that produced by aceto-acetic acid is. If the urine reacts to Rothera's test but not to ferric chloride, it may be inferred that only small quantities of acetone bodies are present, since Gerhardt's test is only positive if aceto-acetic acid is present in considerable amount.

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C H A P T E R V.

The Investigation of Glucose Tolerance, Blood Sugar and Blood Cholesterol in Healthy Controls.

THE INVESTIGATION OF GLUCOSE TOLERANCE, BLOOD SUGAR AND BLOOD CHOLESTEROL IN HEALTHY CONTROLS.

Before one is able to assess any divergence from the normal glucose tolerance, fasting blood sugar and blood cholesterol in diphtheria, it is obviously necessary to delineate, for each, a range of normality above and below which a pathological state may be said to exist.

Authorities are in fairly general agreement regarding fasting blood sugar concentration and the blood sugar curve in health. With regard to the blood cholesterol, however, there is a lack of uniformity in what may be considered normal. This is due, in great part, to the diversity of methods by which blood cholesterol may be estimated. The reader is referred to page 90. for a resume of the results obtained by various workers using different methods of estimation.

A definite figure, such as 160 milligrams, per cent., is used by most observers as representing the cholesterol content of the blood in health. Any figure above or below this value they regard as constituting an abnormality. The normal cholesterol content of the blood, however, varies within wide limits in different individuals, but for a

given individual it is remarkably constant, and tends to remain so for long periods.(1) In order, therefore, definitely to establish the existence of a hypercholesterolaemia or of a hypocholesterolaemia, one must find that the blood cholesterol is raised above the normal maximum limit on the one hand, or that it is less than the normal limit on the other. Similarly, if the blood cholesterol for an individual in health is known, this value should be definitely exceeded or not attained, before an abnormality can be said to exist.

It appears to the writer that a fairer comparison of their variations in disease will be possible if each worker will define their limits in health for himself. The results may then be said to be truly comparable, for he will reduce to a minimum the variability of such factors as the method of determination and the subtle personal ones of technique and individual error1

Selection of Healthy Controls. Difficulty was experienced in obtaining healthy controls for the purpose of assessing normal standards.

The ten cases selected were referred to hospital, their justification for being there having an illusory basis, as

judged by immediate diagnosis and subsequent isolation. Their service as controls was not invoked until the lapse of a period sufficiently long to confirm the opinion of "no appreciable disease". In this way alone was it possible to obtain controls whose age, sex, dietary and environment approximated closely to those suffering from diphtheria. These cases were investigated with a view to determining what might be regarded as standards of normality with reference to the following:-

I. Glucose Tolerance and Fasting Blood Sugar.
II. Blood Cholesterol.

I. The Glucose Tolerance and Fasting Blood Sugar.

For several days prior to the carrying out of the glucose tolerance tests the controls had been receiving the routine hospital dietary. Antecedent dietary factors which affect the tolerance for glucose, were thus reduced to a minimum. All were confined to bed at the time of performance of the tests.

The amount of glucose given varied with the age of the subject, the average being in accordance with the following scale:

5	years	15	grams. glucose.
10	"	30	" "
15	"	50	" "

A maximum concentration of blood sugar was reached, in the cases of nine of the controls, after 30 minutes. In only one was the maximum concentration delayed until 60 minutes, (2).

In eight of the tests the blood sugar had returned to a point slightly below the fasting level in 90 minutes. In one case (5) this fall occurred after 60 minutes, and in one it was delayed until 120 minutes (2). The greatest delay in reaching the maximum concentration and in falling to the sub-fasting level occurred, therefore, in the same control.

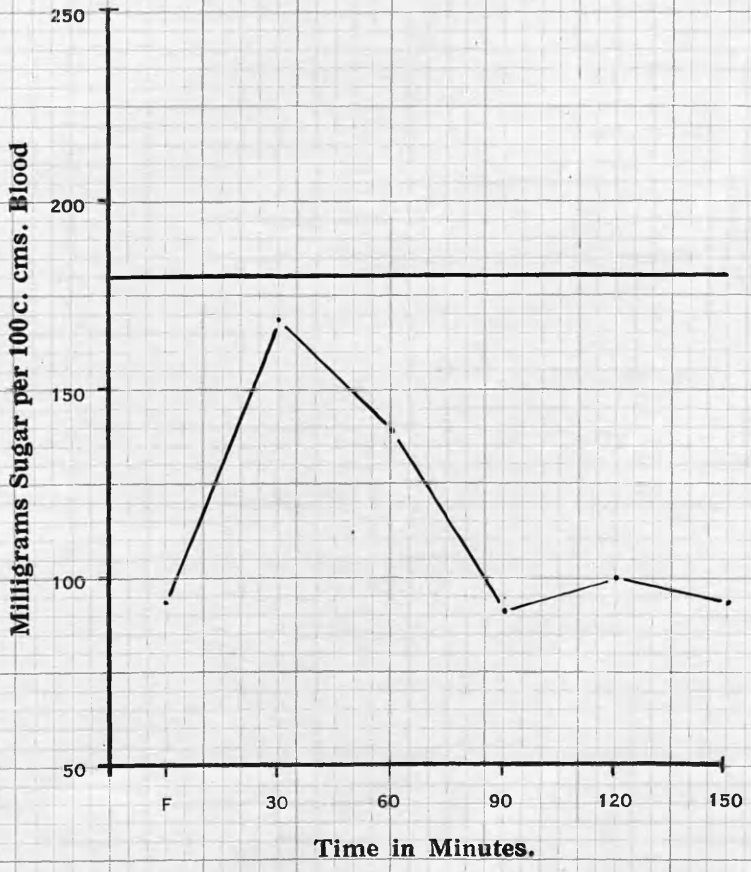
Figure III shows a composite curve representing the average results obtained from glucose tolerance tests carried out on 10 healthy subjects.

The curve displays the following general features. From a fasting level of 93.6 mgms. per cent., the blood sugar rises steeply to a maximum concentration of 168.8 mgms. per cent. in half an hour. The blood sugar thereafter begins to fall and at the end of 60 minutes has reached the level of 138.8 mgms. per cent. The decline

FIGURE III.

The Normal Blood Sugar Curve.

A composite blood sugar curve compiled from the results obtained in ten healthy controls.



in the curve in the next half hour is even more marked, so that, at the end of 90 minutes, it has fallen to a point somewhat less than the fasting level. A slight secondary rise is then seen to occur, before the blood sugar concentration settled to its fasting level.

McLean (2) states that the highest figure may not be attained until as much as one hour after taking the sugar. This occurred in the case of one of this series. Speaking generally, the maximumb blood sugar reading should be attained within an hour.

Variations, no doubt, depend upon inequalities of the digestive functions such as the rate at which the sugar enters the small intestine and the volume of the intestinal contents. The maximum concentration attained varies a good deal. The highest in this series was 182 mgms. per cent and the lowest 162 mgms. per cent. The average of the 10 subjects investigated was 168.8 mgms per cent.

The blood sugar concentration is changing from minute to minute. It is a matter of chance, therefore, whether or not the blood sugar will have attained its highest concentration at the moment of taking a sample

of blood. The maximum point may have occurred minutes before, or may not occur till minutes after, the moment of withdrawing the blood.

Immediately after the maximum has been reached the blood sugar begins to fall. The decline is not quite so steep as the initial rise, but in a healthy young subject the blood sugar is little, if at all, above the fasting level at the end of 90 minutes. Frequently (it occurred in all except one of the healthy controls investigated) the blood sugar may fall below the fasting level after the elapse of this time. The dip below the fasting level varied, in this series, from 2 - 11 milligrams per cent.

The shortest time for the blood sugar to dip to the fasting level, or below it, was 60 minutes, the longest time, 120 minutes, and the average time 90 minutes from the ingestion of the sugar. All urine specimens were sugar-free. The results obtained are shown in Table II.

Normal Blood Sugar Curve. A normal blood sugar curve may be defined, therefore, as one which represents, graphically, the constantly changing concentration of blood sugar resulting from the ingestion of 15-50

Control	Age	Amount of Glucose in grammes	Fasting Blood Sugar	Minutes after the administration of Glucose					Sugar in Urine
				30	60	90	120	150	
1	5	15	86	180	162	80	95	88	Nil
2	7	15	94	156	164	98	92	102	Nil
3	15	50	105	174	115	98	110	104	Nil
4	6	15	86	160	140	80	88	93	Nil
5	10	30	96	182	90	110	104	98	Nil
6	8	30	88	180	150	85	100	86	Nil
7	10	30	104	164	145	102	113	96	Nil
8	14	40	93	162	138	85	100	94	Nil
9	9	30	85	168	152	82	104	88	Nil
10	12	30	99	162	132	88	94	90	Nil
Average =			93.6	168.8	138.8	90.8	100.0	93.9	Nil

TABLE II

The results obtained from Glucose Tolerance Tests carried out upon ten healthy controls.

grammes of glucose, this record being such that, at the time intervals of 60 and 90 minutes after partaking of the sugar, the blood sugar concentration, respectively, has attained its maximum and has returned to its fasting level, and provided, always, that this fluctuation in the blood sugar concentration is unassociated with glycosuria.

With regard to the fasting blood sugar, the values obtained in the ten controls investigated were as follows: The maximum and minimum estimations were respectively 105 mgms. and 86 mgms. per cent. The average fasting blood sugar was therefore 93.6 mgms. per cent.

II. Blood Cholesterol.

Estimations of the total blood cholesterol were carried out on each of the ten healthy controls. As in the case of the fasting blood sugar estimations, the blood was withdrawn from the subjects in the fasting state. In the main part of the work this arrangement was adhered to, as, in addition to its greater convenience, it has the advantage of eliminating any immediate effect that the ingestion of food may have upon the cholesterol of the blood.

Duplicate estimations were made in each specimen of

blood. Table III was compiled from the results obtained, an analysis of which may be summarised as follows:

1. For the series, the highest and lowest estimations recorded are 235 and 150 milligrams of cholesterol per 100 c.cms. blood.

2. The highest and lowest means recorded are 231 and 150 milligrams per 100 c.cms.

3. The average range for the whole series is from 185.9 - 189.6 mgms. per 100 c.cms., the mean being 187.75.

4. The maximum difference between any two estimations of the one specimen of blood is 8 milligrams per 100 c.cms. blood and the average difference is 3.7.

The mean range recorded, 150 - 231 mgms. per 100 c. cms., compares with those of other workers as follows: Bloor (3) using his own method of extraction gives a normal range for whole blood of 190 - 260 mgms. per 100 c.cms. Gorham and Myers (4) found a range of 130 - 190 milligrams per 100 c.cms. with an average of 150 for 14 cases. Autenreith and Funk (5) define the normal range as 140 - 160 mgms. per 100 c.cms. They estimate the unknown against a standard green comparator. Bacmeister and Havers (6) give a range, for whole blood, of 110 - 180 mgms. per 100 c.cms. Chaufard (7) and his collaborators, for whole blood, estimate 150 - 180, while Grigaud (8), estimating the blood cholesterol in four normals, gives for whole blood a range of 150-165mgms

All of the above used the Liebermann-Burchard colour reaction.

In comparing the modified Leiboff method[9] used in this work, with the method of Bloor[10] and of Myers and Wardell,[11] Dutton[12] records the estimations shown in Table IV.

Table IV.

Cholesterol Content of Blood	Estimation.		
in mgms.per cent by method of:	1	2	3
Bloor	168	160	235
Leiboff, using modified tube.	164	152	210
Myers and Wardell	132	128	182

The readings obtained by the Leiboff method will be seen to be higher than those obtained by the method of Myers and Wardell. Leiboff found this discrepancy too, and accounted for it on the ground that loss may occur in the transference to the extraction apparatus of the plaster-of-Paris and in the unequal percolation of the latter by the chloroform.

Owing to the comparatively recent date at which the micro-estimation of blood cholesterol by the modified

Leiboff method was introduced, no further figures for comparison are yet available in the literature.

For the purposes of the present work the mean range of blood cholesterol as determined in the controls will be regarded as normal, viz:

	(Maximum,	231	mgms.	cholesterol	per 100	c.cms.
25	(Minimum,	150	"	"	" 100	"
cases	(Mean,	183.76	"	"	" 100	"

The range of normality, somewhat greater than that of some workers mentioned, is sufficiently comprehensive to embrace border line variations. Anything regarded by these standards as abnormal may, the more reasonably be acknowledged to be definite.

The minimum of the range will be found to be in fairly general agreement with the results of different workers using different methods of estimation. The maximum limit of normality, however, is somewhat higher than most, and the range of normality would, therefore, appear to be greater than what has come to be regarded as normal. (13) These facts have been noted by other workers. Fleming gained the impression from a similar investigation that "the upper normal limit is frequently higher than the commonly accepted value of 200 milligrams per 100 c.cms."

Robinson (14) records that from results obtained by him, he is of the opinion that the normal range of value is greater than is usually realised.

TABLE III

N	Age	Sex	No.of Estimations	Milligrams Cholesterol per c.cms. Blood.			
				I	II	Difference	Mean
1	5	M	2	178	174	4	176.0
2	7	M	2	169	163	6	166.0
3	15	M	2	213	208	5	210.5
4	6	M	2	220	220	0	220.0
5	10	M	2	235	227	8	231.0
6	8	M	2	189	185	4	187.0
7	10	M	2	176	174	2	175.0
8	14	M	2	160	156	4	158.0
9	9	M	2	150	150	0	150.0
10	12	M	2	206	202	4	204.0
				189.6	185.9	3.7	187.75

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C H A P T E R VI.

Clinical Cases of Diphtheria.

CLASSIFICATION of CASES.

The cases which form the basis of the investigation were classified according to the severity of the intoxication. In viewing a case in prospect classification, necessarily, must be anatomical. Needless to say, no such classification, which is based on the extent of the local lesion, can be entirely satisfactory, since it fails to take account of the subtle and elusive factor of toxaemia. The extent of the intoxication is not always directly proportional to the severity of the local disease. The former must always be a matter for the clinician's perception, which in turn is based upon his experience. (1)

The following summarises the classification of Bie which is based mainly upon the anatomical extent of the local lesion.

MILD CASES: The membrane does not folly cover the tonsils. Oral foetor and peri-adenitis, if present, are slight.

MODERATELY SEVERE CASES: Both tonsils and palatine arches are covered with membrane, which usually extends to the uvula. Foetor and peri-adenitis are invariably present.

SEVERE CASES: The membrane covers the tonsils, the palatine arches and the uvula. Frequently it extends also to the hard palate, the buccal mucous membrane or the posterior pharyngeal wall. Foetor oris is intense and glandular enlargement is of the "plum" or "hen's egg" degree. When bilateral, the distortion of the features occasioned warrants the description of "bull neck" or "consular collar".

In viewing a case in retrospect, however, the clinical course of the disease allows of a more accurate interpretation of the severity of the toxaemia. For purposes of treatment this method has no application, but for reviewing the results obtained in an investigation such as this, it has its merits.

No hard and fast criteria were adopted. Classification of the cases in the three grades of severity was made after weighing together the first impression of the case and the subsequent course followed. With regard to toxaemia, clinical experience alone dictated the type of case which should be regarded as mild, moderately severe, or severe. When however, the local lesion suggested, for example, a mild case, but clinical perception demanded a more grave view, the final decision was based upon the latter.

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CASE 1.

Douglas Russell	Age 10 years.
Admitted	26:12:32.
Day of illness	Third.
Dismissed	2:2:33.
Classification	Moderate.
Throat swab	Positive.
Antitoxin	12,000 units.
Journal reference	Ward 1 East.

1. History.

Both tonsils were patched with thick yellowish-white membrane and oral foetor was pronounced. The right tonsillar gland was slightly enlarged and painful. The pulse was rapid and full and the temperature was 99.8°F. The first cardiac sound was soft and muffled, the second sound being split. The urine contained acetone and diacetic acid. 12,000 units of antitoxin were injected intramuscularly. The urine was clear on the 6th day and the throat was normal on the 7th day, by which time also the heart sounds were of regular rhythm and normal intensity. Recovery was uneventful and the patient was dismissed well on the 38th day.

2. Glucose Tolerance and Blood Cholesterol.

Estimations of glucose tolerance and blood cholesterol were made (1) during the acute stage of the illness and (2) on recovery.

Glucose Tolerance.

(1) 4th day of illness: 30 grams glucose.

106 135 157 139 120 103 (Chart 1)
Glycosuria absent during test.

(2) 31st day of illness: 30 grams glucose.

105 118 150 97 100 100 (Chart 2)
Glycosuria absent during test.

Blood Cholesterol.

(1) 4th day of illness: 121 mgms. per 100 c.cms. of blood.

(2) 31st day of illness: 153 " " 100 " " "

3. Note.

During the stage of toxaemia a slight delay in storage was observed in the blood sugar curve, the concentration of blood sugar being still above the fasting level at the end of two and a half hours. The blood cholesterol was abnormally low. Recovery was associated with a normal tolerance for glucose and an appreciation in the cholesterol content.

CASE 2.

Daniel Barclay	Age 8 years.
Admitted	19:1:33.
Day of illness	Fourth.
Dismissed	25:2:33.
Classification	Moderate.
Throat swab	Positive.
Antitoxin	12,000 units.
Journal Reference	Ward 1 East.

1. History.

The tonsils were enlarged and each was extensively patched with greyish-white membranous exudate. There was congestion of the soft palate and peritonsillar tissues, and foetor oris was intense. Both tonsillar glands were slightly enlarged.

On admission the temperature was 100.2°F. and the pulse rate 110. The pulse was regular, of good volume, and moderate tension. The heart sounds were pure but somewhat soft and muffled. Albumen, acetone and diacetic acid were present in the urine.

The temperature and pulse rate were normal on the 6th day of illness, by which time the urine was clear of albumen and contained only traces of acetone and diacetic acid. The throat was clear in the 7th day. Progress thereafter was uneventful and the patient was dismissed well on the 37th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated (1) during the stage of toxaemia, and (2) after recovery.

Glucose Tolerance.

(1) 5th day of illness: 30 grams. glucose.

107 198 163 140 140 126 (Chart 3)
Glycosuria developed during test.

(2) 30th day of illness: 30 grams. glucose.

96 163 120 104 98 100 (Chart 4)
Glycosuria absent during test.

Blood Cholesterol.

(1) 5th day of illness: 179 mgms. per 100 c.cms. blood.

(2) 30th day of illness: 151 " " 100 " "

3. Note.

The initial blood sugar curve shows a decrease of tolerance for glucose with delayed storage and a concentration beyond the renal threshold at the 30 minute interval, with resultant glycosuria. Acetone and diacetic acid were present in the urine. The value for blood cholesterol was within normal limits. The second blood sugar curve shows no abnormality and the blood cholesterol had undergone slight depreciation in value.

CASE 3.

David Torrance ..... Age 7 years.
Admitted ..... 22:10:32.
Day of Illness ..... Fifth.
Dismissed ..... 25:11:32.
Classification ..... Severe.
Throat Swab ..... Positive.
Antitoxin ..... 35,000 units.
Journal Reference .... Ward 1 East.

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1. History.

The patient was in the fifth day of illness on admission. Both tonsils were covered with tough greyish-white membrane which extended across the palatal arches towards the uvula and the naso-pharynx. A profuse sero-purulent rhinorrhoea was present and foetor oris was great. The tonsillar glands were considerably enlarged and tender. The complexion was livid. A soft blowing systolic murmur was audible at the apex and the second sound at the base was split. Vomiting had occurred on three ocasions before admission and acetone and diacetic acid were present in the urine. The temperature was 98°F. 15,000 units of antitoxin were injected intravenously and 20,000 units intramuscularly.

Cardiac arrhythmia developed on the 8th day of illness, occasional premature beats with compensatory pause being perceptible at the wrist. Vomiting had been persistent since admission and on the 9th day was associated with epigastralgia. Acetone and diacetic acid were still present in the urine and a transient and slight reduction of Fehling's solution was also noted.

Improvement in the general condition of the patient was noticeable on the 12th day of illness, and by the 14th day the urine was clear. On the 18th day the pulse was regular in rate, rhythm and volume and the heart sounds were apparently normal. Progress thereafter was satisfactory and the patient was dismissed well on the 35th day of illness.

2. Glucose Tolerance and Blood Cholesterol.

The glucose tolerance and blood cholesterol were estimated (1) during the acute stage of the illness, (2) during the stage of cardiac arrhythmia, and (3) after clinical recovery.

Glucose Tolerance.

(1) 6th day of illness: 30 grams. glucose.

78 185 168 126 132 125 (Chart 5)
Glycosuria present during the test.

(2) 9th day of illness: 30 grams. glucose.

86 165 152 128 96 102 (Chart 6)
Glycosuria absent during the test.

(3) 30th day of illness.

88 170 143 80 92 86 (Chart 7)
Glycosuria absent during the test.

Blood Cholesterol.

(1) 6th day of illness, 226 mgms. per 100 c.cms. blood.
(2) 9th day of illness, 278 " " 100 " "
(3) 30th day of illness, 183 " " 100 " "

3. Note.

During the stage of toxaemia the blood sugar curve shows an initial hypoglycaemia, a storage defect and a maximum concentration above the renal threshold. Glycosuria resulted. Ketone bodies were present in the urine and vomiting was persistent. The blood cholesterol was high. The carbohydrate storage defect persisted during the stage of cardiac involvement, though in less marked degree, and glycosuria was absent. The blood cholesterol had increased to an abnormal degree. Both glucose tolerance and blood cholesterol were normal on the 30th day of illness, and clinical recovery was established.

CASE 4.

James McArthur	Age 6½ years.
Admitted	26:10;32.
Day of Illness	Third.
Died	3:11:32.
Classification	Severe.
Throat Swab	Positive.
Antitoxin	40,000 units.
Journal Reference	Ward 2 East.

1. History.

The case presented the features of an extensive local lesion and a profound toxaemia. In the third day of illness on admission the tonsils, soft palate and uvula were extensively covered with thick greyish-white membrane. The throat was infiltrated and haemorrhagic discoloration was present on the right side. There was considerable enlargement and exquisite tenderness of the cervical glands. The pulse was rapid, regular and of small volume, and the first sound at the apex was weak. The temperature was elevated to 101°F. and albumen, acetone and diacetic acid were present in the urine. 20,000 units of antitoxin were injected intramuscularly and on the following day a further injection of 20,000 units was administered intravenously. On the 5th day of illness a severe epistaxis occurred. A slight arrhythmia was observed in the heart's action and on the 6th day a total and irregular irregularity was present. The first sound at the apex was inaudible, and the complexion was tinged with an ashen cyanosis. The temperature was subnormal. On the 7th day vomiting occurred, the patient complained of abdominal pain and the liver was palpable 1 in. below the costal margin. Vomiting persisted, irrespective of food taken, and the urine contained abundant albumen, acetone and diacetic acid. Fatal syncope occurred on the 10th day of illness.

2. Glucose Tolerance and Blood Cholesterol.

Estimations of glucose tolerance and blood cholesterol were made (1) on the 4th day of illness and the fasting

blood sugar and blood cholesterol were further investigated (2) when cardiac failure was present, and (3) during the stage of severe ketosis which preceded death.

Glucose Tolerance and Fasting Blood Sugar.

(1) 4th day of illness: 30 grams. glucose.

110 223 186 165 148 132 (Chart 8)
Glycosuria developed during the test.

(2) 6th day of illness: 106 mgms. per 100 c.cms. blood.

(3) 9th day of illness: 76 " " 100 " "

Blood Cholesterol.

(1) 4th day of illness: 144 mgms. per 100 c.cms. blood.
(2) 6th day of illness: 276 " " 100 " "
(3) 9th day of illness: 285 " " 100 " "

3. Note.

The fasting blood sugar progressively fell from 110 mgms. per cent on the 4th day of illness to 76 mgms. per cent on the 9th day. Inability to utilise glucose is shown in the blood sugar curve by the high maximum concentration, the delay in storage and the high concentration at the end of two and a half hours. Glycosuria developed during the test. The fall in the values for the fasting blood sugar were associated with cardiac arrhythmia, hepatic congestion, vomiting and ketosis. The blood cholesterol at the same times showed at first a slight fall below, and later a marked rise above, the normal range.

CASE 5.

N.McKinnon ..... Age 18 years.
Admitted ..... 4:11:32.
Day of Illness ..... Sixth.
Dismissed ..... 12:12:32.
Classification ..... Moderate.
Throat Swab ..... Positive.
Antitoxin ..... 8,000 units.
Journal Reference .... Ward 1 East.

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1. History.

Both tonsils were patched with yellowish-white membrane which extended on the left side to the palatal arch and the anterior pillar. A small patch was also present on the uvula. The temperature was 100.2°F. and the pulse rate 92. The pulse was regular in rate, rhythm and volume, and the heart sounds were normal. 8,000 units of antitoxin were injected intramuscularly. The urine contained albumen but acetone and diacetic acid were absent.

The throat cleared and progress was satisfactory until the 17th day of illness when a generalised urticarial rash developed. This serum phenomenon was associated with a rise of temperature to 99°F. and with tachycardia. The rash faded on the 18th day, and had finally disappeared one day later. The temperature and pulse rate were normal on the 22nd day. Traces of albumen persisted in the urine till the 26th day, the urine thereafter being clear. Further progress was uneventful and the patient was dismissed well in the 44th day of illness.

2. Glucose Tolerance and Blood Cholesterol.

The glucose tolerance and the blood cholesterol were estimated (1) during the stage of toxaemia, and (2) on recovery.

Glucose Tolerance.

(1) 7th day of illness: 50 grams. glucose.

95 176 150 131 110 96 (Chart 9)
Glycosuria absent during the test.

(2) 40th day of illness: 50 grams. glucose.

98 172 134 100 94 96 (Chart 10)
Glycosuria absent during the test.

Blood Cholesterol.

(1) 4th day of illness, 148 mgms. per 100 c.cms. blood.
(2) 40th day of illness, 192 " " 100 " "

3. Note.

The initial glucose tolerance test shows only a slight departure from normal in that the blood sugar concentration after an interval of two hours was still above the fasting value. Glycosuria was absent through the test. The final glucose tolerance test was normal. The blood cholesterol was low during the toxic stage and the final reading was normal.

CASE 6.

D. Hughes ..... Age 7 years.
Admitted ..... 18:11:32.
Day of Illness ..... Second.
Dismissed ..... 23:12:32.
Classification ..... Severe.
Throat Swab ..... Positive.
Antitoxin ..... 20,000 units.
Journal Reference .... Ward 2 East.

1. History.

The tonsils were enlarged and covered with greyish-black membrane which extended, on the left side, across the palatal arch to the uvula. Foetor oris was intense, and the tonsillar glands were considerably enlarged and tender.

The complexion was pale and livid. The temperature was elevated to 101°F. and the pulse was rapid, regular and of good volume. Albumen, acetone and diacetic acid were present in the urine. 20,000 units of antitoxin were injected intramuscularly.

On the 4th day of illness the temperature and pulse were normal and the urine was clear of albumen. Acetone and diacetic acid disappeared from the urine finally on the 6th day and thereafter progress was satisfactory. The patient was dismissed well on the 36th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated (1) during the stage of toxaemia, and (2) on recovery.

Glucose Tolerance.

(1) 4th day of illness: 30 grams. glucose.

106 172 156 150 137 118 (Chart 11).
Glycosuria absent during the test.

(2) 30th day of illness: 30 grams. glucose.

86 160 124 84 92 88 (Chart 12)
Glycosuria absent during the test.

Blood Cholesterol.

(1) 4th day of illness: 136 mgms. per 100 c.cms. blood.
(2) 30th day of illness: 212 " " 100 " "

3. Note.

During the stage of toxaemia the glucose tolerance test reveals a definite storage defect and an initial hyperglycaemia. Acetone and diacetic acid were present in the urine. The renal threshold was not exceeded. The blood cholesterol is definitely decreased. Clinical recovery was associated with normal blood sugar and blood cholesterol concentrations and the storage defect is absent from the blood sugar curve.

CASE 7.

Norman Tully ..... Age 30 years.
Admitted ..... 26:11:32.
Day of Illness ..... Fifth.
Dismissed ..... 25:12:32.
Classification ..... Mild.
Throat Swab ..... Positive.
Antitoxin ..... 4,000 units.
Journal Reference .... Ward 2 East.

1. History.

Admitted on the fifth day of illness. The throat was very congested and a large patch of membrane was present on the right tonsil. There was no glandular enlargement and foetor oris was slight. The temperature was elevated to 100.6°F. and the pulse rate was 116 on admission. The pulse was regular and of good volume and no alteration of the heart sounds was observed. The throat swab was positive and 4000 units of antitoxin were administered intramuscularly.

The case progressed satisfactorily and the patient was dismissed well.

2. Glucose Tolerance and Blood Cholesterol.

A glucose tolerance test and estimation of blood cholesterol were made (1) during the acute stage of the illness and (2) on recovery.

Glucose Tolerance.

(1) 7th day of illness: 50 grams. glucose.

118 132 174 108 128 114 (Chart 13).
Glycosuria absent during the test.

(2) 24th day of illness: 50 grams. glucose.

112 156 125 110 106 112 (Chart 14).
Glycosuria absent during the test.

Blood Cholesterol.

(1) 7th day of illness: 196 mgms. per 100 c.cms. blood.
(2) 24th day of illness: 184 " " 100 " "

3. Note.

The case was one of mild faucial diphtheria in an adult. No departure from normal was found in the tolerance for glucose nor in the cholesterol of the blood.

CASE 8.

W. Glendenning ..... Age 8 years.
Admitted ..... 29:11:32.
Day of Illness ..... Fifth.
Dismissed ..... 5:1:33.
Classification ..... Mild.
Throat Swab ..... Positive.
Antitoxin ..... 8000 units.
Journal Reference .... Ward 1 East.

1. History.

Admitted on the fifth day of illness. A small patch of membrane was present on each tonsil and on the uvula. Oral foetor was only slight and glandular enlargement was absent.

The temperature was 99°F. and the pulse rate 92. The colour was good, the pulse regular and of good volume and the heart sounds pure. The urine was clear. The bacteriological report was positive and 8000 units of antitoxin were injected intramuscularly.

Progress was uneventful and the patient was dismissed well on the 37th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance tests and blood cholesterol estimations were made (1) during the acute stage of illness, and (2) on recovery.

Glucose Tolerance.

(1) 7th day of illness: 30 grams. glucose.

116 156 174 131 122 118 (Chart 15)
Glycosuria absent during the test.

(2) 30th day of illness: 30 grams. glucose.

86 162 130 90 105 88 (Chart 16)

Blood Cholesterol.

(1) 7th day of illness, 108 mgms. per 100 c.cms. blood.
(2) 30th day of illness, 167 " " 100 " "

3. Note.

The initial blood sugar curve shows a mild interference with carbohydrate storage and a fasting hyperglycaemia. The blood cholesterol at this time was low. Fasting blood sugar, glucose tolerance, and blood cholesterol were normal on recovery.

CASE 9.

P.Fullerton ..... Age 6 years.
Admitted ..... 30:11:32.
Day of Illness ..... Sixth.
Dismissed ..... 18:2:33.
Classification ..... Severe.
Throat Swab ..... Positive.
Antitoxin ..... 16,000 units.
Journal Reference .... Ward 1 East.

1. History.

Admitted on the 6th day of illness. Both tonsils were enlarged and covered with greyish-white membrane. The tonsillar glands were moderately enlarged and tender and foetor oris was present. The colour was pale and the complexion had a slightly livid tint. The temperature was 98.4°F., and the pulse rate 104. The cardiac rhythm was regular, and the pulse was of normal tension and good volume. Acetone and diacetic acid were present in the urine. The bacteriological report was positive and 16,000 units of antitoxin were injected intramuscularly.

The throat was clear of membrane on the 12th day of illness. Acetone and diacetic acid finally disappeared from the urine two days later. Progress was satisfactory until the 32nd day of illness when nasal speech and regurgitation of fluids became evident. On the 35th day of illness palatal paralysis was complete. Squint and diplopia, affecting the right eye, developed on the 37th day, indicative of paralysis of the 6th nerve. Coincidentally with the occurrence of these paralyses the cardiac rhythm became totally irregular. The first sound was markedly weak, and the second sound was split. Vomiting occurred on the 40th day and was associated with engorgement of the liver, the organ being palpable one inch below the costal margin. Acetone and diacetic acid were present in the urine. Vomiting, ketonuria and cardiac arythema persisted till the 44th day of illness. The patient's condition thereafter was much improved and normal speech was resumed on the 48th day. The heart sounds were then normal.

Three days later no evidence of squint could be found

and the subsequent progress was satisfactory. The patient was dismissed well on the 80th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance tests and estimations of blood cholesterol were made (1) during the acute stage of illness, (2) during the stage of palatal and external ocular paralysis with cardiac involvement, and (3) on recovery.

Glucose Tolerance.

(1) 8th day of illness: 30 grams glucose.

116 215 174 146 120 128 (Chart 17)
Glycosuria developed during the test.

(2) 39th day of illness: 30 grams glucose.

93 186 157 131 108 96 (Chart 18)
Glycosuria developed during the test.

(3) 60th day of illness.

88 172 123 86 90 88 (Chart 19)

Blood Cholesterol.

(1) 8th day of illness, 144 mgms. per 100 c.cms. blood.
(2) 39th day of illness, 253 " " 100 " "
(3) 60th day of illness, 177 " " 100 " "

3. Note.

The case was one of severe faucial diphtheria in whom palatal and ocular paralysis occurred late in the illness, and was accompanied by cardiac involvement and ketosis. The first blood sugar curve reveals the existence of fasting hyperglycaemia and delay in the storage of carbohydrate. Acetone and diacetic acid were present in the urine and sugar appeared, also, during the test. The blood cholesterol was low.

When paralysis was established the delay in storage was

still evident and the renal threshold was again exceeded. The blood cholesterol was found to be abnormally high.

During convalescence the blood sugar, glucose tolerance and blood cholesterol were normal.

CASE 10.

G.Gray ..... Age 7 years.
Admitted ..... 3:12:32.
Day of Illness ..... Third.
Dismissed ..... 4:1:33.
Classification ..... Moderate.
Throat Swab ..... Positive.
Antitoxin ..... 12,000 units.
Journal Reference .... Ward 1 East.

1. History.

Admitted on 3rd day of illness. Faucial and palatal oedema was present. The left tonsil was covered with loosely adherent yellowish-white membrane and on the right tonsil, also, there was a patch of smaller extent: oral foetor was very noticeable, and the tonsillar glands were moderately enlarged.

The complexion was tinged with cyanosis. The temperature was 102°F. and the pulse rate 138. The pulse was regular, slightly soft and full. There was weakening of the first sound at the apex. Acetone and diacetic acid were present in the urine. 12,000 units of antitoxin were injected intramuscularly.

By the 5th day of illness the temperature was 98.4°F. and the cardiac sounds were of normal intensity. The urine still contained traces of acetone and diacetic acid becoming finally clear two days later. The throat was clear of membrane on the 8th day. The faucial and palatal oedema gradually diminished and the throat was normal on the 11th day of illness. The subsequent course of the illness was favourable and the patient was dismissed well on the 32nd day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated (1) during the stage of toxaemia, (2) after the subsidence of the acute symptoms, and (3) during convalescence.

Glucose Tolerance.

(1) 5th day of illness: 30 grams. glucose.

106 184 157 138 115 110 (Chart 20)
Glycosuria developed during the test.

(2) 8th day of illness.

85 169 143 118 90 96 (Chart 21)
Glycosuria absent during the test.

(3) 26th day of illness.

90 162 88 95 115 92 (Chart 22)

Blood Cholesterol.

(1) 5th day of illness, 139 mgms. per 100 c.cms. blood.
(2) 8th day of illness, 165 " " 100 " "
(3) 26th day of illness, 172 " " 100 " "

3. Note.

A fasting hyperglycaemia, a definite delay in storage and a maximum concentration above the renal threshold with resultant glycosuria are evident during the toxic stage. The blood cholesterol was low. The urine contained acetone and diacetic acid. The storage defect is still obvious after the acute symptoms had passed. The urine was now clear of acetone and diacetic acid, the fasting blood sugar was normal and the test was unassociated with glycosuria. The blood cholesterol was 165 mgms. per cent.

The blood sugar curve, during convalescence, is normal but atypical in the sense that the blood sugar concentration falls to a level below the fasting value at the 60 minute interval, this dip in the curve being followed by a secondary rise and subsequent fall. The blood cholesterol at this time was normal.

CASE 11.

R.McIntosh ..... Age 10 years.
Admitted ..... 9:12:32.
Day of Illness ..... Third.
Died ..... 12:12:33.
Classification ..... Severe.
Throat Swab ..... Positive.
Antitoxin ..... 80,000 units.
Journal Reference .... Ward 1 East.

1. History.

The case was one of severe faucial diphtheria ending fatally on the sixth day. On admission the patient was in the throes of an overwhelming toxaemia. The soft palate, the uvula and the tonsils were considerably oedematous so that the individual structures could not be distinguished in the resulting swelling. Thick adherent greyish-black membrane covered the parts and extended forwards to the hard palate. A profuse sero-purulent discharge exuded from the anterior nares and enlarged painful glands formed a "consular" collar around the neck. Foetor oris was intense.

The complexion was cyanosed and the expression apathetic. The extremities were cold and livid. On admission the temperature was 100.2°F. and the pulse rate 120. The pulse was regular in rate and rhythm. The heart sounds were forceful indicating the laboured action of the heart. The first sound was soft and muffled, the second sound loud and booming. A systolic murmur was present, its greatest intensity being along the left sternal border. The liver was congested and palpable ¾" below the costal margin. The urine contained acetone and diacetic acid. 20,000 units of antitoxin were injected intramuscularly and 20,000 units intravenously.

Cardiac arrhythmia developed on the following day, groups of premature beats being felt frequently at the wrist. The general and local condition of the patient had not improved and a further intravenous injection of 20,000 units of antitoxin was given. On the 5th day of illness an additional 20,000 units of antitoxin were administered

intramuscularly. On the same day vomiting occurred at frequent intervals, and the cardiac rhythm became totally irregular. The intensity of the symptoms remained unrelieved and the patient died, on the sixth day, of early cardiac failure.

2. Glucose Tolerance and Blood Cholesterol.

Glucose Tolerance and Blood Cholesterol were estimated on the 4th day of illness. Further estimations were deemed inadvisable owing to the extreme condition of the patient.

Glucose Tolerance.

4th day of illness: 30 grams. glucose.

76 175 122 146 115 108 (Chart 23)

Blood Cholesterol.

4th day of illness, 242 mgms. per 100 c.cms. of blood.

3. Note.

The case was one of severe faucial diphtheria, ending fatally, by early cardiac failure, on the sixth day. The blood sugar curve shows a fasting hypoglycaemia, a maximum concentration in excess of the renal threshold at the 60 minute interval, and a definite delay in storage. Glycosuria developed during the test. At the 2½ hour interval the blood sugar is still above fasting level. The blood cholesterol was abnormally high.

CASE 12.-

D.Kennedy ..... Age 11 years.
Admitted ..... 6:1:33.
Day of Illness ..... Fourth.
Dismissed ..... 8:2:33.
Classification ..... Mild.
Throat Swab ..... Positive.
Antitoxin ..... 8,000 units.
Journal Reference .... Ward 1 East.

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1. History.

Both tonsils were enlarged and congested. A small patch of membrane was present on the right tonsil. Foetor oris was absent and there was no glandular enlargement.

The temperature was 98.2°F. and the pulse rate 96. The pulse was regular in rate, rhythm and volume. The heart sounds were pure and of normal intensity, and the colour was good. The urine was clear of acetone and diacetic acid. 8,000 units of antitoxin were administered intramuscularly. The throat was clear of membrane on the 8th day and the further progress of the patient was uneventful. He was dismissed well on the 36th day.

2. Glucose Tolerance and Blood Cholesterol.

The glucose tolerance and blood cholesterol were estimated (1) during the acute stage, and (2) during convalescence.

(1) 5th day of illness: 30 grams. glucose.

93 152 176 108 88 95 (Chart 24)

(2) 30th day of illness: 30 grams. glucose.

96 168 124 90 102 98 (Chart 25)

Blood Cholesterol.

(1) 5th day of illness, 179 mgms. per 100 clcms. blood.
(2) 30th day of illness, 187 " " 100 " "

3. Note.

The case was one of mild faucial diphtheria presenting no features of special interest during its course. The blood sugar, glucose tolerance and blood cholesterol were apparently normal, during the acute stage and on recovery.

CASE 13.

R. Monteith ..... Age 8 years.
Admitted ..... 7:1:33.
Day of Illness ..... Sixth.
Dismissed ..... 11:2:33.
Classification ..... Moderate.
Throat Swab ..... Positive.
Antitoxin ..... 28,000 units.
Journal Reference .... Ward 1 East.

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1. History.

Admitted on the sixth day of illness, the patient was in a very toxic condition. The tonsils and soft palate were intensely inflamed and oedematous. The left tonsil was completely covered with thick yellow membrane and on the right tonsil, also, there were numerous small patches The breath was markedly foetid and the tonsillar glands were slightly enlarged. Pallor and lividity of the face were noticeable. The temperature was 102°F. and the pulse rate 138. The pulse was regular in rate and rhythm but the volume was variable and, at times, thready. On auscultation the first and second sounds were everywhere soft and muffled. Acetone and diacetid acid were present in the urine. 28,000 units of antitoxin were administered intramuscularly.

On the 8th day of illness the throat was clearing and the general condition of the patient was much improved. On the 9th day the temperature and pulse rate were normal and the urine was clear of acetone and diacetic acid. The heart sounds were of normal intensity by the 11th day, at which time the throat was completely clear of exudation, congestion and oedema. The further progress was uneventful and the patient was dismissed well on the 40th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated (1) during the toxic stage, and (2) after recovery.

Glucose Tolerance.

(1) 7th day of illness: 30 grams. glucose.

106 148 175 118 100 112 (Chart 26)
Glycosuria absent during the test.

(2) 30th day of illness: 30 grams. glucose.

94 175 118 87 100 92 (Chart 27)

Blood Cholesterol.

(1) 7th day of illness, 158 mgms. per 100 c.cms. blood.
(2) 30th day of illness, 161 " " 100 " "

3. Note.

The initial glucose tolerance test revealed only a slight departure from normal. A mild fasting hyperglycaemia is evident in the blood sugar curve. The point of maximum concentration was not reached till the 60 minute interval and the return to normal was delayed until two hours had elapsed. At the end of $2\frac{1}{2}$ hours the blood sugar concentration was still above the fasting level. Glycosuria was absent throughout the test. The blood sugar curve, compiled during convalescence, shows no abnormality. The blood cholesterol on both occasions was normal.

CASE 14.

J.McLeod ..... Age 12 years.
Admitted ..... 11:1:33.
Day of Illness ..... Fourth.
Dismissed ..... 6:2:33.
Classification ..... Moderate.
Throat Swab ..... Positive.
Antitoxin ..... 8,000 units.
Journal Reference .... Ward 1 East.

1. History.

Admitted on the 4th day of illness. The tonsils had obviously been removed but inneach tonsillar fossa membranous exudate was present. The right tonsillar gland was enlarged slightly and foetor oris was present. The face was pale and the complexion livid. The heart sounds were soft and muffled. The cardiac rhythm was regular and the pulse was full. Acetone and diacetic acid were present in the urine. 8,000 units of antitoxin were injected intramuscularly.

Recovery was uneventful. Temperature and pulse rate were normal on the 6th day and acetone and diacetic acid finally disappeared one day later. The throat was completely clear of exudate on the 9th day. Progress thereafter was uneventful and the patient was dismissed well on the 29th day of illness.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were investigated (1) during the stage of toxaemia, and (2) after recovery.

Glucose Tolerance.

(1) 5th day of illness: 30 grams. glucose.

110 178 165 125 134 110 (Chart 28)
Glycosuria absent during the test.

(2) 24th day of illness: 30 grams, glucose.

96 168 113 93 102 100 (Chart 29).

Blood Cholesterol.

(1) 5th day of illness, 168 mgms. per 100 c.cms. blood.
(2) 24th day of illness, 185 " " 100 " "

3. Note.

A slight fasting hyperglycaemia and a mild degree of interference with carbohydrate storage are evident from the initial blood sugar curve. Glycosuria was absent during the test. Acetone and diacetic acid were present in the urine. A further glucose tolerance test during convalescence gave a normal curve. The blood cholesterol showed no departure from normal.

CASE 15.

D.Henderson ..... Age 11 years
Admitted ..... 8:1:33.
Day of Illness ..... Fourth.
Dismissed ..... 29:3:33.
Classification ..... Severe
Throat Swab ..... Positive
Antitoxin ..... 26,000 units
Journal Reference ... Ward 1 East.

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1. History.

The patient was admitted on the 4th day of illness. The tonsils, soft palate and uvula were infiltrated and extensively patched with yellowish-white membranous exudate. The tonsillar glands were visibly enlarged and foetor oris was noticeable. The temperature was 99.2°F and the pulse rate 84.

The complexion was pale and slightly livid. The pulse was regular in rate and rhythm and was soft and full. The heart sounds were everywhere muffled. Acetone and diacetic acid were present in the urine. 26,000 units of antitoxin were administered intramuscularly.

The temperature and pulse rate were normal on the 5th day of illness. On the 7th day the throat was clear of membrane, and acetone and diacetic acid were absent from the urine. Albumen was present in traces.

Progress was satisfactory until the 39th day of illness, when nasal speech and cardiac arrhythmia developed. The cardiac sounds were distant and soft and premature contractions were numerous. The pulse varied markedly in rate and rhythm, and there was a tendency for the arrhythmia to take the form of coupling of the beats. On the 40th day complete palatal paralysis and regurgitation were present. On the 42nd day the patient complained of abdominal pain and commenced to vomit. The liver was palpable and tender one inch below the costal margin. The complexion had a dusky cyanotic tinge. Vomiting became persistent, the patient being unable to retain anything taken by the mouth. Albumen, acetone and diacetic acid were present in the urine.

Hepatic congestion, abdominal pain and vomiting remained for two days. Thereafter the symptoms gradually abated and on the 45th day the cardiac rhythm was regular. Albumen, acetone and diacetic acid were still present in traces in the urine, the latter becoming finally clear on the 50th day. Normal speech was resumed on the 53rd day, and the further progress was uneventful. The patient was dismissed well on the 82nd day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated (1) during the stage of toxaemia, (2) at the onset of complete palatal paralysis, and cardiac arrhythmia, and (3) during convalescence.

Glucose Tolerance.

(1) 5th day of illness: 30 grams glucose.

80 167 138 142 112 105 (Chart 30)
Glycosuria absent during test.

(2) 40th day of illness: 30 grams. glucose.

93 170 155 131 118 125 (Chart 31)
Glycosuria absent during test.

(3) 60th day of illness: 30 grams glucose.

106 175 158 100 110 108 (Chart 32)

Blood Cholesterol.

(1) 5th day of illness, 100 mgms. per 100 c.cms blood.
(2) 40th day of illness, 265 " " 100 " "
(3) 60th day of illness, 214 " " 100 " "

3. Note.

During the stage of toxaemia, the glucose tolerance test revealed a low fasting blood sugar and a marked delay in storage. Acetone and diacetic acid were present

in the urine and the blood cholesterol was markedly decreased. When palatal paralysis supervened on the 40th day, the delay in storage was still manifest and the blood cholesterol was abnormally high. Acetone and diacetic acid were again present in the urine. Both tests were unaccompanied by glycosuria. On the 60th day of illness, the fasting blood sugar, blood cholesterol and glucose tolerance were normal.

CASE 16.

R. Gould ..... Age 11 years.
Admitted ..... 11:1:33.
Day of Illness ..... Fourth.
Dismissed ..... 10:2:33.
Classification ..... Mild.
Throat Swab ..... Positive.
Antitoxin ..... 8,000 units.
Journal reference ... Ward 1 East.

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1. History.

Admitted on the 4th day of illness, the right tonsil was covered with thick yellow membrane. The breath was noticeably foetid and the right tonsillar gland was enlarged slightly. The temperature was 98.6°F. on admission, and the pulse rate 90. The urine was clear of albumen but contained acetone and diacetic acid. The heart sounds were pure and of normal intensity. The pulse was regular in rate and rhythm, and of good volume. 8,000 units of antitoxin were administered intramuscularly.

The throat was clear of membrane on the 6th day and acetone and diacetic acid were absent from the urine by the 8th day. The further progress of the case was uneventful and the patient was dismissed well on the 34th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated (1) during toxaemia, and (2) after recovery.

Glucose Tolerance.

(1) 5th day of illness: 30 grams glucose.

96 174 143 110 113 98 (Chart 33)
Glycosuria absent during test.

(2) 30th day of illness: 30 grams. glucose.
98 172 131 92- 105 95 (Chart 34)

Blood Cholesterol.

(1) 5th day of illness, 167 mgms. per 100 c.cms. blood.
(2) 30th day of illness, 178 " " 100 " "

3. Note.

The case was one of mild severity. During the stage of toxaemia a slight departure from normal is noticed in the blood sugar curve, the blood sugar concentration at the end of the two hours' interval being still above the fasting value. Acetone and diacetic acid were present in the urine. During convalescence the glucose tolerance showed no departure from normal. The blood cholesterol was normal on both occasions.

CASE 17.

W.Leask ..... Age 7 years.
Admitted ..... 7:1:33.
Day of Illness ..... Fifth.
Dismissed ..... 6:2:33.
Classification ..... Mild.
Throat Swab ..... Positive.
Antitoxin ..... 8,000 units.
Journal Reference .... Ward 1 East.

1. History.

The left tonsil appeared to have been removed. The right tonsil was enlarged and was covered with numerous small patches of yellow exudate. Filmy exudate was also present in the left tonsillar fossa. The tonsillar glands were both slightly enlarged. Oral foetor was pronounced.

The temperature was 99°F. and the pulse rate 96. The heart sounds were slightly blurred but otherwise normal. The pulse was regular in rate, rhythm and volume.

The urine contained no acetone nor diacetic acid. 8,000 units of antitoxin were injected intramuscularly. Progress was uneventful and the patient was dismissed well on the 34th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated during the toxic stage.

Glucose Tolerance.

(1) 6th day of illness: 30 grams. glucose.

83 168 94 80 92 85 (Chart 35)

Blood Cholesterol.

(1) 6th day of illness, 193 mgms. per 100 c.cms. blood.

3. Note.

The case was one of mild faucial diphtheria. Glucose tolerance and blood cholesterol were found to be normal during the toxaemia.

CASE 18.

R. Daly ..... Age 10 years.
Admitted ..... 14:1:33.
Day of Illness ..... Second.
Dismissed ..... 17:2:33.
Classification ..... Mild.
Throat Swab ..... Positive.
Antitoxin ..... 8,000 units.
Journal Reference ... Ward 1 East.

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1. History.

Admitted on the 2nd day of illness, the tonsils were enlarged and patched with membrane. The palate and uvula were congested, and foetor oris was pronounced. The temperature was 99°F and the pulse rate 88. The pulse was regular and of good quality and the heart sounds were pure. Acetone and diacetic acid were present in the urine in traces. 8,000 units of antitoxin were injected intramuscularly.

The throat was clear of membrane on the 5th day of illness and on the 7th day acetone and diacetic acid were absent from the urine. The subsequent course of the case was uneventful and the patient was dismissed well on the 34th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated (1) during the toxaemia, and (2) after recovery.

Glucose Tolerance.

(1) 3rd day of illness: 30 grams glucose.

120 173 139 118 125 120 (Chart 36)
Glycosuria absent during test.

(2) 30th day of illness: 30 grams glucose.

100 175 130 95 108 105 (Chart 37)

Blood Cholesterol.

(1) 3rd day of illness, 162 mgms. per 100 c.cms.blood.
(2) 30th day of illness, 167 " " 100 " "

3. Note.

During the height of the toxaemia, the blood sugar curve shows an initial fasting hyperglycaemia, but no other abnormality. Acetone and diacetic acid were present in the urine but glycosuria was absent throughout the test. After recovery the fasting blood sugar and glucose tolerance were normal. The blood cholesterol showed no departure from normal on either occasion.

CASE 19.

A.Morecambe ..... Age 12 years.
Admitted ..... 14:1:33.
Day of Illness ..... Fifth.
Dismissed ..... 15:2:33.
Classification ..... Severe.
Throat Swab ..... Positive.
Antitoxin ..... 30,000 units.
Journal Reference .... Ward 1 East.

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1. History.

Admitted on the 5th day of illness, the throat was markedly congested and oedema of the palate was present. Both tonsils were covered with thick greyish-white membrane. The tonsillar glands were visibly enlarged and foetor oris was pronounced. The temperature was 100.6°F on admission and the pulse rate 112. The colour was poor and tinged with ashen cyanosis. The heart sounds were soft and distant, but pure, and of regular rhythm. The pulse was rapid, regular, of small volume and low tension. Acetone and diacetic acid were present in the urine and a transient slight reduction of Fehling's solution was also observed. 20,000 units of antitoxin were administered intramuscularly, and 10,000 units intravenously.

The temperature and pulse rate were normal on the 7th day of illness. The throat was clear of membrane on the 8th day, but congestion and oedema remained for some time thereafter, the throat finally becoming clear on the 12th day.

On the 15th day, the pulse became irregular in rate and rhythm, and a soft blowing systolic murmur could be heard at the apex and along the left border of the sternum. The cardiac sounds were muffled and the pulse rate varied between 70 and 120 beats per minute. Numerous premature contractions could be felt at the wrist. Acetone and diacetic acid were still present in the urine and slight traces of albumen were also noted.

Cardiac arrhythmia persisted until the 20th day, by which time the quality of the heart sounds was much improved. The urine became clear of albumen, acetone and diacetic acid on the 24th day. The further progress of the case was uneventful and the patient was dismissed well on the 36th day.

2. Glucose Tolerance and Blood Cholesterol.

The glucose tolerance and blood cholesterol were estimated (1) during the toxic stage, (2) during the stage of cardiac arrhythmia, and (3) on recovery.

Glucose Tolerance.

(1) 6th day of illness: 30 grams glucose.

80 196 165 142 103 100 (Chart 38)
Glycosuria developed during test.

(2) 18th day of illness.

83 173 145 109 115 106 (Chart 39)
Glycosuria absent during test.

(3) 30th day of illness.

100 150 175 98 104 95 (Chart 40)
Glycosuria absent during test.

Blood Cholesterol.

(1) 6th day of illness, 190 mgms. per 100 c.cms blood.
(2) 18th day of illness, 244 " " 100 " "
(3) 30th day of illness, 179 " " 100 " "

3. Note.

The case was one of severe faucial diphtheria admitted to hospital relatively late in the toxic stage. The initial blood sugar curve shows a slight fasting hypoglycaemia and a marked delay in storage accompanied

clinically by the development of glycosuria. The blood cholesterol during this stage was normal. On the 15th day myocarditis and cardiac arrhythmia developed and a further blood sugar curve at this stage shows a persistence of the carbohydrate storage defect. The blood cholesterol was abnormally high.

When clinical recovery was established the blood sugar, glucose tolerance and blood cholesterol showed no departure from normal.

Case 20.

R. Moore	Age 5 years
Admitted	17:1:33
Day of Illness	Second
Dismissed	5:4:33
Classification	Moderate
Throat Swab	Positive
Antitoxin	12,000 units
Journal Reference	Ward 1 East

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1. History.

Both tonsils were slightly enlarged and covered with yellowish-white membrane. The soft palate and peritonsellar tissues were markedly congested and the breath was foul. Glandular enlargement was absent.

The temperature was 99.4 F and the pulse rate 128. The complexion was pale and slightly livid. The pulse was regular in rate and rhythm. Its volume was small and its tension low. The cardiac sounds were weak and distant. The urine contained albumen acetone and diacetic acid.

Tachycardia persisted and on the 10th day of illness an intermittency of the pulse rate developed and extra beats with compensatory pause were numerous. The pulse was small and thready, the cardiac sounds were soft and distant and a systolic murmur became audible at the apex. Acetone and diacetic acid were again present in the urine. The pulse remained rapid and more or less irregular until the 29th day of illness. On the 20th day sickness became troublesome and persisted for two days.

The condition of the patient gradually improved and by the 40th day of illness the pulse was regular in rate, rhythm and volume and the heart sounds were puree and of normal intensity. The urine was then clear. Progress thereafter was satisfactory and the patient was dismissed well.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated

(1) during the toxic stage, (2) during the stage of cardiac arrhythmia and tachycardia and (3) after clinical recovery.

Glucose Tolerance.

(1) 3rd day of illness: 30 grams glucose.

90 150 203 145 113 100 (Chart 41)
Glycosuria developed during the test.

(2) 17th day of illness: 30 grams glucose.

86 135 165 120 95 97 (Chart 42)
Glycosuria absent during the test.

(3) 42nd day of illness: 30 grams glucose.

94 160 122 98 90 90 (Chart 43)
Glycosuria absent during the test.

Blood Cholesterol.

(1) 3rd day of illness: 194 mgms per 100 c.cms blood
(2) 17th day of illness: 244 " " " " "
(3) 42nd day of illness: 189 " " " " "

3. Note.

During the stage of toxaemia the fasting blood sugar was normal. The blood sugar curve showed a definite delay in returning to normal and glycosuria developed. The blood cholesterol was normal. Tachycardia persisted till the 29th day of illness and from the 10th day was associated with cardiac arrhythmia. On the 17th day the blood sugar curve showed a persistent delay in falling to fasting level but glycosuria was absent and the fasting blood sugar was low. At this stage the blood cholesterol was abnormally high. Ketone bodies were present in the urine until the 6th day and from the 15th day until the 22nd. The blood sugar curve, on recovery showed a concentration above the fasting level at the end of two hours. This delay however was only trivial.

CASE 21.

J. Nicol ..... Age 12 years.
Admitted ..... 17:1:33.
Day of Illness ..... Third.
Dismissed ..... 16:2:33.
Classification ..... Severe.
Throat Swab ..... Positive.
Antitoxin ..... 40,000 units.
Journal Reference .... Ward 1 East.

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1. History.

Both tonsils were enlarged and extensively covered with thick greyish-white membrane, which extended across the palatal arches and covered the uvula. The palatal and peritonsillar tissues were markedly congested and infiltrated, and foetor oris was intense. The tonsillar glands were considerably enlarged and were hard and painful. On admission the temperature was 102.6°F and the pulse rate 112. There was pallor and cyanosis of the complexion. On auscultation the cardiac sounds were forceful. The first sound was soft and blurred, the second sound loud and booming. The pulse was regular in rate and rhythm and of moderate volume and tension. The urine contained acetone and diacetic acid. 20,000 units of antitoxin were injected intramuscularly and 20,000 units intravenously.

The temperature and the pulse rate were normal on the 7th day of illness and the urine was free of acetone and diacetic acid one day later. The throat was clear of membrane on the 10th day and was normal by the 13th. Progress was uneventful and the patient was dismissed well on the 34th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated (1) during the toxic stage, and (2) after clinical recovery.

Glucose Tolerance.

(1) 5th day of illness: 30 grams glucose.

78 195 162 134 110 112 (Chart 44).
Glycosuria developed during test.

(2) 30th day of illness: 30 grams glucose.

97 172 126 90 105 100 (Chart 45)
Glycosuria absent during test.

Blood Cholesterol.

(1) 5th day of illness, 256 mgms. per 100 c.cms blood.
(2) 30th day of illness, 193 " " 100 " "

3. Note.

The glucose tolerance test carried out during the stage of toxaemia showed a fasting hypoglycaemia, a maximum concentration in excess of the renal threshold, with resulting glycosuria, and a definite delay in the removal of the excess of sugar from the blood. The blood cholesterol during this stage was increased.

During convalescence the fasting blood sugar, glucose tolerance and blood cholesterol showed no departure from normal.

CASE 22.

N. Bryce ..... Age 10 years.
Admitted ..... 25:1:33.
Day of Illness ..... Third.
Dismissed 27:2:33
Classification ..... Mild.
Throat Swab ..... Positive.
Antitoxin ..... 12,000 units.
Journal Reference .... Ward 1 East.

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1. History.

Admitted on the 3rd day of illness, the case was one of mild faucial diphtheria. The tonsils were both slightly enlarged and the right tonsil was partly covered with a patch of dirty greyish-white membrane. The breath was not markedly foetid and glandular enlargement was absent. Toxaemia was slight. The temperature and pulse rate on admission were respectively 102.2°F and 116. The heart sounds were pure though slightly blurred and the pulse was regular in rate and rhythm, of good volume and moderate tension. The urine contained both acetone and diacetic acid. 12,000 units of antitoxin were injected intramuscularly.

The temperature was normal on the 4th day. The throat was clear of membrane on the 8th day and acetone and diacetic acid remained until the 10th day. Tachycardia associated with a regular cardiac rhythm persisted until the 12th day, when the pulse rate fell to normal. The further progress was uneventful and the patient was dismissed well on the 36th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated (1) during the height of the illness, and (2) after recovery.

Glucose Tolerance.

(1) 5th day of illness: 30 grams glucose.

116 162 134 120 125 118 (Chart 46)

Glycosuria absent during test.

(2) 30th day of illness: 30 grams glucose.

92 158 121 85 96 90 (Chart 47)
Glycosuria absent during test.

Blood Cholesterol.

(1) 5th day of illness,.234.mgms..per 100 c.cms. blood.
(2) 30th day of illness, 173 " " 100 " "

3. Note.

The first glucose tolerance test demonstrated a fasting hyperglycaemia and an inability to store and utilize sugar. This condition was associated with ketone bodies in the urine and a high cholesterol content in the blood. The defect in carbohydrate metabolism was not accompanied by sugar excretion in the urine.

CASE 23.

R.Martin ..... Age 11 years.
Admitted ..... 25:1:33.
Day of Illness ..... Sixth.
Dismissed ..... 2:3:33.
Classification ..... Mild.
Throat Swab ..... Positive.
Antitoxin ..... 12,000 units.
Journal Reference .... Ward 1 East.

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1. History.

The patient was admitted to hospital on the 6th day of illness. A small patch of membrane was present on the right tonsil and follicular exudate was observed on the left. Foetor oris was slight. Glandular enlargement and palatal infiltration were absent.

The temperature was 98.2°F on admission and the pulse rate 96. The heart sounds were pure though slightly muffled. The pulse was regular in rate and rhythm, of small volume and low tension. Albumen, acetone and diacetic acid were present in the urine. 12,000 units of antitoxin were administered intramuscularly.

The temperature and pulse rate were normal on the 7th day. Exudate remained on the throat till the 8th day and the urine became finally clear on the 10th. The further progress was uneventful and the patient was dismissed well on the 36th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated (1) during the acute stage, and (2) on recovery.

Glucose Tolerance.

(1) 7th day of illness: 30 grams glucose.

76 178 141 123 100 95 (Chart 48)
Glycosuria developed during test.

(2) -30th day of illness: 30 grams glucose.

88 167 150 90 96 92 (Chart 49)
Glycosuria absent during test.

Blood Cholesterol.

(1) 6th day of illness, 159 mgms. per 100 c.cms.blood.
(2) 30th day of illness, 171 " " 100 " "

3. Note.

This case, although mild, was admitted relatively far advanced in toxaemia. Fasting hypoglycaemia, delay in carbohydrate storage with development of glycosuria, were noted during the acute stage of the disease. On recovery, the fasting blood sugar and glucose tolerance showed no departure from normal. The blood cholesterol was normal on both occasions.

CASE 24.

A. Toal ..... Age 8 years.
Admitted ..... 2:2:33.
Day of Illness ..... Second.
Dismissed ..... 8:3:33.
Classification ..... Mild.
Throat Swab ..... Positive.
Antitoxin ..... 8,000 units.
Journal Reference .... Ward 1 East.

1. History.

Admitted on the second day of illness, the throat was slightly inflamed and follicular exudate was present in both tonsils. Oral foetor, palatal oedema and glandular enlargement were absent. The temperature on admission was 100°F and the pulse rate 124. The colour was good and the heart sounds normal. The pulse was regular, rapid and full. Acetone and diacetic acid were not present in the urine. 8,000 units of antitoxin were injected intramuscularly.

The temperature and pulse were normal on the 5th day of illness and the throat was clear on the 7th day. Progress was satisfactory and without event, and the patient was dismissed well on the 34th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated (1) during the acute stage, and (2) after recovery.

Glucose Tolerance.

(1) 3rd day of illness: 30 grams glucose.

115 162 174 105 125 110 (Chart 50)
Glycosuria absent during test.

(2) 30th day of illness: 30 grams glucose.

96 170 143 - 98 102 100 (Chart 51)

Blood Cholesterol.

(1) 3rd day of illness, 134 mgms. per 100 c.cms.blood.
(2) 30th day of illness, 168 " " 100 " "

3. Note.

The case was one of mild faucial diphtheria recovering uneventfully. The initial blood sugar curve shows a fasting hyperglycaemia. Storage and utilization of sugar were unaffected. Acetone and diacetic acid were not present in the urine, and the blood cholesterol was low.

Recovery was associated with normal findings with regard to the fasting blood sugar, glucose tolerance and blood cholesterol.

CASE 25.

J. Carr .....Age 10 years.
Admitted ..... 22:2:33.
Day of Illness ..... Seventh.
Dismissed ..... 29:3:33.
Classification ..... Moderate.
Throat Swab ..... Positive.
Antitoxin ..... 8,000 units.
Journal Reference .... Ward 1 East.

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1. History.

The patient was admitted to hospital on the 7th day of illness. Small patches of membrane were present on both tonsils. Oral foetor was slight and glandular enlargement and palatal infiltration were absent.

The temperature was 98.2°F on admission and the pulse rate 90. The face was pale and slightly livid. The heart sounds were regular, though of muffled quality, and the pulse was small and of low tension. The urine contained albumen, acetone and diacetic acid. 8,000 units of antitoxin were injected intramuscularly.

The temperature and pulse rate were normal on the 9th day of illness and the throat was clear by the 12th. On the 16th day of illness tachycardia developed, the pulse rate ranging from 90 to 110 beats per minute. Simultaneously a soft blowing systolic murmur could be heard at the apex. Albumen, acetone and diacetic acid were still present in the urine. Tachycardia persisted until the 23rd day of illness, the heart sounds being then pure and of normal intensity.

The urine was clear of acetone and diacetic acid on the 26th day, albuminuria persisting in slight traces for some days thereafter. The urine finally became clear on the 30th day.

The further progress was satisfactory and the patient was dismissed well on the 41st day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated (1) during the acute stage of the illness, (2) during the stage of tachycardia, and (3) during convalescence.

Glucose Tolerance.

(1) 8th day of illness: 30 grams. glucose.

96 192 147 124 102 95 (Chart 52)
Glycosuria developed during test.

(2) 18th day of illness: 30 grams glucose.

90 170 136b 105 100 98 (Chart 53)
Glycosuria absent during test.

(3) 36th day of illness: 30 grams glucose.

98 162 106 95 90 102 (Chart 54)

Blood Cholesterol.

(1) 8th day of illness, 216 mgms. per 100 c.cms. blood.
(2) 18th day of illness, 273 " " 100 " "
(3) 36th day of illness, 198 " " 100 " "

3. Note.

The case was one of mild faucial diphtheria presenting no features of special interest beyond the fact of the relatively late admission to hospital and the subsequent development of tachycardia. The initial glucose tolerance test showed a fasting hypoglycaemia, a maximum concentration above the renal threshold with development of glycosuria and a definite delay in carbohydrate storage. When tachycardia developed this abnormality of carbohydrate metabolism was still present though in less marked degree, the fasting blood sugar more closely approximating to normal and glycosuria being absent. The blood cholesterol shows a marked increase during the

latter stage. No departure from normal was found in the estimations during convalescence.

CASE 26.

G. Reid ..... Age 7 years.
Admitted ..... 16:1:33.
Day of Illness ..... Third.
Dismissed ..... 5:4:33.
Classification ..... Severe.
Throat Swab ..... Positive.
Antitoxin ..... 32,000 units.
Journal Reference .... Ward 1 East.

1. History.

The tonsils were covered with thick yellowish-white membrane, and palatal and peritonsillar infiltration was intense. Oral foetor was present and the cervical glands were enlarged and tender particularly on the left side. The temperature on admission was 102°F and the pulse rate 92.

The face was pale and livid, the heart sounds soft and distant and the pulse, though regular in rate and rhythm, was of small volume and low tension. The urine contained albumen, acetone and diacetic acid. 20,000 units of antitoxin were administered intramuscularly and 12,000 units intravenously.

On the 6th day of illness, the temperature and the pulse rate were normal. The urine was clear of acetone and diacetic acid on the 8th day and the throat was normal on the 10th day. Albuminuria persisted in traces until the 20th day.

Progress continued satisfactorily until the 33rd day of illness, when palatal paresis and nasal speech developed. Complete palatal paralysis and regurgitation supervened on the 35th day and persisted until the 43rd day, normal speech being resumed 5 days later. Acetone and diacetic acid were present in the urine from the 34th till the 46th day. The patient was dismissed well on the 80th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated (1) during the acute stage, (2) during the stage of palatal paralysis and ketonuria, and (3) after clinical recovery.

Glucose Tolerance.

(1) 4th day of illness: 30 grams glucose.

96 193 157 132 110 115 (Chart 55)
Glycosuria developed during test.

(2) 38th day of illness: 30 grams glucose.

83 171 123 110 120 105 98 (Chart 56)
Glycosuria absent during the test.

(3) 78th day of illness: 30 grams glucose.
90 162 110 85 90 92 (Chart 57)
Glycosuria absent during test.

Blood Cholesterol.

(1) 4th day of illness, 136 mgms. per 100 c.cms. blood.
(2) 38th day of illness, 264 " " 100 " "
(3) 78th day of illness, 189 " " 100 " "

3. Note.

During the acute stage of the disease the glucose tolerance test showed a definite degree of delay in carbohydrate storage and a point of maximum concentration in excess of the renal threshold, with resultant glycosuria. Ketone bodies were present in the urine and the blood cholesterol was markedly decreased.

The storage defect was still present when palatal paralysis supervened. Glycosuria did not result from the test at this stage but acetone and diacetic acid were present in the urine. The blood cholesterol was abnormally high.

Glucose tolerance and blood cholesterol were normal after clinical recovery. The fasting blood sugar showed no departure from normal throughout.

CASE 27.

D. Casey ..... Age 12 years.
Admitted ..... 24:2:33.
Day of Illness ..... Fourth.
Dismissed ..... 29:3:33.
Classifidation ..... Mild.
Throat Swab ..... Positive.
Antitoxin ..... 12,000 units.
Journal Reference .... Ward 1 East.

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1. History.

The tonsils were both enlarged and on each there was a small patch of yellowish-white membranous exudate. The peritonsillar tissues and the soft palate were slightly inflamed. Oral foetor and glandular enlargement were absent.

On admission the temperature was 100°F and the pulse rate 120. The cardiac sounds were normal and the pulse was regular in rate and rhythm. The urine contained albumen in traces. Acetone and diacetic acid were absent. 12,000 units of antitoxin were administered intramuscularly.

The temperature and pulse were normal on the 6th day. On the 7th day the throat was clear of membrane and albumen was absent from the urine. The further progress was uneventful and the patient was dismissed well on the 40th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were investigated (1) during the acute stage, and (2) after recovery.

Glucose Tolerance.

(1) 5th day of illness: 30 grams glucose.

113 176 121 109 110 115 (Chart 58)
Glycosuria absent during test.

(2) 30th day of illness: 30 grams glucose.

95 161 113 98 97 b 95 (Chart 59)
Glycosuria absent during test.

Blood Cholesterol.

(1) 5th day of illness, 152 mgms. per 100 c.cms. blood.
(2) 30th day of illness, 176 " " 100 " "

3. Note.

The initial glucose tolerance test showed a slight fasting hyperglycaemia. No defect in the removal of the excess of blood sugar occurred. The blood cholesterol was within normal limits.

CASE 28.

J.Aitken ..... Age 7 years.
Admitted ..... 27:2:33.
Day of Illness ..... Fifth.
Died ..... 5:3:33.
Classification ..... Severe.
Throat Swab ..... Positive.
Antitoxin ..... 36,000 units.
Journal Reference .... Ward 1 East.

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1. History.

The fauces and soft palate were intensely congested and infiltrated. Firmly adherent greyish-black membrane covered each tonsil and extended across the palatal arches to the uvula. Exudate was also present on the hard palate. The glands at the angles of the jaw were enlarged and tender and gave the patient the so-called "bull neck" appearance. Foetor oris was intense and a sero-purulent discharge exuded from the nostrils. On admission his temperature was 100.6°F. and the pulse rate 136.

The complexion was pale and cyanosed and the extremities were cold and livid. The pulse was rapid, regular in rate and rhythm, and thready. The heart sounds were soft and blurred, the first sound being decidedly shortened and the second sound reduplicated. The liver was enlarged and could be felt ¾" below the costal margin. Albumen, acetone and diacetic acid were present in the urine. 16,000 units of antitoxin were injected intramuscularly on admission and 20,000 units were administered intravenously on the following day.

The patient's condition progressively deteriorated. On the 7th day of illness a sharp nasal haemorrhage occurred, Extrasystoles were numerous on the 8th day and on the 9th a total arrhythmia developed. Reduplication of the first sound with gallop rhythm was present. Active sickness occurred and persisted, irrespective of food taken, until near the end. The material vomited was streaked with blood. The patient died of cardiac failure on the 11th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were investigated (1) on the 7th day of illness, and fasting blood sugar and blood cholesterol estimations were made (2) on the 8th, and (3) on the 10th day.

Glucose Tolerance.

(1) 7th day of illness: 30 grams glucose.

80 215 164 168 156 126 (Chart 60)
Glycosuria present during test.

Fasting Blood Sugar.

(2) 8th day of illness, 76 mgms. per 100ccms. of blood.
(3) 10th day of illness, 72 " " 100 " " "

Blood Cholesterol.

(1) 7th day of illness, 206 mgms. per 100 c.cms. blood.
(2) 8th day of illness, 234 " " 100 " "
(3) 10th day of illness, 268 " " 100 " "

3. Note.

The case was one of severe diphtheria terminating by cardiac failure on the 11th day of illness. The glucose tolerance test showed a definite degree of delay in the removal of the excess of blood sugar and a point of maximum concentration such that glycosuria occurred during the test. The estimations of the fasting blood sugar made later in the illness reveal a hypoglycaemia. Acetone and diacetic acid were present in the urine throughout and the blood cholesterol was abnormally increased.

CASE 29.

D. Russell ..... Age 7 years
Admitted ..... 2:3:33.
Day of Illness ..... Third.
Dismissed ..... 6:4:33.
Classification ..... Mild.
Throat Swab ..... Positive.
Antitoxin ..... 12,000 units.
Journal Reference .... Ward 1 East.

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1. History.

A small patch of yellowish-white membrane was present on each tonsil. Oral foetor was not marked and glandular enlargement was absent. On admission the temperature was 100.4°F and the pulse rate 90. The pulse was regular, of good volume and moderate tension, and the heart sounds were pure though slightly muffled. Acetone and diacetic acid were present in the urine. 12,000 units of antitoxin were injected intramuscularly.

The temperature and the pulse rate were normal and the urine clear, on the 4th day of illness. Progress continued uneventfully and the patient was dismissed well on the 38th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated (1) during the acute stage of the illness, and (2) after recovery.

Glucose Tolerance.

(1) 4th day of illness: 30 grams glucose.

112 169 129 105 128 118 (Chart 61)
Glycosuria absent during test.

(2) 30th day of illness: 30 grams glucose.

87 172 143 90 95 88 (Chart 62)
Glycosuria absent during test.

Blood Cholesterol.

(1) 4th day of illness, 153 mgms.per 100 c.cms blood.
(2) 30th day of illness, 171 " " 100 " "

3. Note.

The case was one of mild faucial diphtheria presenting no features of unusual clinical interest. The glucose tolerance test during the toxic stage showed no departure from normal with regard to storage but revealed a definite hyperglycaemia in the fasting blood. The blood cholesterol was within normal limits when the patient had recovered, no departure from normal was observed in glucose tolerance, fasting blood sugar or blood cholesterol.

CASE 30.

D.Cruden ..... Age 14 years.
Admitted ..... 7:3:33.
Day of Illness ..... Third.
Dismissed:..... 8:4:33.
Classification ..... Moderate.
Throat Swab ..... Positive.
Antitoxin ..... 12,000 units.
Journal Reference .... Ward 1 East.

1. History.

The tonsils were enlarged and covered with thick adherent greyish-white membrane. The soft palate and peritonsillar tissues were inflamed and infiltrated, and foetor oris was present. Both tonsillar glands were enlarged and tender.

On admission the temperature was 99.6°F and the pulse rate 100. The face was pale and slightly cyanosed. The pulse was regular, of good volume and moderate tension. The heart sounds were pure but soft and distant. Acetone and diacetic acid were present in the urine. 12,000 units of antitoxin were injected intramuscularly.

On the 6th day of illness the temperature and the pulse rate were normal. Acetone and diacetic acid disappeared from the urine on the 7th day and the throat was clear of exudate and infiltration on the 10th day. Progress continued satisfactorily and the patient was dismissed well on the 35th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated (1) during the toxic stage, and (2) after recovery.

Glucose Tolerance.

(1) 4th day of illness: 50 grams glucose.

124 169 142 117 120 125 (Chart 63)
Glycosuria absent during test.

(2) 30th day of illness: 50 grams glucose.

103 171 98 116 100 105 (Chart 64)
Glycosuria absent during test.

Blood Cholesterol.

(1) 4th day of illness, 123 mgms. per 100 c.cms.blood.
(2) 30th day of illness, 161 " " 100 " "

3. Note.

The initial blood sugar curve shows a fasting hyperglycaemia but no defect in the carbohydrate storage mechanism was evident. The blood cholesterol was abnormally low.

After recovery the fasting blood sugar, blood cholesterol and glucose tolerance showed no departure from normal.

CASE 31.

J. Irvine ..... Age 12 years.
Admitted ..... 8:3:33.
Day of Illness ..... Fourth.
Dismissed ..... 10:4:33.
Classification ..... Moderate.
Throat Swab ..... Positive.
Antitoxin ..... 12,000 units.
Journal Reference .... Ward 2 East.

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1. History.

Both tonsils were enlarged and covered with numerous small patches of membranous exudate. Foetor oris was slight and palatal infiltration and glandular enlargement were absent.

On admission the temperature was 101°F and the pulse rate 96. The colour was good. The heart sounds were of good quality and the pulse was regular in rate, rhythm and bolume. The tension was moderate. The urine contained acetone and diacetic acid. 12,000 units of antitoxin were injected intramuscularly.

On the 6th day the temperature and the pulse rate were normal and the urine was free of acetone and diacetic acid. The throat was clear on the 8th day. Progress thereafter was satisfactory and the patient was dismissed well on the 37th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated (1) during the toxic stage, and (2) after recovery.

Glucose Tolerance.

(1) 5th day of illness: 30 grams glucose.

108 186 137 118 120 114 (Chart 65)
Glycosuria present during test.

(2) - 30th day of illness: 30 grams glucose.

97 170 125 75 100 100 (Chart 66)
Glycosuria absent during test.

Blood Cholesterol.

(1) 5th day of illness, 123 mgms. per 100 c.cms blood.
(2) 30th day of illness, 155 " " 100 " "

3. Note.

During the toxic stage, the blood sugar concentration was still above the fasting value at the end of 2½ hours. The renal threshold was passed and glycosuria developed during the test. The blood cholesterol was markedly decreased. A further glucose tolerance test, during convalescence, gave results in all respects normal. The blood cholesterol was then also within normal limits.

CASE 32.-

S.McGowan ..... Age 8 years.
Admitted ..... 8:3:33.
Day of Illness ..... Second.
Dismissed ..... 15:5:33.
Classification ..... Moderate.
Throat Swab ..... Positive.
Antitoxin ..... 12,000 units.
Journal Reference .... Ward 2 East.

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1. History.

Both tonsils were enlarged and extensively covered with loosely adherent yellowish-white membrane. Foetor oris was intense and both tonsillar glands were enlarged and tender. On admission the temperature was 99.8°F., and the pulse rate 128. The colour was pale and slight lividity was present in the complexion. The pulse was regular in rate and rhythm, and of good volume and high tension. On auscultation the first sound was everywhere soft and blurred and the second sound was accentuated and had a booming character. Albumen, acetone and diacetic acid were present in the urine. 12,000 units of antitoxin were administered intramuscularly.

The temperature was normal on the 4th day, but tachycardia was present until the 7th day. Albuminuria remained until the 8th day and by the 10th day the urine was finally clear and exudation had disappeared from the throat.

Progress continued satisfactorily until the 27th day of illness when the pulse became rapid, irregular and thready. The cardiac sounds were distant and soft, both the first and second sounds having a muffled quality. On the 29th day the liver was palpable one inch below the costal margin and the patient complained of abdominal pain. On the 30th day extrasystoles were present in abundance and reduplication of the first sound gave rise to typical "bruit de galop". Vomiting occurred and remained troublesome during the 31st and 32nd days, during which time nothing would lie in the stomach. Acetone and diacetic acid were present in the urine until the 34th day. Tachycardia, arrhythmia and hypotension persisted until the 36th day. The general condition of the patient gradually improved and he was dismissed well on the 69th day.

2..Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were investigated (1) during the stage of toxaemia, (2) during the stage of tachycardia, arrhythmia, hypotension and hepatic engorgement, and (3) after clinical recovery.

Glucose Tolerance.

(1) 3rd day of illness: 30 grams glucose.

113 193 157 135 128 130 (Chart 67)
Glycosuria developed during test.

(3) 28th day of illness: 30 grams glucose.

75 169 130 clotted 110 91 (Chart 68)
Glycosuria absent during test.

(3) 60th day of illness: 30 grams glucose.

95 160 160 102 90 100 (Chart 69)
Glycosuria absent during test.

Blood Cholesterol.

(1) 3rd day of illness, 171 mgms. per 100 c.cms. blood.
(2) 28th day of illness, 289 " " 100 " "
(3) 60th day of illness, 196 " " 100 " "

3. Note.

During the acute stage of the illness fasting hyperglycaemia, glycosuria and delay in carbohydrate storage resulted from the glucose tolerance test. The blood cholesterol was normal and acetone and diacetic acid were present in the urine. During the stage of cardiac involvement a similar storage defect was present but the fasting blood sugar was low and glycosuria did not result. The blood cholesterol at this time was markedly increased. After clinical recovery the findings with regard to glucose tolerance, fasting blood sugar and blood cholesterol showed no departure from normal.

CASE 33.

M.Farmer	Age 7 years.
Admitted	15:3:33.
Day of Illness	Second.
Dismissed	21:4:33.
Classification	Moderate.
Throat Swab	Positive.
Antitoxin	8,000 units.
Journal Reference	Ward 2 East.

1. History.

The tonsils were both enlarged and extensively covered with yellowish-white membranous exudate. The breath was foetid and the tonsillar glands were slightly enlarged and tender. The temperature was 100°F. and the pulse rate 90. The colour was good. The heart sounds were pure and the second sound at the aortic base was accentuated. The pulse was regular in rate and rhythm, of good volume and slightly increased tension. Acetone and diacetic acid were present in the urine. An intramuscular injection of 8,000 units of antitoxin was administered.

The temperature fell to normal on the 4th day of illness by which time also the urine was clear of acetone and diacetic acid. The pulse rate was normal on the 5th day and the throat was clear by the 7th day. Progress continued satisfactorily and the patient was dismissed well on the 39th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were investigated (1) during the acute stage of the illness, and (2) after recovery.

Glucose Tolerance.

(1) 3rd day of illness: 30 grams glucose.

109 172 153 125 114 120 (Chart 70)
Glycosuria absent during test.

(2) 28th day of illness:

80 150 150 90 83 87 (Chart 71)
Glycosuria absent during test.

Blood Cholesterol.

(1) 3rd day of illness, 173 mgms. per 100 c.cms. blood.
(2) 28th day of illness, 194 " " 100 " "

3. Note.

A fasting hyperglycaemia and slight delay in storage are noticeable in the first blood sugar curve. Glycosuria was absent during the test. Diacetic acid and acetone were present in the urine. A later glucose tolerance test carried out after recovery showed no abnormality. The blood cholesterol throughout was within normal limits.

CASE 34.

A.McLaughlin	Age 17 years.
Admitted	16:3:33.
Day of Illness	Fourth.
Dismissed	5:5:33.
Classification	Severe.
Throat Swab	Positive.
Antitoxin	25,000 units.
Journal Reference	Ward 2 East.

1. History.

The patient looked pale and toxic. Extensive greyish-white membrane covered the tonsils, the soft palate and the uvula. There was marked infiltration and congestion of the parts and oral foetor was intense. The glands at the angles of the jaw were enlarged and painful and gave the patient a "bull neck" appearance. On admission the temperature was 99°F. and the pulse rate 96. The pulse was regular in rate and rhythm, the beats were of equal and good volume and the tension was high. The first cardiac sound was soft and distant in all areas and the second sound was loud and booming, particularly at the aortic base. Acetone, diacetic acid and albumen were present in the urine. 25,000 units of antitoxin were administered intramuscularly.

The temperature and the pulse rate fell to normal on the 7th and 8th days respectively. On the latter day the urine was clear of acetone and diacetic acid and albuminuria finally disappeared on the 10th day. On the 12th day the throat was clear of exudation and infiltration. The general condition of the patient was very much improved.

Progress continued satisfactorily until the 19th day of illness when the pulse became markedly irregular in rate and rhythm and unequal in volume. Numerous premature beats with compensatory pause were present and coupling of the beats was prominent. On auscultation both the first and second sounds had a muffled quality. On the 22nd day of illness the patient complained of mild abdominal pains and the liver was found to be enlarged and palpable ¾" below the costal margin. Vomiting of food also occurred and ketone bodies were present in the urine.

On the 27th day of illness reduplication of the first cardiac sound was present, this sound at the apex having the rhythm known as "bruit de galop". The pulse was totally irregular and unequal as regards rate, rhythm and volume. Its force was diminished, its tension was low and it had a "running" character. In rate it varied from 66 - 120 beats per minute.

Cardiac arrhythmia, hypotension, hepatic congestion and ketosis remained until the 35th day when the symptoms commenced gradually to recede. By the 40th day of illness the urine was clear, the liver could not be palpated, the heart sounds were of good quality, and the pulse was regular. The patient was dismissed well on the 54th day.

2 .Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol estimations were made (1)during the acute stage of the illness, (2) during the stage of secondary complications, and (3) after clinical recovery.

Glucose Tolerance.

(1) 5th day of illness: 50 grams glucose.

105 121 185 150 143 120 (Chart 72)
Glycosuria developed during test.

(2) 28th day of illness: 50 grams glucose.

75 168 162 124 110 115 (Chart 73)
Glycosuria absent during test.

(3) 48th day of illness: 50 grams glucose.

100 168 164 120 106 108 (Chart 74)
Glycosuria absent during test.

Blood Cholesterol.

(1) 5th day of illness, 218 mgms. per 100 c.cms. blood.
(2) 28th day of illness, 255 " " 100 " "
(3) 48th day of illness, 223 " " 100 " "

3. Note.

During the acute stage the blood sugar curve showed a defect degree of delay in the removal of the excess of blood sugar associated with the development of glycosuria during the test. Acetone and diacetic acid were present in the urine. The second glucose tolerance test showed a fasting hypoglycaemia and a persistence of the storage defect, though on this occasion glycosuria did not result from the test. After recovery the blood sugar curve was almost normal. The blood cholesterol was remarkably high especially during the stage of secondary complications.

CASE 35.

J. Haddow ..... Age 18 years.
Admitted ..... 17:3:33.
Day of Illness ..... Sixth.
Dismissed ..... 21:4:33.
Classification ..... Moderate.
Throat Swab ..... Positive.
Antitoxin ..... 25,000 units.
Journal Reference .... Ward 2 East.

1. History.

The throat was infiltrated and the tonsils were covered with numerous small patches of membrane. The glands at the angles of the jaw were palpably enlarged and oral foetor was present. The face was flushed and circum oral pallor was present. On admission the temperature was 90°F and the pulse rate 84. The heart sounds were pure and distinct and the second sound at the aortic base was accentuated. The urine contained albumen in slight traces. 25,000 units of antitoxin were administered intramuscularly.

The temperature and the pulse rate were normal on the 8th day. Albuminuria ceased on the 10th day and the throat was finally clear on the 12th day. The further progress was uneventful and the patient was dismissed well on the 41st day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated (1) during the acute stage, and (2) after recovery.

Glucose Tolerance.

(1) 7th day of illness: 50 grams glucose.

118 156 102 115 106 110 (Chart 75)
Glycosuria absent during test.

(2) 32nd day of illness: 50 grams glucose.

102 131 174 108 112 105 (Chart 76)
Glycosuria absent during test.

Blood Cholesterol.

(1) 7th day of illness, 128 mgms. per 100 c.cms. blood.
(2) 32nd day of illness, 174 " " 100 " "

3. Note.

The glucose tolerance tests show no departure from normal except a fasting hyperglycaemia during the acute stage of the illness. At this time, however, the blood cholesterol was markedly reduced in amount.

CASE 36.

D. Campbell	Age 19 years.
Admitted	25:3:33.
Day of illness 1.....	Third.
Dismissed	14:14:33.
Classification	Mild.
Throat swab	Positive.
Antitoxin	6,000 units.
Journal reference	Ward 1 East.

1. History.

Follicular exudate was present on both tonsils. The throat was markedly inflamed and foetor oris was present. There was no glandular enlargement. On admission the temperature was 102.2°F., and the pulse rate 112. The heart sounds were pure and of normal intensity, and the pulse was regular in rate, rhythm and volume. The urine was clear. The throat swab was positive and 6,000 units of antitoxin were injected intramuscularly.

The throat was clear on the 8th day and the patient was dismissed well on the 25th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated during the acute stage of the illness.

Glucose Tolerance.

4th day of illness: 50 grams. glucose.

108 163 105 130 105 110 (Chart 77)
Glycosuria absent during test.

Blood Cholesterol.

4th day of illness: 153 mgms. per 100 c.cms. of blood.

3. Note.

The case was one of mild diphtheria. No abnormality was found in the blood sugar, glucose tolerance or blood cholesterol.

CASE 37.

A. Foot ..... Age 7 years.
Admitted ..... 29:3:33.
Day of Illness ..... Fourth.
Dismissed ..... 3:5:33.
Classification ..... Mild.
Throat Swab ..... Positive.
Antitoxin ..... 8,000 units.
Journal Reference .... Ward 1 East.

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1. History.

The tonsils were enlarged and follicular exudate was present on both. Foetor oris and glandular enlargement were absent. There was slight congestion of the palate. The colour was pale and there was no lividity nor cyanosis of the complexion. On admission the temperature was 98.4°F and the pulse rate 112. The heart sounds were somewhat soft and the second sound was accentuated. The pulse was regular in rate and rhythm, of good volume, increased force and high tension. Acetone and diacetic acid were present in the urine. 8,000 units of antitoxin were injected intramuscularly.

On the 7th day the pulse rate was normal. The throat was clear on the 9th day and ketone bodies were absent from the urine. The further progress was uneventful and the patient was dismissed well on the 39th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated (1) during the acute stage, and (2) after recovery.

Glucose Tolerance.

(1) 5th day of illness.

109 172 134 105 110 106 (Chart 78)
Glycosuria absent during test.

(2) 30th day of illness.

82 160 160 78 89 85 (Chart 79)
Glycosuria absent during test.

Blood Cholesterol.

(1) 5th day of illness, 136 mgms. per 100 c.cms. blood.
(2) 30th day of illness, 224 " " 100 " "

3. Note.

The only abnormality revealed by the glucose tolerance tests was a hyperglycaemia in the fasting blood during the toxic stage. The blood cholesterol was abnormally low. Fasting blood sugar, glucose tolerance and blood cholesterol showed no departure from normal when clinical recovery was established.

CASE 38.-

A. Cothill ..... Age 5 years.
Admitted ..... 3:4:33.
Day of Illness ..... Fifth.
Dismissed ..... 5:5:33.
Classification ..... Moderate.
Throat Swab ..... Positive.
Antitoxin ..... 16,000 units.
Journal Reference .... Ward 1 East.

1. History.

Both tonsils were enlarged and extensively covered with loosely adherent yellowish-white membrane. The fauces and soft palate were markedly infiltrated and foetor oris was present. Both tonsillar glands were slightly enlarged and tender. On admission the temperature was 98.4°F and the pulse rate 104. The face was pale but cyanosis and lividity were absent. On auscultation the first cardiac sound was muffled and the second sound was accentuated. The pulse was regular in rate and rhythm. Acetone and diacetic acid were present in the urine. 16,000 units of antitoxin were administered intramuscularly.

The urine was clear on the 7th day and the pulse rate fell to normal on the 8th. Exudate remained until the 10th day, the throat being finally clear of infiltration and congestion, and the glands normal, by the 12th day. The further progress was satisfactory and the patient was dismissed well on the 37th day.

2. Glucose Tolerance and Blood Cholesterol.

The glucose tolerance and blood cholesterol were investigated (1) during the acute stage, and (2) after recovery.

Glucose Tolerance.

(1) 6th day of illness: 20 grams glucose.

94 196 135 116 121 114 (Chart 80)
Glycosuria developed during test.

(2) 28th day of illness: 20 grams glucose.

85 169 126 90 81 92 (Chart 81)
Glycosuria absent during test.

Blood Cholesterol.

(1) 6th day of illness, 203 mgms. per 100 c.cms. blood.
(2) 28th day of illness, 172 " " 100 " "

3. Note.

During the toxic stage the blood sugar curve shows a definite degree of delay in the removal of the excess of sugar from the blood, and a maximum concentration in excess of the renal threshold with coincident excretion of sugar in the urine. The fasting blood sugar level is slightly raised. Acetone and diacetic acid were present in the urine. After recovery no abnormality was detected. The blood cholesterol throughout was within normal limits, though somewhat increased in amount, during the toxic stage when compared with the value after recovery.

CASE 39.-

H. Grant ..... Age 7 years.
Admitted ..... 5:4:33.
Day of Illness ..... Fourth.
Dismissed ..... 12:5:33.
Classification .....Severe.
Throat Swab ..... Positive.
Antitoxin ..... 45,000 units.
Journal Reference .... Ward 1 East.

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1. History.

The throat was very congested and infiltrated with oedema. Both tonsils were completely covered with greyish-black membrane which extended backwards across the palatal arches to cover the uvula and forwards on to the hard palate. Foetor oris was intense and the glands at the angles of the jaw formed two large painful swellings. On admission the temperature was 102.2°F and the pulse rate 140. The face was pale and livid. The pulse was rapid and regular, of moderate volume and increased force. The tension was high. The heart sounds were regular in rate and rhythm but of muffled quality. There was slight shortening of the first sound and the second sound was accentuated. Albumen, acetone and diacetic acid were present in the urine. 15,000 units of antitoxin were injected intramuscularly and on the following day a further intravenous injection of 20,000 units was given.

The pulse, which had become irregular on the 5th day, continued to be so, and varied between 90 and 110 beats per minute until the 9th day. The arrhythmia took the form of extrasystoles. The throat was clear on the 10th day, but ketone bodies and albumen continued to be present in the urine.

Cardiac arrhythmia persisted until the 12th day, until which time the temperature also tended to be subnormal. During this period weakening of the first cardiac sound and reduplication of the second sound, particularly at the pulmonic base, were noticed. The urine was clear of acetone and diacetic acid on the 15th day, and of albumen on the 22nd day. The further progress was uneventful and the patient was dismissed on the 42nd day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated (1) during the acute stage, (2) after the disappearance of the acute symptoms, and (3) when recovery was established.

Glucose Tolerance.

(1) 6th day of illness: 30 grams glucose.

93 187 152 110 107 104 (Chart 82)
Glycosuria developed during test.

(2) 15th day of illness: 30 grams glucose.

78 173 147 83 92 87 (Chart 83)

(3) 35th day of illness: 30 grams glucose.

80 163 127 93 82 87 (Chart 84).

Blood Cholesterol.

(1) 6th day of illness, 98 mgms. per 100 c.cms blood.
(2) 15th day of illness, 157 " " 100 " "
(3) 35th day of illness, 163 " " 100 " "

3. Note.

The case was one of severe faucial diphtheria in which glucose tolerance tests revealed a definite defect in carbohydrate metabolism. The first blood sugar chart shows a fasting hyperglycaemia and a point of maximum concentration in excess of the renal threshold with glycosuria. The removal of the excess of blood sugar was delayed. During this stage acetone and diacetic acid were present in the urine and the blood cholesterol was markedly reduced in amount.

On the 15th day of illness the urine was clear of acetone and diacetic acid and the general condition was much improved. The blood sugar curve was now almost normal though the blood sugar concentration did not fall to the fasting

level within the period of 2⅓ observed. The blood cholesterol was now within normal limits.

CASE 40.

T.Smellie ..... Age 8 years.
Admitted ..... 8:4:33.
Day of Illness ..... Second.
Dismissed ..... 12:5:33.
Classification ..... Moderate.
Throat Swab ..... Positive.
Antitoxin ..... 16,000 units.
Journal Reference .... Ward 1 East.

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1. History.

The patient was pale and looked toxic. Both tonsils were enlarged and extensively patched with yellow-white membrane. The glands at the angles of the jaw were slightly enlarged and oral foetor was intense. The soft palate was congested and infiltrated with oedema. On admission the temperature was 102°F and the pulse rate 120. The complexion was tinged with cyanosis and ashen pale. The pulse was regular in rate and rhythm, full, of increased force and high tension. The heart sounds were normally spaced but muffled, and accentuation of the second sound was observed. The urine contained acetone and diacetic acid. 16,000 units of antitoxin were administered intramuscularly.

The temperature was normal on the 3rd day, and the urine was clear on the 5th day. The pulse rate fell to normal on the 6th day of illness. The throat was completely clear of exudation and infiltration by the 10th day of illness and the glands were then normal. Albumen appeared in the urine on the 9th day and persisted in traces until the 15th day of illness. Thereafter progress was uneventful and the patient was dismissed well on the 36th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were investigated (1) during the acute stage, and (2) after recovery.

Glucose Tolerance.

(1) 3rd day of illness: 30 grams glucose.

116 168 134 120 132 130 (Chart 85)
Glycosuria absent during test.

(2) 29th day of illness: 30 grams glucose.

90 170 123 96 87 95 (Chart 86)
Glycosuria absent during test.

Blood Cholesterol.

(1) 3rd day of illness, 154 mgms. per 100 c.cms. blood.
(2) 29th day of illness, 162 " " 100 " "

3. Note.

During the toxic stage the glucose tolerance test showed a fasting hyperglycaemia and delayed storage without the development of glycosuria. Acetone and diacetic acid were present in the urine. The blood cholesterol was within normal limits. After recovery the fasting blood sugar and glucose tolerance were normal.

CASE 41.

R. Hewitt ..... Age 7 years.
Admitted ..... 24:5:33.
Day of illness ..... Sixth.
Dismissed ..... 10:7:33.
Classification ..... Severe.
Throat Swab ..... Positive.
Antitoxin ..... 31,000 units.
Journal Reference .... Ward 2 East.

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1. History.

The tonsils were enlarged until they almost met in the mid line. Their apposing surfaces and the soft palate were extensively covered with yellowish-white membranous exudate. There was marked infiltration and congestion of the soft palate and the peritonsillar tissues. The breath was foetid and the glands at the angles of the jaw were visibly enlarged and tender. On admission the temperature was 98°F and the pulse rate 100.

The colour was pale and the complexion had an ashen, cyanotic hue. The pulse was regular, rapid, of small volume and decreased tension. The heart sounds were soft and distant and the first sound was decidedly weak. The urine contained acetone and diacetic acid. 16,000 units of antitoxin were administered intramuscularly and on the following day a further injection of 15,000 units was given intravenously.

The temperature and the pulse rate were normal on the 8th day of illness. The urine was clear on the 10th and exudation disappeared from the throat on the 12th day. On the 14th day cardiac arrhythmia developed. The pulse was irregular in rate and rhythm, the irregularity taking the form of extrasystoles with a tendency to coupling of the beats. The force and tension of the pulse were diminished. The first cardiac sound at the apex was shortened. On the 15th day reduplication of the first sound with typical "gallop rhythm" was noticed. Cardiac arrhythmia remained until the 19th day of illness. During this period the pulse rate varied from 90 - 120 beats per minute and the urine

contained acetone andndiacetic acid. On the 22nd day the general condition was much improved, the cardiac rhythm was regular and the urine was clear. Progress was maintained and the patient was dismissed well on the 53rd day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were investigated (1) during the acute stage, (2) during the stage of cardiac arrhythmia, and (3) after recovery.

Glucose Tolerance.

(1) 8th day of illness.

100 225 175 143 118 115 (Chart 87)
Glycosuria developed during test.

(2) 16th day of illness.

73 172 135 89 96 95 (Chart 88)
Glycosuria absent during test.

(3) 42nd day of illness.

86 169 134 90 90 92 (Chart 89)
Glycosuria absent during test.

Blood Cholesterol.

(1) 8th day of illness, 91 mgms. per 100 c.cms blood.
(2) 16th day of illness, 220 " " 100 " "
(3) 42nd day of illness, 167 " " 100 " "

3. Note.

The case was one of severe faucial diphtheria admitted far advanced in toxaemia. During the acute stage of the illness there was a state of hyperglycaemia with inability to store or utilize carbohydrate with resultant glycosuria. Acetone and diacetic acid were present in the urine. The blood cholesterol at this time was markedly decreased.

When cardiac arrhythmia developed the abnormality in carbohydrate metabolism was still present, though glycosuria did not result. It is notable that the fasting blood showed a hyp oglycaemia while the blood cholesterol had undergone a substantial increase. Clinical recovery was associated with normal findings with regard to fasting blood sugar, glucose tolerance and blood cholesterol.

CASE 42.

A. Neilson ..... Age 8 years.
Admitted ..... 5:6:33.
Day of Illness ..... Second.
Dismissed ..... 10:7:33.
Classification ..... Moderate.
Throat Swab ..... Positive.
Antitoxin ..... 16,000 units.
Journal Reference .... Ward 2 East.

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1. History.

The palate and fauces were inflamed and oedematous. Both tonsils were enlarged and covered with numerous small patches of yellowish-white membranous exudate. Foetor oris was absent and glandular enlargement was only slight. On admission the temperature was 100.2°F and the pulse rate 130. The colour was good though the patient was somewhat pale. The heart sounds were pure but soft and muffled, and the second sound was accentuated at the aortic and pulmonary valve areas. The pulse was regular in rate and rhythm, of good volume and increased force and tension. Acetone and diacetic acid were present in the urine. 16,000 units of antitoxin were administered intramuscularly.

The temperature fell to normal on the 5th day and the urine was clear of acetone and diacetic acid. The pulse rate however remained elevated, varying from 90 - 110 beats per minute, and a slight irregularity was observed also in its rhythm, in the form of premature beats with compensatory pause. Exudate disappeared from the throat on the 6th day.

On the 7th day an urticarial rash developed, commencing at first in the vicinity of the serum injection and later becoming generalised. It was associated with oedema, especially of the face, hands and feet, the face having a particularly "bloated" appearance. The wrist, the elbow, the knee and the ankle joints were enlarged and painful. The temperature was elevated to 101°F and the pulse rate was 120. The first cardiac sound was so shortened as to be almost inaudible and loss of accentuation of the second

sound was noticed. The pulse decreased in force and diminished in tension, had a particularly "running" character. The colour was poor and tinged with ashen cyanosis. Albumen, acetone and diacetic acid were present in the urine

On the 8th day the symptoms were less severe. No further vomiting had occurred and the rash had faded. Swelling of the joints persisted until the 12th day, when the urine also became clear. On the 13th day the temperature and pulse rate were normal and the heart sounds had improved in quality. The pulse was regular in rate and rhythm. Its tension and force were normal.

Progress was maintained without further event and the patient was dismissed on the 37th day of illness.

Although the original inquiry regarding previous serum injection was answered in the negative by the parents, it later transpired that, four years previously in America, the patient had been given "an injection for a cut knee". Presumably the injection was a prophylactic measure against tetanus.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were investigated (1) during the acute stage, (2) during the stage of serum sickness, and (3) after recovery.

Glucose Tolerance.

(1) 3rd day of illness: 30 grams glucose.

103 167 182 149 116 122 (Chart 90)
Glycosuria developed during test.

(2) 7th day of illness: 30 grams glucose.

65 169 140 113 102 90 (Chart 91)
Glycosuria absent during test.

(3) 32nd day of illness: 30 grams glucose.

89 150 124 93 - 95 95 (Chart 92)
Glycosuria absent during test.

Blood Cholesterol.

(1) 3rd day of illness, 105 mgms. per 100 c.cms. blood.
(2) 7th day of illness, 179 " " 100 " "
(3) 32nd day of illness, 165 " " 100 " "

3. Note.

Fasting hyperglycaemia delayed storage and a point of maximum concentration in excess of the renal threshold with glycosuria were deduced from the first glucose tolerance test. Ketone bodies were present in the urine and the blood cholesterol was abnormally low. On the 7thbday serum sickness developed when hypoglycaemia and delayed storage were present. Ketone bodies were again present but the blood cholesterol was now within normal limits. Further estimations after recovery gave normal results for fasting blood sugar, glucose tolerance and blood cholesterol.

CASE 43.

D. Boyle	Age 9 years.
Admitted	9:6:33.
Day of illness	Third.
Dismissed	14:7:33.
Classification	Mild.
Throat Swab	Positive.
Antitoxin	6,000 units.
Journal reference	Ward 1 East.

1. History.

The throat was inflamed and the tonsils were enlarged. A patch of membranous exudate was present in the left tonsil. Both submaxillary glands were enlarged and tender. Foetor oris was present. On admission the temperature was 99.4°F. and the pulse rate 110. No abnormality was detected in the heart on auscultation. The pulse was regular in rate and rhythm. Acetone and diacetic acid were present in the urine. The throat was clear on the 8th day and the patient was dismissed well on the 37th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated on the 4th day.

Glucose Tolerance.

4th day of illness: 30 grams. glucose.

97 163 120 95 100 100 (Chart 93)
Glycosuria absent during test.

Blood Cholesterol.

4th day of illness: 157 mgms. per 100 c.cms. of blood.

3. Note.

The estimations show no departure from normal with regard to blood sugar, glucose tolerance and blood cholesterol.

CASE 44.

F. Allan ..... Age 7 years.
Admitted ..... 12:6:33.
Day of Illness ..... Ninth.
Dismissed ..... 6:9:33.
Classification ..... Severe.
Throat Swab ..... Positive.
Antitoxin ..... 24,000 units.
Journal Reference .... Ward 2 East.

1. History.

The patient was admitted on the 9th day of illness. 24,000 units of antitoxin had been administered intramuscularly on the 3rd day of illness. There was no exudate on the throat on admission, but the tonsils, peritonsillar tissues and the soft palate were inflamed and oedematous.

The face was pale and cyanosed. On admission the temperature was 98°F and the pulse rate 100. The heart sounds were soft and distant, both the first and second sounds having a muffled quality. The pulse was rapid, regular, increased in force, and raised in tension. The urine contained albumen, acetone and diacetic acid.

Nasal speech was observed on the 11th day of illness, and on the 13th day complete palatal paralysis with regurgitation of fluids developed. The pulse rate remained in the vicinity of 100 beats per minute and was regular until the 20th day of illness when a marked arrhythmia developed. Reduplication of the first cardiac sound with typical gallop rhythm was present and premature beats appeared in abundance. On the 22nd day the liver was enlarged and tender on palpation. Albuminuria was not observed after the 19th day of illness, but acetone and diacetic acid were still present. On the 23rd and 24th days of illness vomiting occurred, in all on three occasions, but was not troublesome thereafter.

On the 26th day the symptoms had abated and the general condition was much improved. The heart's action though now regular in rate and rhythm, was still rapid, and nasal

speech and regurgitation were troublesome.

Regurgitation of fluids persisted until the 34th day. The urine was clear on the 38th day and speech was greatly improved by the 43rd day. The pulse rate had gradually fallen to normal, and the pulse was now regular in rate and rhythm and of moderate volume and tension. Speech was normal on the 48th day. The further progress was without event and the patient was dismissed well on the 95th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were investigated (1) when palatal paralysis developed, (2) during the stage of cardiac arrhythmia and hepatic congestion, (3) when the symptoms were abating, and (4) after recovery.

Glucose Tolerance.

(1) 14th day of illness: 30 grams glucose.

78 207 139 107 113 110 (Chart 94)
Glycosuria developed during test.

(2) 22nd day of illness: 30 grams glucose.

64 193 clotted 116 100 94 (Chart 95)
Glycosuria developed during test.

(3) 30th day of illness: 30 grams glucose.

73 169 95 100 104 97 (Chart 96)
Glycosuria absent during test.

(4) 80th day of illness: 30 grams glucose.

84 150 163 87 90 90 (Chart 97)
Glycosuria absent during test.

Blood Cholesterol.

(1) 14th day of illness, 231 mgms. per 100 c.cms. blood.
(2) 22nd day of illness, 287 " " 100 " "
(3) 30th day of illness, 233 " " 100 " "
(4) 80th day of illness, 152 " " 100 " "

3. Note.

The case was not studied during the acute stage. When palatal paralysis developed, a glucose tolerance test showed delay in storage and a point of maximum concentration above the renal threshold with excretion of sugar in the urine. An almost similar state of affairs existed when cardiac arrhythmia supervened, and the fasting blood showed a definite degree of hypoglycaemia. When the symptoms were abating the glucose tolerance test differed only in degree, glycosuria being absent on this occasion. The urine, throughout, contained acetone and diacetic acid and the blood cholesterol was abnormally high.

On the 80th day the patient's condition was entirely satisfactory and a further glucose tolerance test was normal. The blood cholesterol as compared with previous values showed a sharp diminution.

Case 45.

A. Bradford	Age 6 years.
Admitted	14:6:33
Day of Illness	Fifth.
Dismissed	20:9:33
Classification	Severe.
Throat swab	Positive.
Antitoxin	
Journal Reference	Ward 2 East.

1. History.

The tonsils were markedly enlarged and infiltration of the peritonsillar tissues and palate was present. The right tonsil was extensively patched with dirty yellowish grey membrane which had spread across the right palatal arch to invest the uvula. Foetor oris was intense. The tonsillar glands were slightly enlarged.

The complexion was pale and an ashen cyanotic tint was present. The heart sounds were soft and muffled. The pulse was rapid and regular, of small volume and low tension. The urine contained albumen, acetone and diacetic acid.

The temperature was normal on the 8th day of illness, but the pulse was still of poor quality, irregular and slightly increased in rate. The urine was clear of acetone and diacetic acid on the 11th day of illness. On the 14th day complete palatal paralysis and regurgitation were present. The pulse was again rapid and irregular. The left border of cardiac dullness extended ½" beyond the nipple. The liver was enlarged and palpable 1" below the costal margin. Vomiting became troublesome on the 16th day and acetone and diacetic acid were again present in the urine. Vomiting persisted until the 27th day, when the pulse rate was more regular, though still rapid. The urine was now free of acetone and diacetic acid. The urine was finally clear of albumen on the 35th day. The pulse was regular in rate and rhythm, and of improved quality, on the 47th day. Regurgitation remained until the 30th day, but normal speech was not resumed until the 68yh day. Thereafter progress was satisfactory, if slow, and the patient was dismissed on the 103rd day of illness.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated (1) during the toxic stage, (2) during the stage of cardiac involvement and paralysis, and (3) after recovery.

Glucose Tolerance.

(1) 6th day of illness: 30 grams. glucose.

75 213 clotted 169 143 136 (Chart 98)
Glycosuria developed during test.

(2) 15th day of illness: 30 grams glucose.

93 168 143 118 107 110 (Chart 99)
Glycosuria absent during test.

(3) 45th day of illness: 30 grams glucose.

84 154 120 100 105 100 (Chart 100)

Blood Cholesterol.

(1) 6th day of illness, 136 mgms. per 100 c.cms. blood.
(2) 15th day of illness, 168 " " 100 " "
(3) 45th day of illness, 183 " " 100 " "

3. Note.

The initial blood sugar curve revealed a low value for the fasting blood sugar, a definite delay in the fall of the curve, a high maximum concentration and glycosuria. The blood cholesterol was abnormally low. Ketone bodies were present in the urine. During the stage of paralysis and cardiac involvement the lag in the blood sugar curve was still present, but glycosuria was absent and the fasting blood sugar was normal. The concentration of blood cholesterol was normal at this stage. Two days later ketosis with vomiting supervened. A further glucose tolerance test carried out after the subsidence of the acute symptoms showed a low fasting blood sugar and a slight delay. Glycosuria was absent.

CASE 46.

A. Smith ..... Age 18 years.
Admitted ..... 6:7:33.
Day of Illness ..... Third.
Dismissed ..... 11:8:33.
Classification ..... Mild.
Throat Swab ..... Positive.
Antitoxin ..... 12,000 units.
Journal Reference .... Ward 2 East.

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1. History.

Both tonsils were enlarged and on each filmy yellowish-white membrane was present. The soft palate was slightly inflamed and the breath was foul. There was no glandular enlargement. On admission the temperature was 100.6°F and the pulse rate 108. The pulse was regular in rate and rhythm, full and bounding. The heart sounds were normal in rhythm and forceful but slightly muffled. The urine was clear. 12,000 units of antitoxin were injected intramuscularly.

The temperature and pulse rate were normal on the 6th day and the throat was free of exudate and inflammation on the 9th day. The further progress was satisfactory and the patient was dismissed well on the 38th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated (1) during the acute stage, and (2) after recovery.

Glucose Tolerance.

(1) 5th day of illness: 50 grams glucose.

106 165 120 108 103 105 (Chart 101)
Glycosuria absent during test.

(2) 34th day of illness: 50 grams glucose.

93 159 131 99 102 95 (Chart 102)
Glycosuria absent during test.

Blood Cholesterol.

(1) 5th day of illness, 175 mgms. per 100 c.cms. blood.
(2) 34th day of illness, 182 " " 100 " "

3. Note.

The case was one of mild faucial diphtheria in an adult. No departure from normal was present in glucose tolerance, blood sugar, or blood cholesterol.

Case 47.

D. Smith.....	Age 7 years.
Admitted	16:8:33.
Day of Illness	First.
Dismissed	16:9:33.
Classification	Mild.
Throat swab	Positive.
Antitoxin	4,000 units.
Journal Reference	Ward 1 East.

1. History.

The tonsils were enlarged and follicular exudate was present in each. Foetor oris and glandular enlargement were absent. On admission the temperature was 102.2°F. and the pulse rate 110. The pulse was regular in rate and rhythm, of full volume and high tension. The heart sounds were forceful and the second aortic sound was accentuated. The urine contained acetone and diacetic acid. The throat swab was positive and 4,000 units of antitoxin were injected intramuscularly. The urine was clear on the 4th day and the throat was normal by the 7th day. The patient was dismissed well on the 31st day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated (1) during the acute stage, and (2) after recovery.

Glucose Tolerance.

(1) 2nd day of illness: 30 grams. glucose.

113 185 153 126 120 120 (Chart 103)
Glycosuria absent during test.

(2) 18th day of illness: 30 grams. glucose.

87 150 103 82 90 93 (Chart 104)
Glycosuria absent during test.

Blood Cholesterol.

(1) 2nd day of illness, 123 mgms. per 100 c.cms. blood.
(2) 18th day of illness, 169 " " 100 " "

3. Note.

During the acute stage of the illness the glucose tolerance test showed a fasting hyperglycaemia, a maximum concentration beyond the renal threshold and a marked delay in storage. The blood cholesterol was abnormally decreased. When the toxaemia had subsided the blood cholesterol, glucose tolerance and fasting blood sugar were normal.

CASE 48.

J. McVey ..... Age 10 years.
Admitted ..... 12:9:33.
Day of Illness ..... Fifth.
Died ..... 14:9:33.
Classification ..... Severe.
Throat Swab ..... Positive.
Antitoxin ..... 60,000 units.
Journal Reference .... Ward 2 East.

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1. History.

The tonsils, peritonsillar tissues and soft palate were considerably enlarged with oedema, the combined swelling completely blocking the pharynx from view. The greatly swollen parts were thickly plastered with tough, adherent greyish-black membrane. The breath was foetid and the tonsillar submaximally and sublingual glands formed large painful swellings around the neck. A sero-purulent rhinorrhoea exuded from the nostrils. The complexion had a dusky cyanotic hye, and there were numerous small purpuric spots scattered over the neck and the upper part of the chest. On admission the temperature was 99°F and the pulse rate 108. The pulse was regular in rate and rhythm, and thready. The heart sounds were faint and distant, the first sound being shortened. Acetone and diacetic acid were present in the urine. 40,000 units of antitoxin were injected intramuscularly and 20,000 units intravenously.

On the 6th day of illness the temperature was subnormal and the cardiac rhythm irregular. Gallop rhythm, coupling of the beats, loss of accentuation of the second sound at the base and a running pulse spoke to the failing state of the circulation. On the 7th day the liver was palpable below the costal margin and vomiting of brown fluid occurred on several occasions. Acetone and diacetic acid were present in the urine throughout.

The patient gradually became worse and died of cardiac failure on the 7th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were investigated on the 6th day.

Glucose Tolerance.

6th day of illness; 30 grams glucose.

70 193 161 147 113 122 (Chart 105)
Glycosuria developed during test.

Blood Cholesterol.

6th day of illness,..... 293 mgms. per 100 c.cms. blood.

3. Note.

The case was one of severe faucial diphtheria terminating by cardiac failure on the 7th day. Cardiac failure with hepatic congestion and ketosis were the main features of the case clinically. The blood sugar curve showed a marked fasting hypoglycaemia, a point of maximum concentration resulting in glycosuria and a definite failure to assimilate the excess of sugar from the blood. The blood cholesterol was abnormally high.

CASE 49.

J. Scullon ..... Age 10 years.
Admitted ..... 25:9:33.
Day of Illness ..... Second.
Dismissed ..... 29:10;33.
Classification ..... Severe.
Throat Swab ..... Positive.
Antitoxin ..... 40,000 units.
Journal Reference .... Ward 1 East.

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1. History.

The tonsils, soft palate and uvula were oedematous and thick adherent yellowish-white membrane extensively covered the parts. Oral foetor was pronounced and both tonsillar glands were enlarged.

On admission the temperature was 100.8°F and the pulse rate 128. The pulse was regular in rate and rhythm and running in character. The cardiac sounds were surprisingly forceful, though soft and distant, and the second sound had a booming quality. The face was flushed and a tinge of lividity was present. The urine contained acetone and diacetic acid. 20,000 units of antitoxin were administered intramuscularly and on the following day a further intramuscular injection of 20,000 units was given.

The temperature and the pulse rate were normal on the 4th day of illness, the urine was clear on the 6th, and membrane disappeared from the throat on the 7th day. The further progress was uneventful and the patient was dismissed well on the 38th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were investigated (1) during the toxic stage, and (2) after recovery.

Glucose Tolerance.

(1) 3rd day of illness: 30 grams glucose.

123 189 155 147 139 131 (Chart 106)
Glycosuria developed during test.

(2) 14th day of illness: 30 grams glucose.

97 174 136 100 102 98 (Chart 107)
Glycosuria absent during test.

Blood Cholesterol.

(1) 3rd day of illness, 101 mgms. per 100 c.cms. blood.
(2) 14th day of illness, 158 " " 100 " "

3. Note.

During the toxic stage the blood sugar curve showed a fasting hyperglycaemia, delayed assimilation of excess sugar and a rise above the renal threshold at the 30 minute interval, associated with excretion of sugar in the urine. Ketone bodies were present in the urine. The blood cholesterol was abnormally decreased in amount.

Case 50.

R. Little	Age 11 years.
Admitted	2:10:33,
Day of Illness	First.
Dismissed	15:11:33.
Classification	Severe.
Throat swab	Positive.
Antitoxin	52,000 units.
Journal Reference	Ward 1 East.

1. History.

The patient was admitted to hospital on the first day of illness. Both tonsils, the soft palate and the uvula were covered with thick yellowish-white membrane. Oral foetor was intense and both tonsillar glands were enlarged.

The pulse rate was 100 and the temperature 99.8°F. The throat swab was positive and 32,000 units were given intramuscularly.

Acetone and diacetic acid were present in the urine during the first 4 days; the throat was clear on the 6th day. No complications developed during this period, but on the 15th day an irregularity in the pulse rate with tachycardia was present. This continued till the 23rd day of illness, but no further estimations were carried out. The patient was dismissed well on the 45th day.

2. Glucose Tolerance and Blood Cholesterol.

Glucose tolerance and blood cholesterol were estimated on the 2nd and 6th days of illness.

Glucose Tolerance.

(1) 2nd day of illness: 30 grams. glucose.

93 168 150 135 clotted 104 (Chart 108)
Glycosuria absent during test.

(2) 6th day of illness: 30 grams glucose.

96 163 146 122 93 98 (Chart 109)
Glycosuria absent during test.

Blood Cholesterol.

(1) 2nd day of illness, 109 mgms. per 100 c.cms. blood.
(2) 6th day of illness, 124 " " 100 " "

3. Note.

The case was one of severe diphtheria, admitted to hospital on the first day of illness. A glucose tolerance test carried out on the second day showed a normal fasting glycaemia, and a definite if slight delay in the fall of the curve. Glycosuria was absent throughout the test. The blood cholesterol was abnormally low. An almost similar state of affairs was present on the 6th day. No estimations are available beyond this stage.

C H A P T E R VII

Summary of Results.

SUMMARY OF RESULTS.

Fifty cases of diphtheria were investigated. These were graded, according to the severity of the intoxication, as mild, moderately severe, and severe. The mild and moderately severe groups were comprised of sixteen cases each while the severe cases numbered eighteen.

Glucose tolerance tests and blood sugar and cholesterol estimations were carried out, firstly during the toxic stage of the disease, secondly upon the advent of any complication of note and thirdly when clinical recovery was assured. The last mentioned determinations were intended to serve for comparison with the earlier observations in each case. Though this was the procedure adopted in the majority of instances, the following constitute departures from it:

Glucose tolerance was investigated in Cases 4 and 28 during the toxic stage only, the condition of the patients, later in the illness, being such as to render unjustifiable the disturbance occasioned by the administration of glucose and the frequent withdrawal of blood specimens. Estimations during the early stages were not possible in Case 44, as the patient was admitted to hospital eight days after having

received antitoxin and was not, therefore, suffering from the acute effects of toxaemia. Case 50 was not investigated during convalescence.

Blood Sugar.

Of the forty-nine cases investigated during the toxic stage, thirty-four revealed abnormalities in the fasting blood sugar concentration. Hyperglycaemia was present in twenty-four cases, whilst hypoglycaemia occurred in ten. An important observation made was the greater frequency of the association of hyperglycaemia with the mild and moderate type of case, and of hypoglycaemia with the severe form. Thus in the mild group consisting of sixteen cases, hyperglycaemia was present in eight (Cases 8, 18, 22, 24, 27, 29, 37, 47) whilst hypoglycaemia occurred in one only (Case 23). In the moderate group there was a greater incidence of abnormality, twelve of the sixteen cases revealing unusually high or low blood sugar values. Hyperglycaemia was present in eleven (Cases 10, 13, 14, 20, 30, 31, 32, 33, 35, 40, 42) hypoglycaemia again occurring in one only (Case 5). Of the eighteen severe cases investigated, thirteen were abnormal in respect of blood sugar, but hypo-

glycaemia now showed the greater frequency, being present in eight (Cases 3, 11, 15, 19, 21, 28, 45, 48) hyperglycaemia occurring in the remaining five (Cases 4, 6, 9, 41, 49). It may be argued that the duration of the illness, prior to making these determinations, accounts for the fact that hyperglycaemia tends to be associated with the less severe and hypoglycaemia with the more severe forms of the disease. Diphtheria, however, is an acute disease, generally with a well marked onset. In point of time, therefore, the cases differ from each other, at the most, only by a matter of a day or two. Such differences are unlikely to render the results incomparable.

Glucose Tolerance.

Thirty-six cases of the series revealed a decrease in glucose tolerance. The decrease, in this instance, would seem to parallel more closely the severity of the case. Thus it occurred in five of the sixteen mild cases (Cases 8, 16, 22, 23, 47), thirteen of the sixteen moderately severe cases (Cases 1, 2, 5, 10, 13, 14, 20, 25, 31, 32, 33, 40, 42), and all of the seventeen severe cases investigated. The extent of the decrease in glucose

tolerance also points to the tendency of the defect to increase with the degree of toxaemia. In this respect the occurrence of glycosuria is assumed to indicate a greater inability to utilise or store ingested carbohydrate in the usual way, provided that such an inability is associated with an abnormally high blood sugar concentration. Glycosuria is notably absent from the cases constituting the mild group. In the moderate group six of the cases in which decreased sugar tolerance was present showed an abnormally high maximum concentration of blood sugar, the tests being accompanied by glycosuria. In the severe group, however, high maximum concentrations with glycosuria were even more obtrusive accompaniments of the tolerance tests, since these departures from normal occurred in all of the cases in which tolerance for glucose was decreased.

Type of Blood Sugar Curve.

Excluding the occurrence of glycosuria, the degree of intoxication does not seem to be reflected in the type of blood sugar curve obtained. The charts in the three groups investigated follow the same general tendency, namely an abnormally slow decline in falling to the fasting blood sugar

level. Such a curve is appropriately referred to as a "lag curve", a term which has been applied to it by most observers. The tendency for the blood sugar concentration progressively to rise after the administration of glucose, as so characteristically happens in the diabetic, is conspicuously absent from the cases under review.

Blood Cholesterol.

Twenty-seven of the forty-nine cases observed during the toxic stage were abnormal in respect of blood cholesterol. Of these twenty-seven cases, twenty-one showed abnormally low and six abnormally high blood cholesterol values. It would appear that hypocholesterolaemia is a frequent accompaniment of diphtheritic toxaemia. That is incidence would also appear to increase with the severity of the intoxication is a fair inference, since of five mild, nine moderate and thirteen severe cases in which the blood cholesterol was abnormal, hypocholesterolaemia occurred respectively in four (Cases 8, 24, 37, and 47), seven (Cases 1, 5, 10, 30, 31, 35, and 42) and ten (Cases 4, 6, 9, 15, 26, 39, 41, 45, 49, 50).

Complications.

No complications were observed in the mild group. In each case the illness took the form of a mild faucial diphtheria progressing uneventfully to recovery.

In the moderately severe group three cases developed complications (Cases 20, 32, 42). With regard to Case 20, tachycardia was a prominent symptom from the outset, and on the tenth day arrhythmia developed. Vomiting and ketosis were troublesome features of the case, in which evidence of myocardial damage was also present.

Case 32 progressed satisfactorily until the twenty-seventh day of illness, when an irregularity of cardiac rhythm and tachycardia developed. Passive congestion of the liver, vomiting and ketosis were also present.

The results obtained in both of these cases were identical, decreased sugar tolerance, low blood sugar and high blood cholesterol constituting the abnormalities found. The third case (Case 42) was complicated by the development of serum sickness on the seventh day. Decreased sugar tolerance was again in evidence, and the fasting blood sugar reached the abnormally low figure of 65 mgms. per cent. The blood cholesterol in this case was, however, normal.

The incidence of complications was greatest in the severe group, nine of the eighteen cases investigated being involved. Paralysis, most frequently of the palate, occurred as the only abnormality present in Case 26. Cardiac involvement was present alone in four cases (Cases 3, 19, 34, 41) while in four cases also (Cases 9, 15, 44, 45) paralysis and cardiac involvement were present together.

Three cases were normal in respect of blood sugar concentration; the remaining six (Cases 3, 19, 26, 34, 41, 44) revealing a more or less marked hypoglycaemia. Decreased sugar tolerance was present in all of the complications investigated. An interesting observation was the frequency with which hypercholesterolaemia occurred in the complicated group. Seven cases (Cases 3, 9, 15, 19, 26, 34, 44) showed abnormally high values, the remaining two being normal.

In reviewing the complicated cases generally, one is struck by the fact that decreased sugar tolerance would appear to be a manifestation, not only of the toxic stage but also of its later sequelae. Whether or not this later deficiency was a progressive development from the outset

or merely a recurrence of the defect which had subsided with the initial toxaemia, is unfortunately not ascertainable from the results of the investigation.

Only two of the complicated cases developed glycosuria during the tests for glucose tolerance. In both instances these were of the severe type (Cases 9, 44). All but one (Case 15) of the complicated group developed glycosuria during the toxic stage, however.

Fatal Cases.

Four of the cases investigated died (Cases 4, 11, 28, 48). All of them were of the severe type. The results obtained during the toxic stage are included in the account of the severe cases already given. Subsequent determinations were made with the following results: In Cases 4 and 11 further glucose tolerance tests were not practicable Cases 28 and 48, however, showed diminished glucose tolerance and glycosuria just prior to death. Observations made at the same time revealed marked degrees of hypoglycaemia and hypercholesterolaemia.

Ketosis.

Peters[1] has shown how profound the condition of Ketosis can be in diphtheria, persistent vomiting often occurring in the absence of suitable treatment in the more severe forms of the disease.

Ketone bodies are invariably present in the urine during the toxic stage. In the milder cases they are usually slight and transient, but in the more severe forms they are present in more marked degree and are of a more persistent nature.

Not only are ketone bodies present in the urine during the toxic stage but they tend to occur in those cases which develop complications during the illness. Vomiting is a troublesome and often grave symptom of the prolonged disease and is frequently seen in cardiac cases associated with hypotension. In this connection it is interesting to note the observation of Moor[2], who investigated the blood pressure in cases of diphtheria and found, in the more severe forms, a tendency for the blood pressure progressively to fall after the third day of illness. If the fall continued until the pressure was only 80 m.m. he found that vomiting invariably set in. Moor regards "cardiac" vomiting as a

means of increasing the cerebral circulation by compression of the abdominal vessels. He has observed such vomiting to raise the blood pressure by 62-68 m.m.

Cardiac vomiting usually occurs in the second or third week of the disease. Vomiting, however, need not always be an ominous symptom, as it may occur relatively early in the disease, when its occurrence is equivocal. It may then be due merely to toxaemia, to serum sickness, or to grave cardiac involvement. Whether due to the last mentioned or to the ketosis occasioned by the toxaemia, vomiting introduces a vicious circle causing a lack of nourishment, the starvation which results bringing about ketosis or aggravating it if, already, it exists. It seems a fair inference that in the majority of cases in which ketosis exists without vomiting the initial factor in determining its onset is the toxaemia. Ketosis, so arising, will be seen, naturally, during the toxic stages. Later in the disease the cardiac condition and hypotension may be the means by which ketosis then reasserts itself.

With regard to the investigation in hand, ketosis was found to be an almost invariable accompaniment of all cases of diphtheria during the toxic stage. Ketosis and vomiting

however, were only observed in connection with the complicated and fatal cases. Cases 20, 32 and 42 of the moderate group and Cases 3, 9, 15, 34, 44 and 45 of the severe group all developed complications during the presence of which ketosis and vomiting were manifest. That ketosis may exist apart from vomiting in the complicated cases is evidenced by the fact that it so occurred in Cases 19, 26 and 41. As in the great majority of cases during the toxic stage the occurrence of ketosis without vomiting suggests that the former has a basis in some other defect than vomiting - that the ketosis, in fact, precedes the vomiting. It would appear as if the failure of the power to utilise the blood sugar initiated the ketosis and that a vicious circle supervened causing the symptoms-complex to persist. Cammidge (3) has pointed out that change in the acid-base equilibrium of the systemic circulation may result in hyperglycaemia and glycosuria. It is believed, however, that these effects of acidosis are only pronounced if there are associated defects of carbohydrate metabolism.

Ketosis and vomiting occurred in all of the fatal cases and became more pronounced as these cases progressively deteriorated. In all cases in which evidence of ketosis

was present the glucose tolerance tests revealed some interference with carbohydrate storage or utilization. This may be the source from which the disorders arise.

Duration of Abnormal Findings.

The determinations carried out during convalescence indicate a complete return to normality at this stage of the illness. The defects recorded would, therefore, appear to be the results of toxaemia and when this has passed a return to normal is usual. The persistence of the defects noted by other workers has not been confirmed.

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C H A P T E R VIII.

Discussion.

DISCUSSION.

The evidence presented in this thesis, though limited in extent, sets forth certain definite findings with regard to metabolic activity during the course of diphtheritic intoxication. It has been shown that during the toxic stage the fasting blood sugar tends to be high in mild and moderate cases, whereas in those of more severe degree, it tends to be low. When the disease is uneventfully recovered from the blood sugar returns to its normal level but if complications should manifest themselves and the disease be, therefore, more prolonged, the blood sugar concentration becomes lowered. This occurred, irrespective of whether high or low blood sugar obtained during the toxic stage, and was most marked just prior to death in those cases where the disease progressed to a fatal termination.

Evidence has also been produced that, side by side with these variations in the blood sugar concentration, there exists in the disease a diminution in glucose tolerance which is reflected in the type of blood sugar curve obtained from tolerance tests. The characters

exhibited by this type of curve are those of a delayed fall or "lag", frequently associated, in the more severe forms of the disease, with a high maximum concentration and attendant glycosuria.

The blood cholesterol in most cases during the toxic stage is abnormally low. During the stage of complications however the tendency is for the blood cholesterol to undergo a more or less marked increase. Where the above findings obtained evidence of ketosis was invariably present.

The theories offered in explanation of the disorders of carbohydrate metabolism have been reviewed in Chapter III. That of thyroid adrenal stimulation by the toxin gathers to it a certain amount of pathological conviction. Loschke (1910)(1) who examined the adrenals of the victims of diphtheria found an almost total disappearance of lipoids. In the medulla itself he observed an absence of affinity for chrome salts and a disappearance of adrenalin. Moltschanoff (1912)(2) who examined the adrenals of nineteen children who had suffered from diphtheria, noticed that the adrenals, especially the medulla showed definite hyperaemia and frequently extravasations

of blood, the degree of vascularity being related more to the severity of the disease than to its duration. In cases fatal within four days, Moltschanoff found an increase in the lipoid content. He also observed an increase in the number of spongiocytes and in the number of cells, generally, which exhibited lipoid formation. In cases dying between the fourth and sixth days he found, in addition, a large number of small cells with spongy protoplasm and nuclei poor in chromatin. Ranging between these cells and the fully developed spongiocytes there were many transitional cells. Moltschanoff believed that the small cells represented an atrophic state of the spongiocytes resulting from increased functional activity. In cases dying on the eighth to the tenth day Moltschanoff noted the onset of degenerative changes. In the medulla he found a diminution or disappearance of the chrome reaction. Besides taking an active part in the destruction of the diphtheria toxin, he considered that in the early stages of diphtheria there is an increased functional activity which in severe intoxication passes into a state of exhaustion with atrophy of the cellular elements which may lead to death.

Hannes (1910)[3], however, could trace no relationship between death in diphtheria and the state of the adrenals. Of a total of forty-seven cases investigated, disappearance of chrome reaction occurred in only eight and diminution in thirteen. In the remaining twenty-six cases it was strongly present. Thomas (1910)[4] and Ingier and Schmorl (1910)[5] agreed in the main with Hannes that the cause of death is not to be found in an exhaustion of chromaffin function.

Lawrence and Buckley's theory of increased glycogenolysis involves the adrenals in a specific stimulation by the toxin. According to this theory, toxaemia causes first of all a stimulation of adrenal function and later in the disease an exhaustion. Assuming this to be correct, stimulation would lead to an increased level for blood sugar and exhaustion would lead to an abnormal depression. In accordance with this view, the blood sugar would tend to be high during the early, and low during the later stages of the disease. In the most severe forms of the disease the greater degree of toxaemia may determiner an early exhaustion of adrenal function and a low blood sugar from the outset.

In the later stages of the complicated disease the blood sugar level has been shown to be low. It is possible that exhaustion of liver glycogen may account for the failure to maintain the blood sugar concentration at its normal level. In this connection it is interesting to note that Schwentkner and Nod (6) found a marked reduction, in most cases indeed a complete absence, of hepatic and muscle glycogen, during the toxaemia.

In the light of this theory, decreased sugar tolerande is due to the adrenal stimulation antagonising the effective action of insulin. During the course of a glucose tolerance test the hypoglycaemia action of insulin is, to a greater or less extent, annulled and the blood sugar curve manifests an abnormal rise and a delayed fall. Lawrence and Buckley's theory fails to take account of the fact that when adrenal exhaustion may be presumed to have come about a similar type of blood sugar curve is still obtained. The antagonism of the adrenal to insulin action being removed, one would naturally expect unrestrained action of the latter to exist with consequent speedy removal of the glucose from the blood. This however does not occur, the low blood sugar of the more severe or pro-

longed cases being associated with a type of curve similar to that obtained during the early stages of the disease.

According to Sweeney's conception, insulin action is annulled by the direct effect of the toxin upon the islet tissue of the pancreas. Diphtheritic intoxication according to this theory would, therefore, appear to occasion an acute form of diabetes, more or less severe. If this theory could be substantiated, it would throw light upon many of the features of the disease. In particular it would explain the asthenia and wasting of the victim of severe diphtheria on the ground that the inability to utilise carbohydrate led to incomplete combustion of fat with its attendant ketosis. It would also explain why protein was broken down in the disease, a fact, the evidence of which has been alluded to elsewhere. In view of the cholesterol findings in the present investigation, such evidence would point, in explanation, to a possible rise in the blood fat by mobilisation from the fat depots in response to the needs of metabolism.

In the view of the author, however, such a trend of events seems unlikely. The type of blood sugar curve

obtained in this investigation, and also by other workers in the field, is not conducive to the establishment of such a theory. A "lag" curve in diabetic symptomatology, if it indicates diabetes at all, is suggestive of the incipient or mildest form of the disease only. It seems unjustifiable, therefore, to conclude that the severity of diphtheria is due to insufficiency or inactivity of insulin.

Nor does the theory of insulin inhibition offer more acceptable explanation. One must admit from the outset that the essence of toxaemia is involvement of the body tissues generally. Not only may metabolism be impaired centrally in the factories of insulin and adrenalin, but also peripherally amidst that great public of humble tissue cells. The changes encountered in the blood sugar and glucose tolerance may therefore be due merely to action of the toxin upon the tissues generally and not to any syndrome peculiar to the disease. The liver must not be left out of the reckoning. Toxin hepatitis may lead to a decreased ability to store glucose as glycogen with consequent accumulation of the former in the blood stream, following ingestion. Nor must the ability of the tissues

to oxidise the excess be forgotten. The investigation of laevulose tolerance and of the respiratory quotient in the subjects of diphtheria seems to the author to be indicated before any hard and fast conclusions can be drawn.

The matter is of fundamental importance in the therapeutics of the disease. If the view is held that diphtheria is complicated by a metabolic syndrome, further progress in the treatment of the disease may be ordered along these lines. In recent years recognition of the latter has led to the institution of glucose-insulin therapy. Though restricted in its scope, this investigation impressed the author with the futility of such a procedure, which scarcely seems indicated from this and other work upon the subject. In contrast, if one acknowledges that the metabolic effects are due to the action of the toxin upon the tissues generally and that the latter suffer the brunt of the attack in equal proportion, one naturally concludes that the surest implement with which to combat severity in the disease is antitoxin and that the most valuable therapeutic measure is to administer it early.

With regard to the blood cholesterol, the relationship

of the adrenal cortex to cholesterol metabolism is too uncertain at the present time to invite prophecy. The blood cholesterol is known to be decreased in many diseases due to infection, of which diphtheria is one. Why this should be must await an explanation. Nor does it seem clear why the blood cholesterol should increase in the later stages of the complicated disease. As Josephs (7) has indicated with regard to protein in diphtheria, it is possible that the increase in blood cholesterol may be due, also, to toxic destruction of tissue. Those cases in which paralysis occurred were significantly associated with high cholesterol values in the blood. Cholesterol derived from the breakdown of tissue in the body is supposed to be retained in the blood and not excreted.

With regard to the duration of the abnormal findings, the author is at variance with those who suggest that the defects observed persist for some time after the disease has been recovered from. The effects would seem, rather, to be due to toxic action and to subside when the latter has been removed. The persistence of the abnormalities in the protracted cases may be an expression

of the fact that in these cases a certain amount of toxin has been fixed before the administration of serum. In this respect it is noteworthy that it is in the more severe cases that complications develop.

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CHAPTER IX

Conclusions.

CONCLUSIONS.

1. The blood sugar, glucose tolerance, and blood cholesterol of clinical cases of diphtheria have been investigated.

2. The blood sugar has been found to vary with the severity of the intoxication. Hyperglycaemia has been found to be a more frequent accompaniment of the mild and moderately severe cases, whereas hypoglycaemia showed a greater frequency in the most severe cases of all. In fatal cases the blood sugar was abnormally low prior to death. The advent of complications has been shown to be accompanied, usually, by hypoglycaemia, irrespective of whether the blood sugar was high or low during the toxic stage.

3. A decrease in the tolerance of diphtheria patients for glucose has been noted. The type of blood sugar curve obtained in these cases has been defined as a "lag" curve, the characteristic of which is a delay in the fall to fasting level after the ingestion of glucose, associated, in the more severe type of case, with a high maximum con-

centration and glycosuria. The occurrence of glycosuria indicates that the extent of the decrease in glucose tolerance is greatest in the severe cases.

4. In protracted cases in which complications developed, evidence of decreased sugar tolerance has been obtained. Judged by the incidence of glycosuria, the extent of the decrease during this stage would appear to be less than during the period of initial toxaemia. It has not been possible to ascertain whether this is a persistence of the similar defect observed during the toxic stage, or whether it represents a recurrence of the abnormality.

5. A tendency for the blood cholesterol to be low during the toxic stage of diphtheria has been noted. During the stage of complications, however, the blood cholesterol has been found to undergo an abnormal increase.

6. The frequency of ketosis in diphtheria has been alluded to; its relationship to the metabolic disorders has been briefly discussed.

7. The results obtained after clinical recovery suggest

that the condition of disordered metabolism met with in diphtheria passes off with, and is therefore directly due to, the intoxication. No persistence of the defect was noted during convalescence.

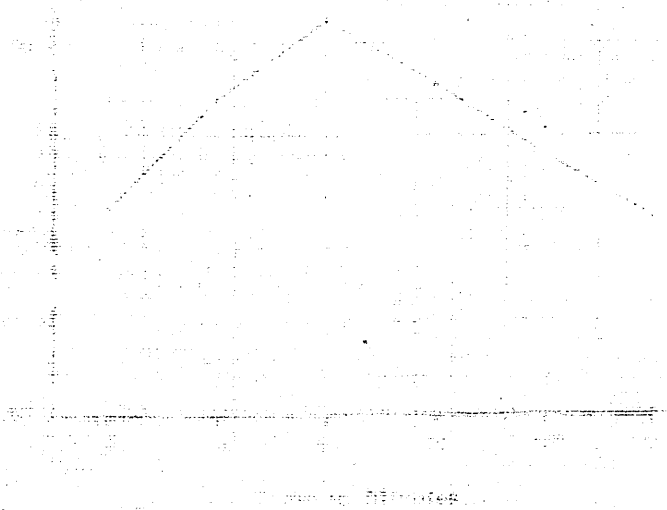
8. The view is expressed that the disorders met with are due to the action of the toxin upon the body tissues generally and that no existing theory of a metabolic syndrome can be substantiated.

9. Possible lines along which further investigation may be carried on have been suggested, and the therapeutic inference has been made that antitoxin administered early in the disease is a more certain measure with which to combat severity than glucose insulin therapy, if the former procedure is neglected.

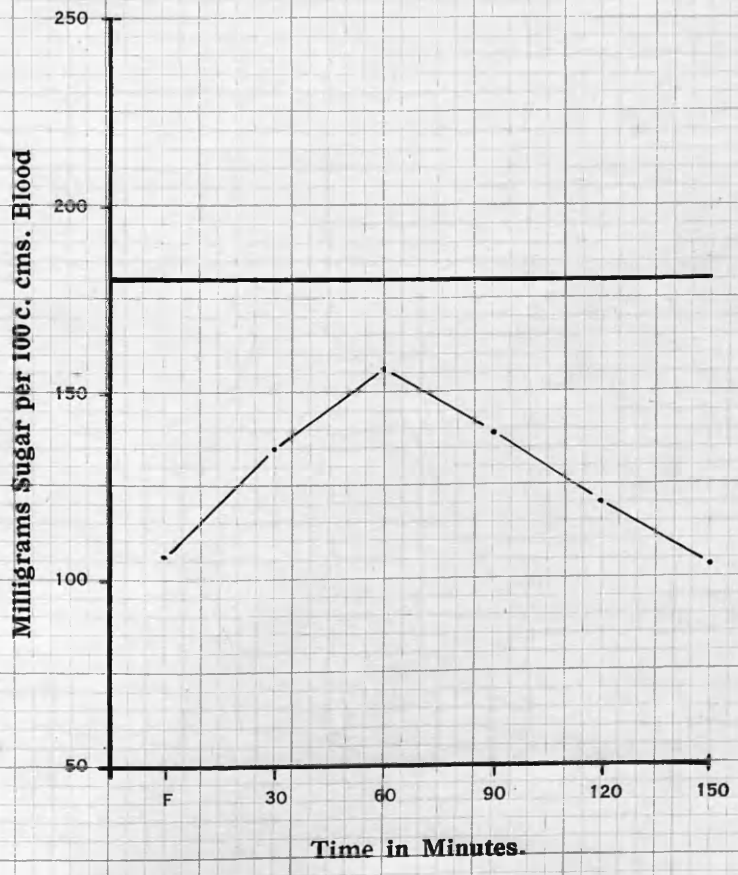
10. The literature of the experimental aspect of the subject has been reviewed.

.BLOOD SUGAR CHARTS

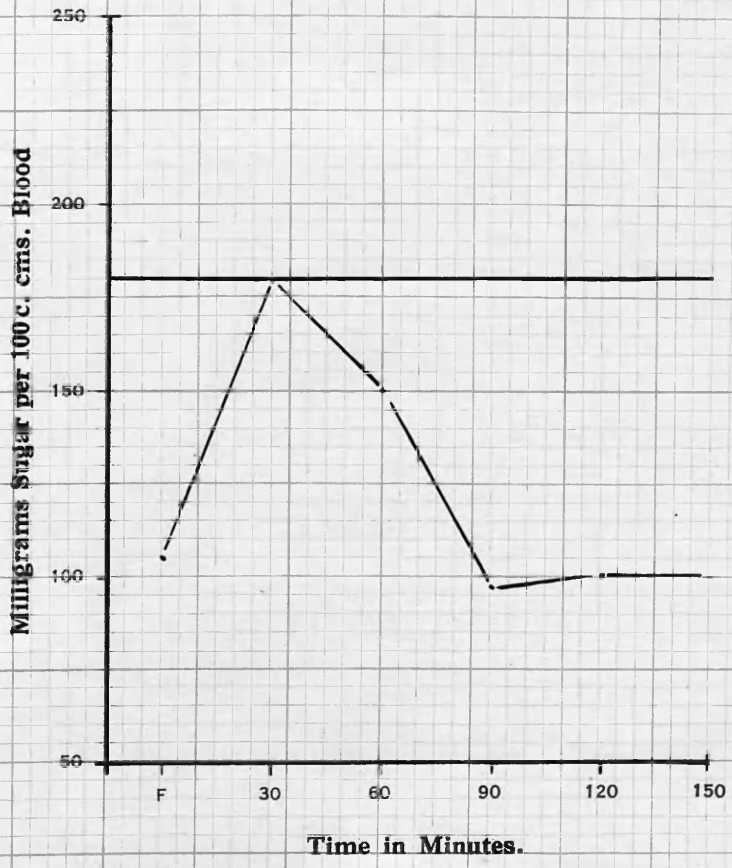
1 - 109.



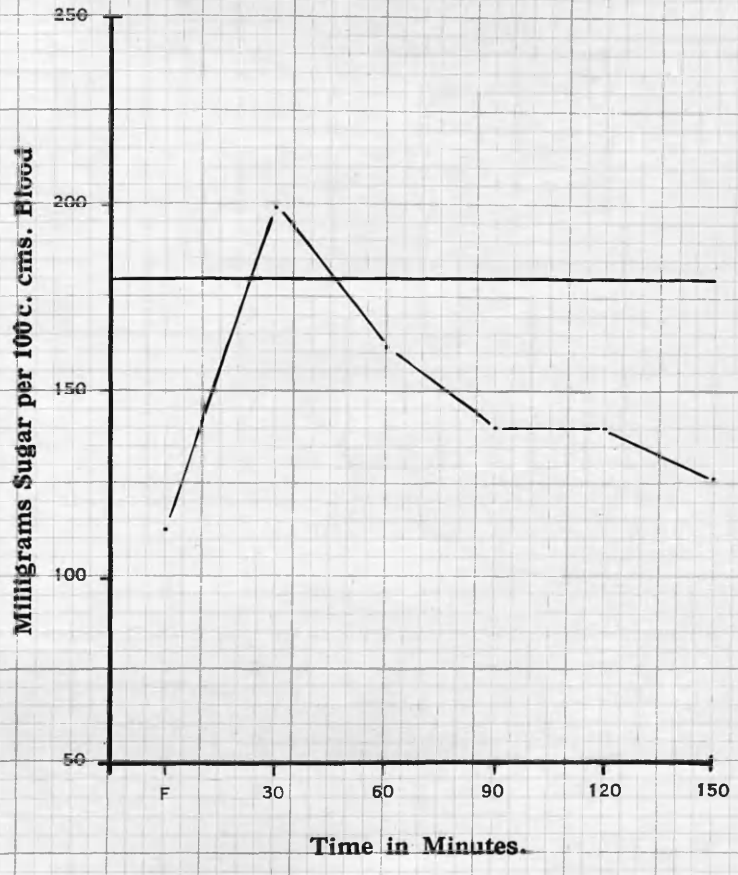
Case 1:
Chart 1.



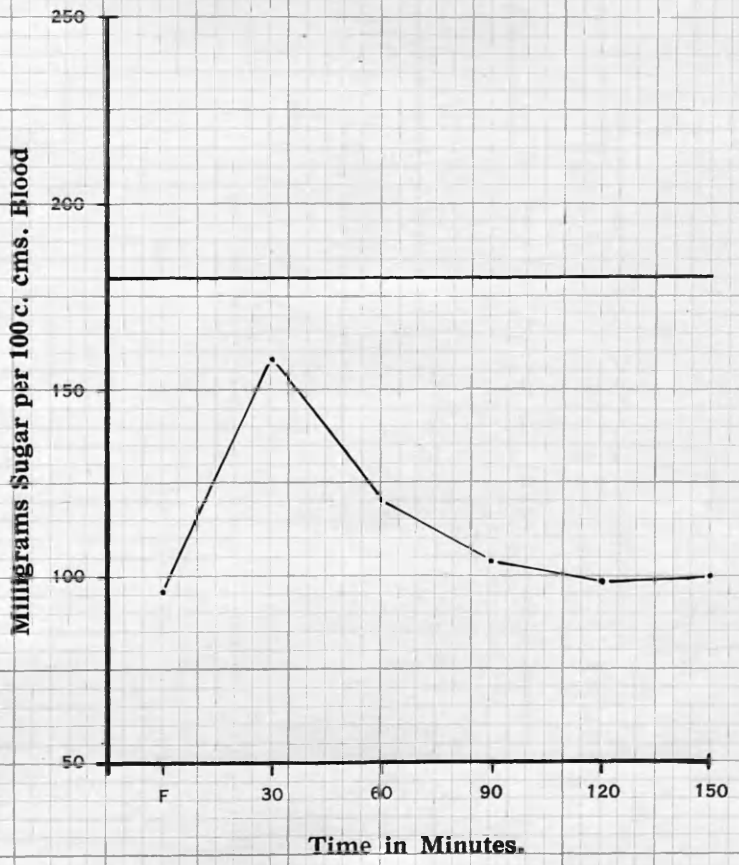
Case 2:
Chart 2.



Case 2:
Chart 3.



Case 2:
Chart 4.



Case 3:
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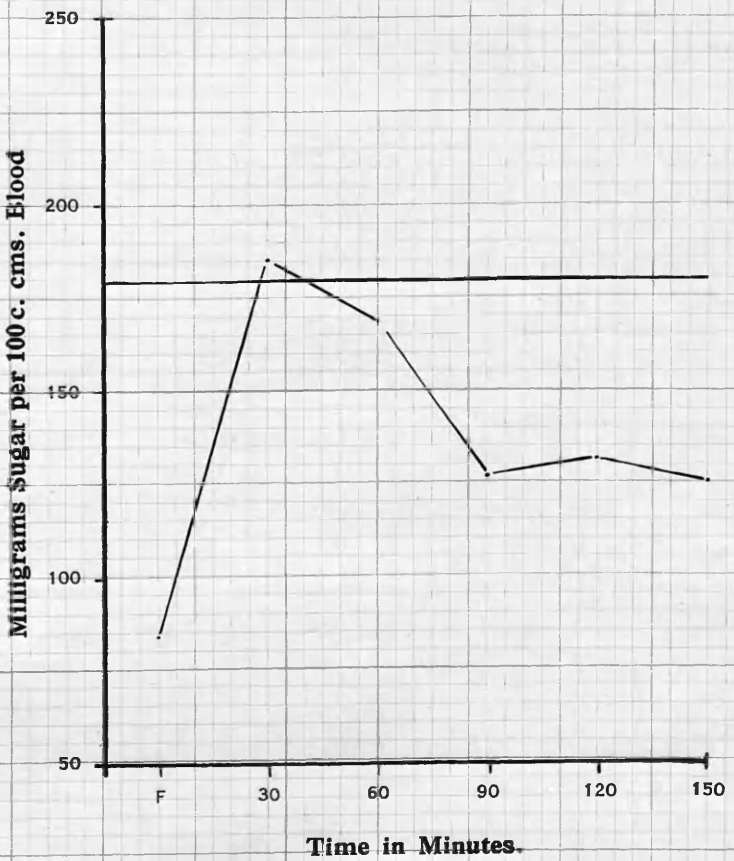

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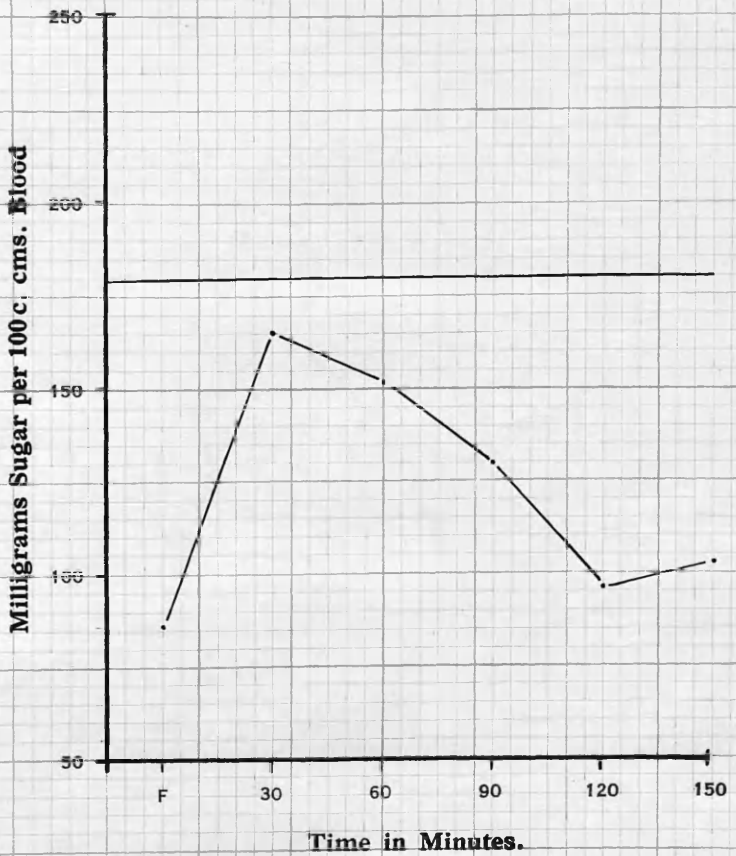

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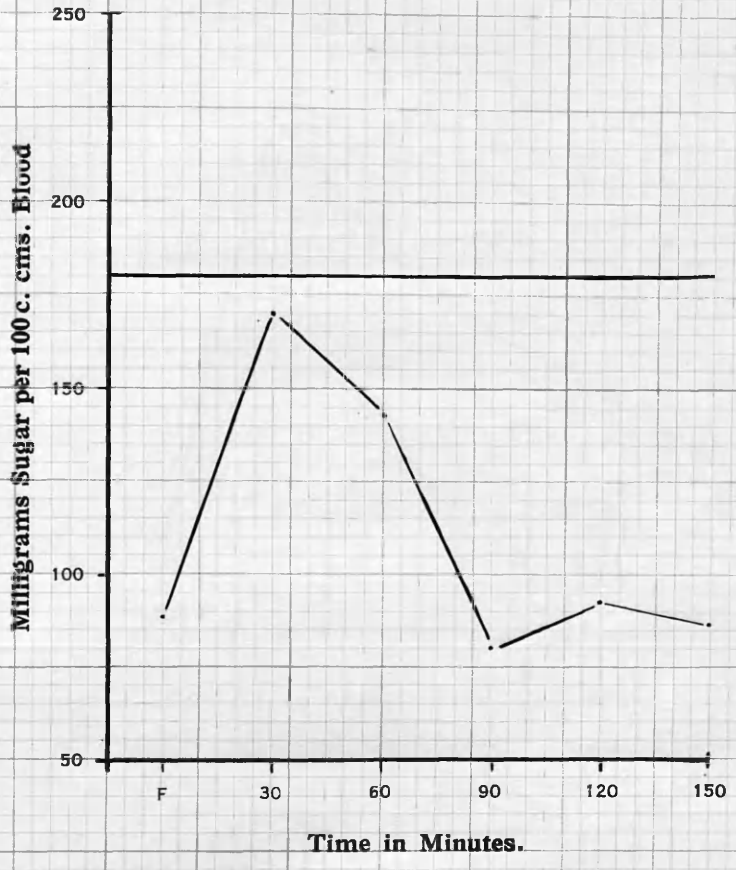

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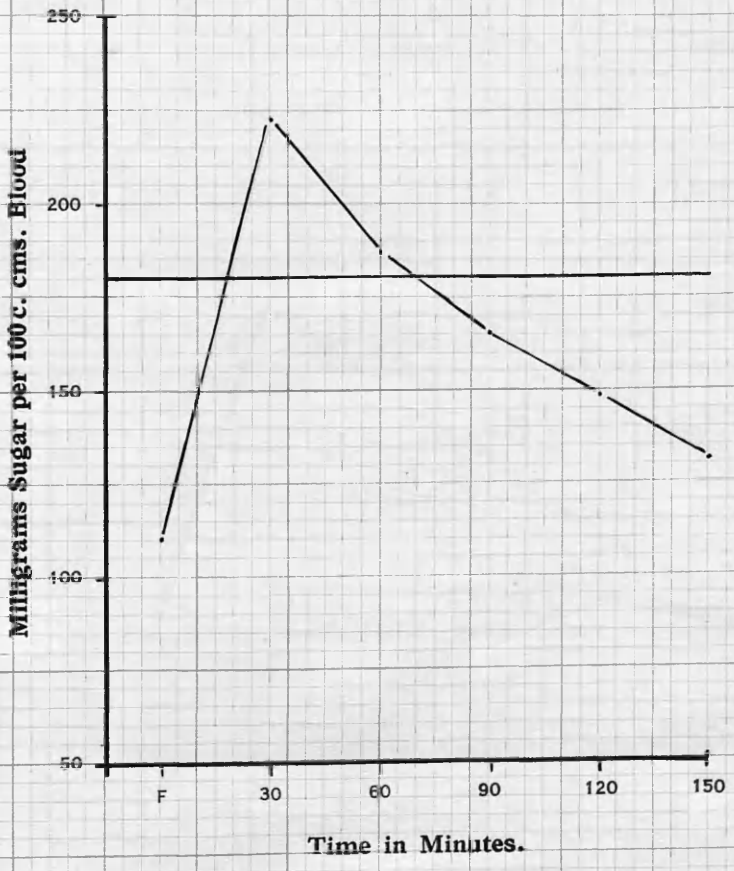

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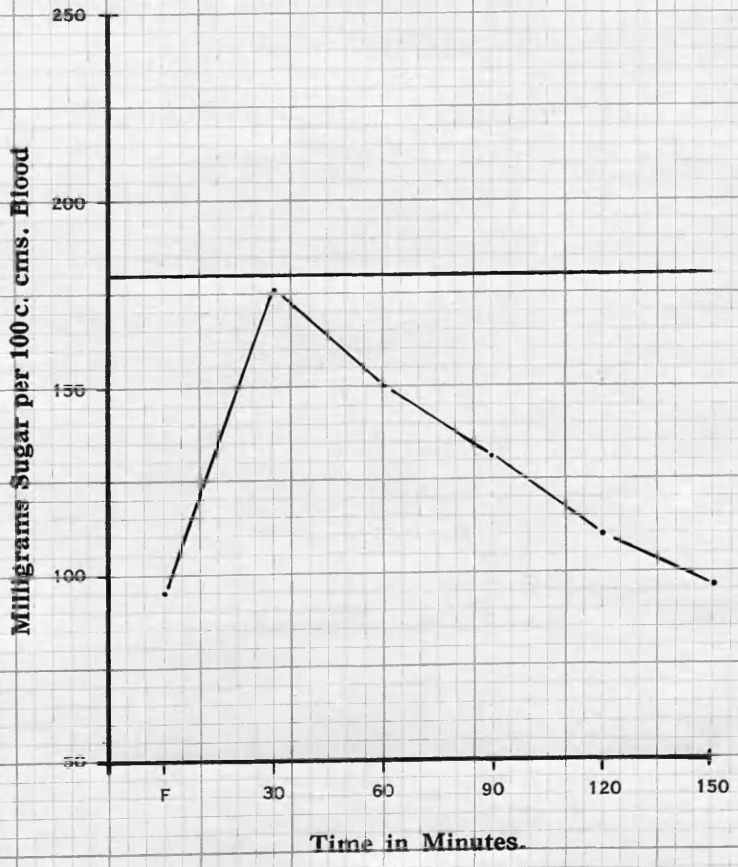

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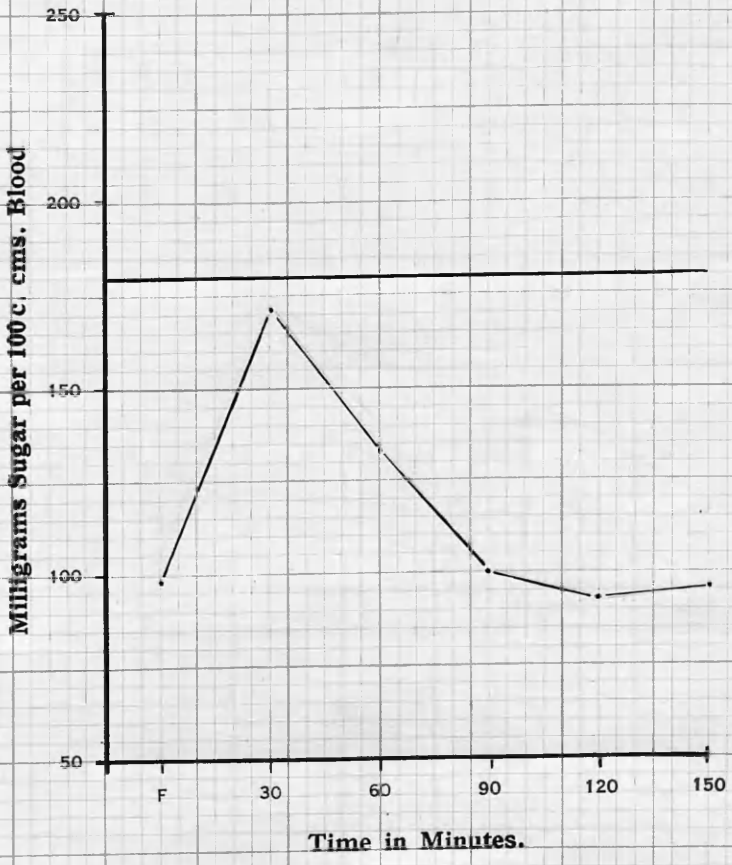

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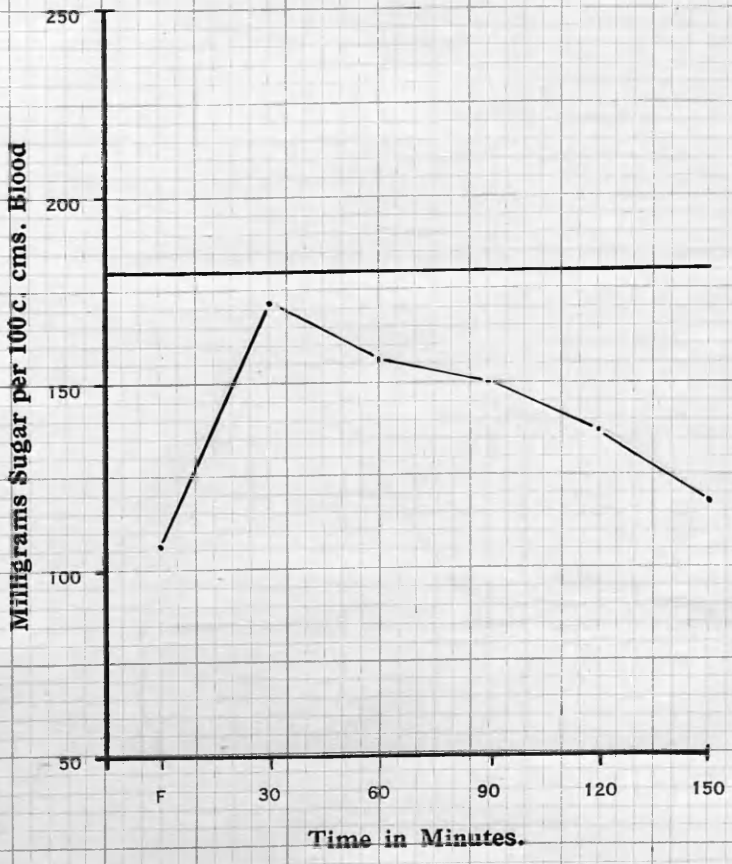
Chart 11.



Case 6:
Chart 12.

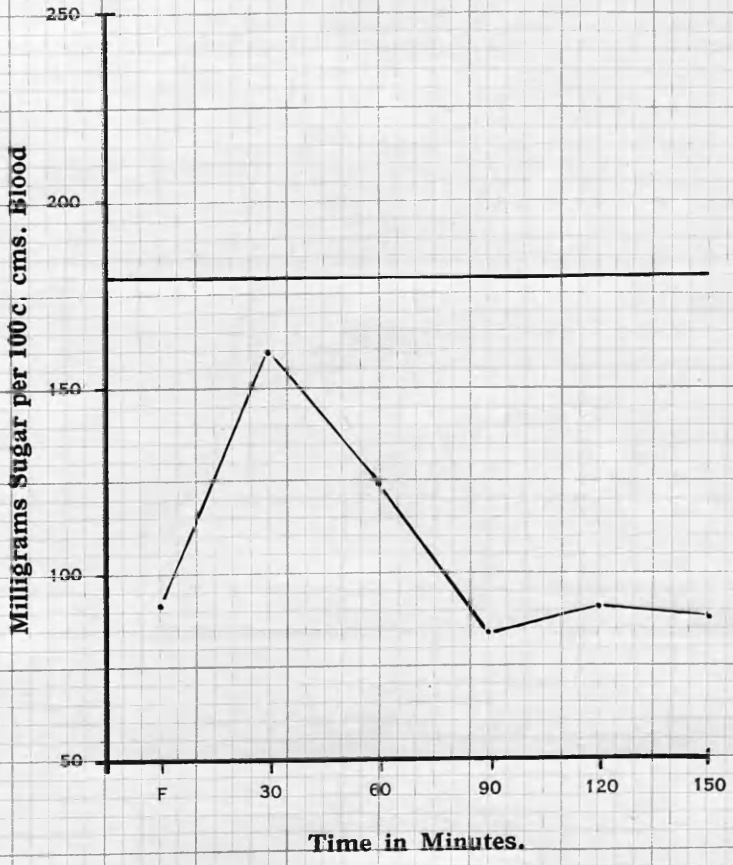


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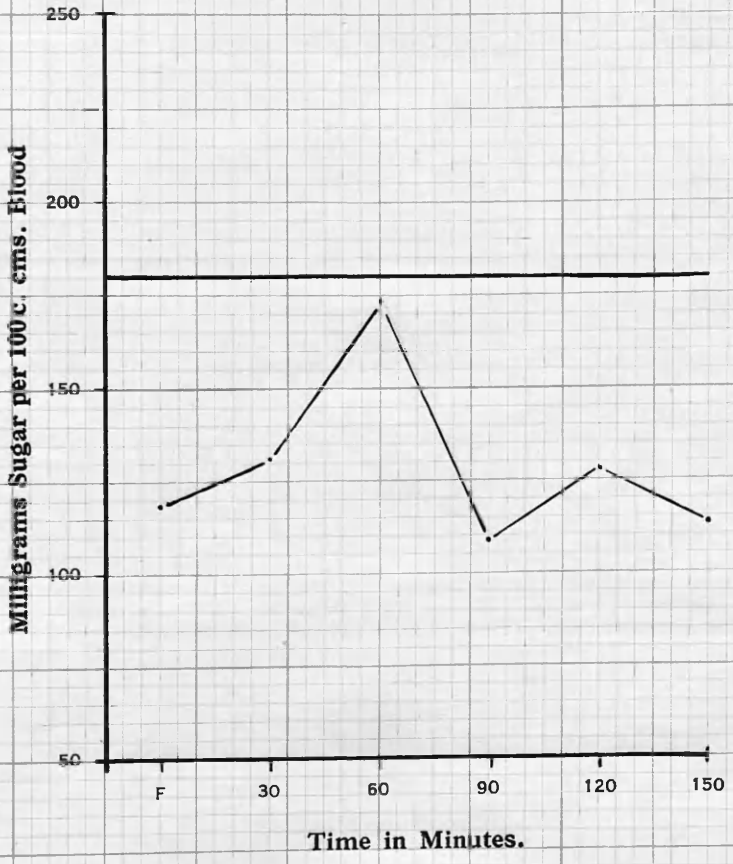
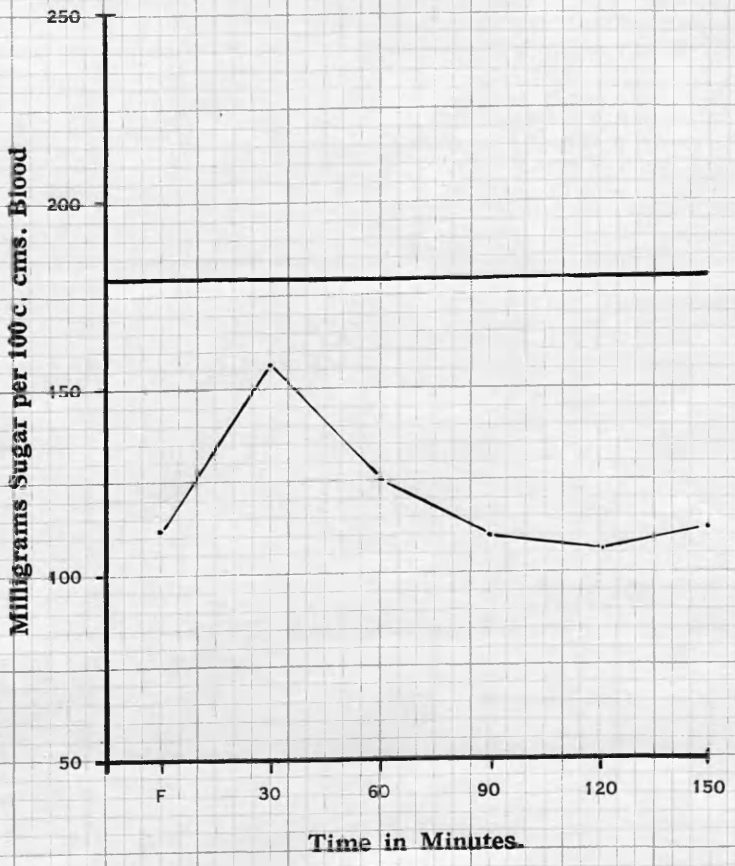
Chart 13.



Case 7.

Chart 14.



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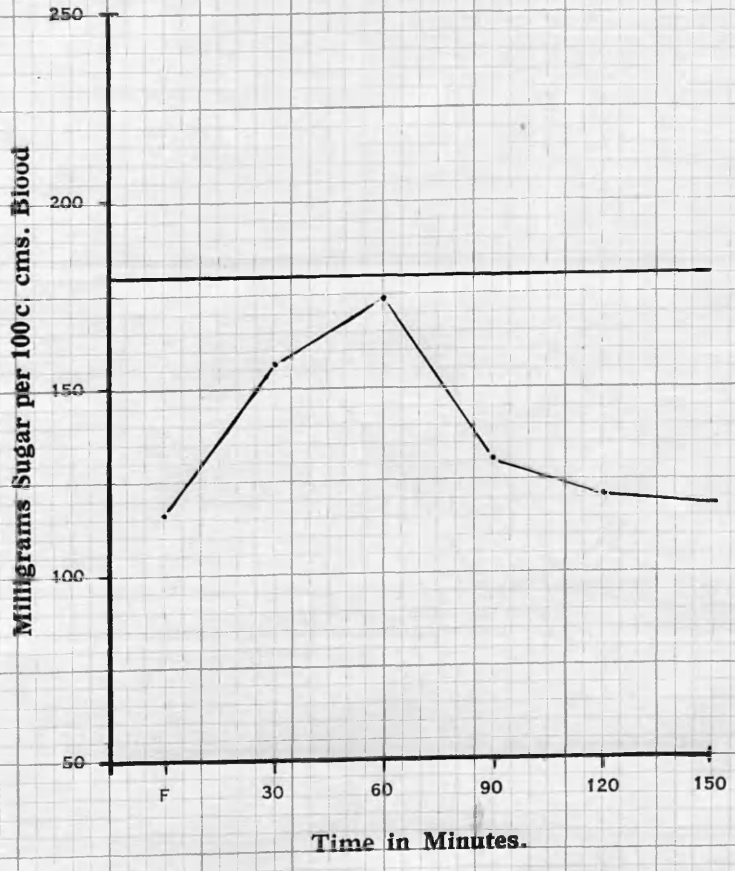

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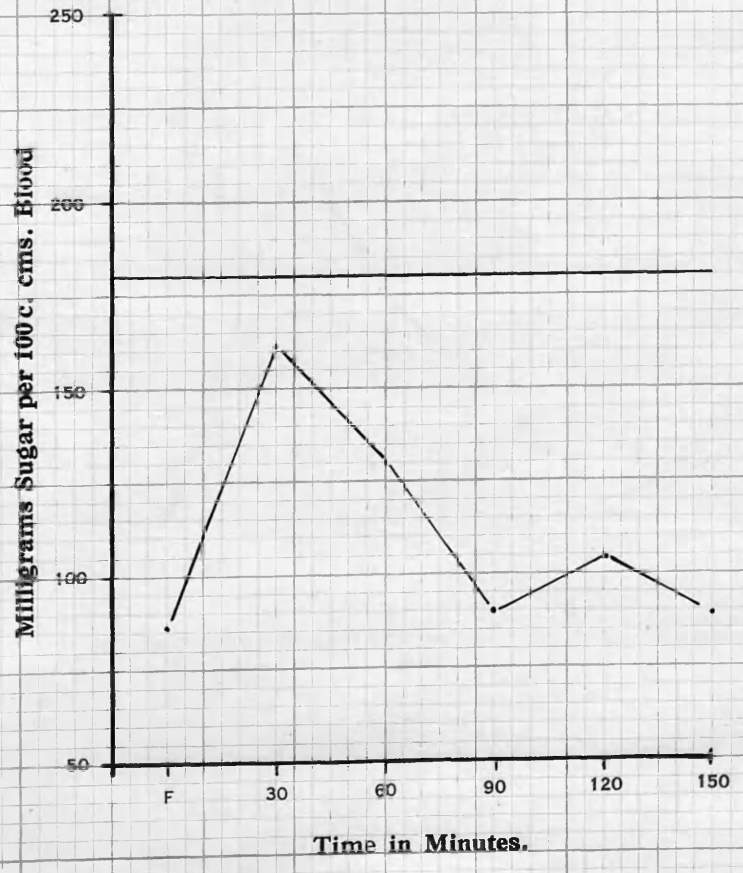

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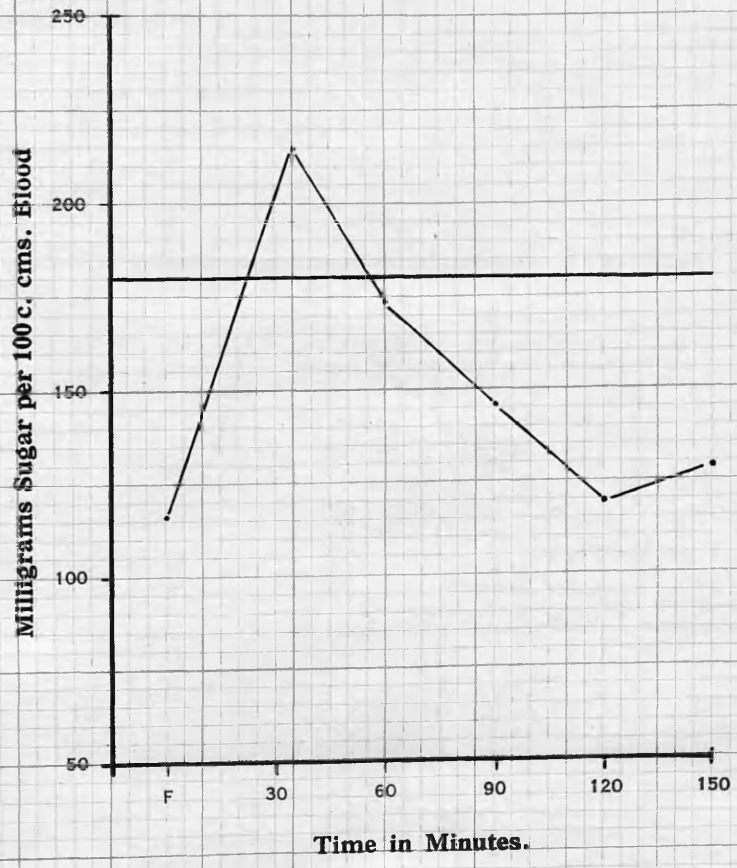

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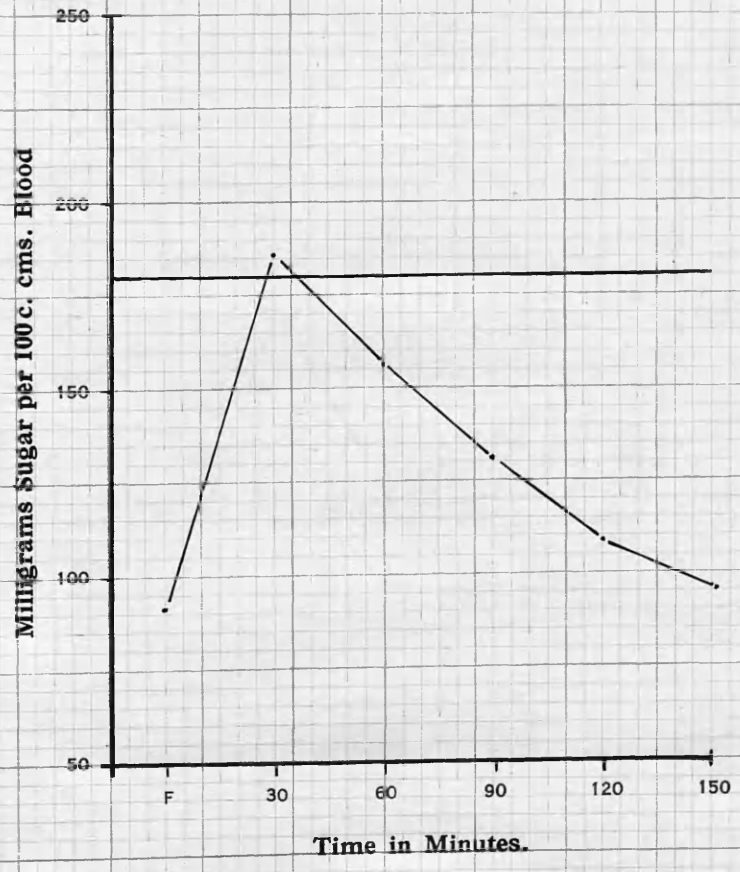

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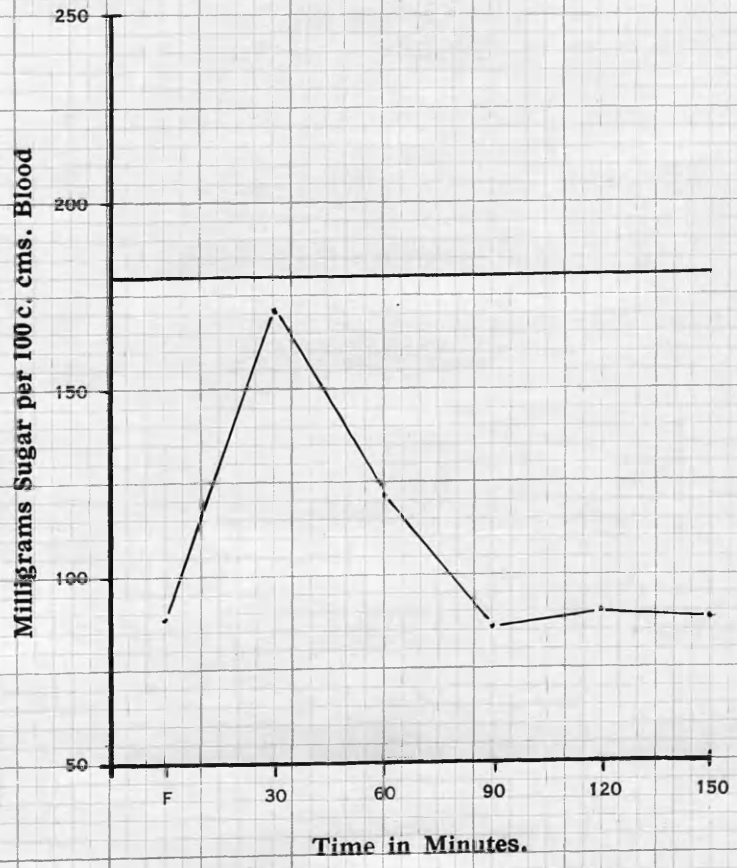

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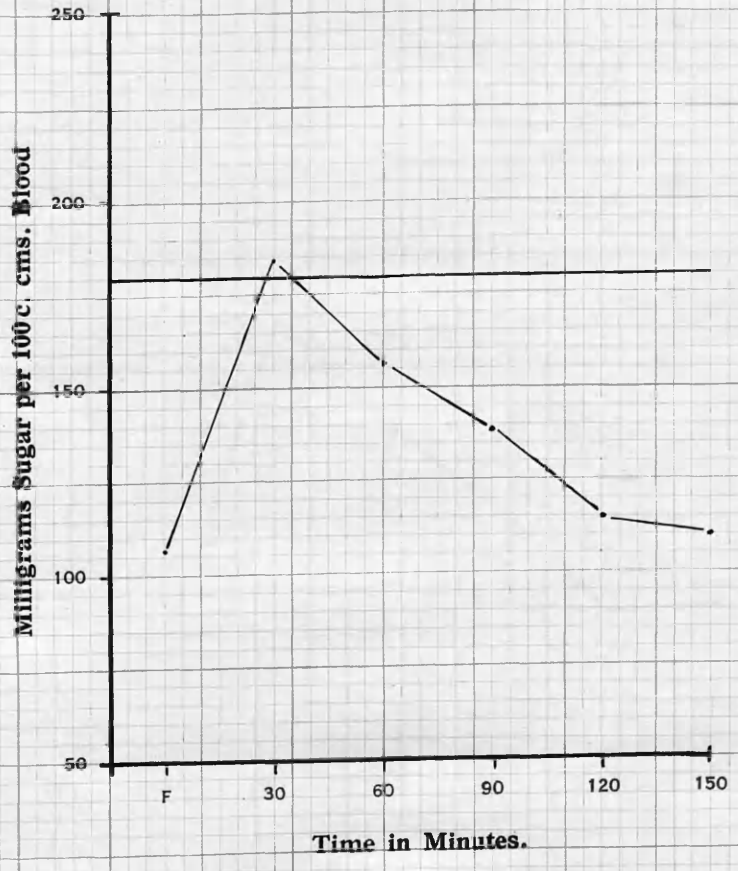

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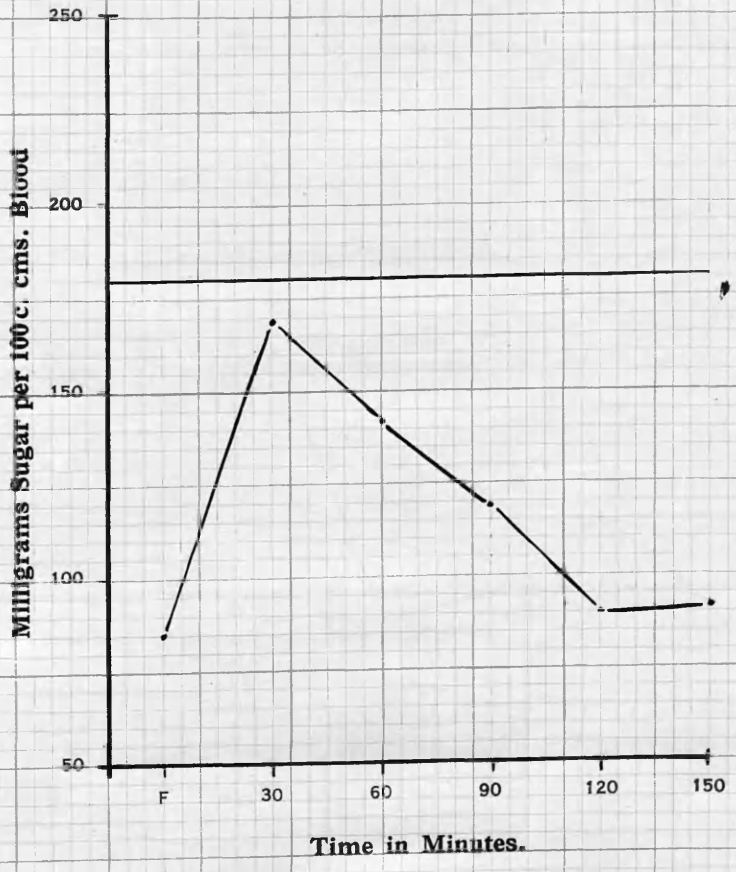

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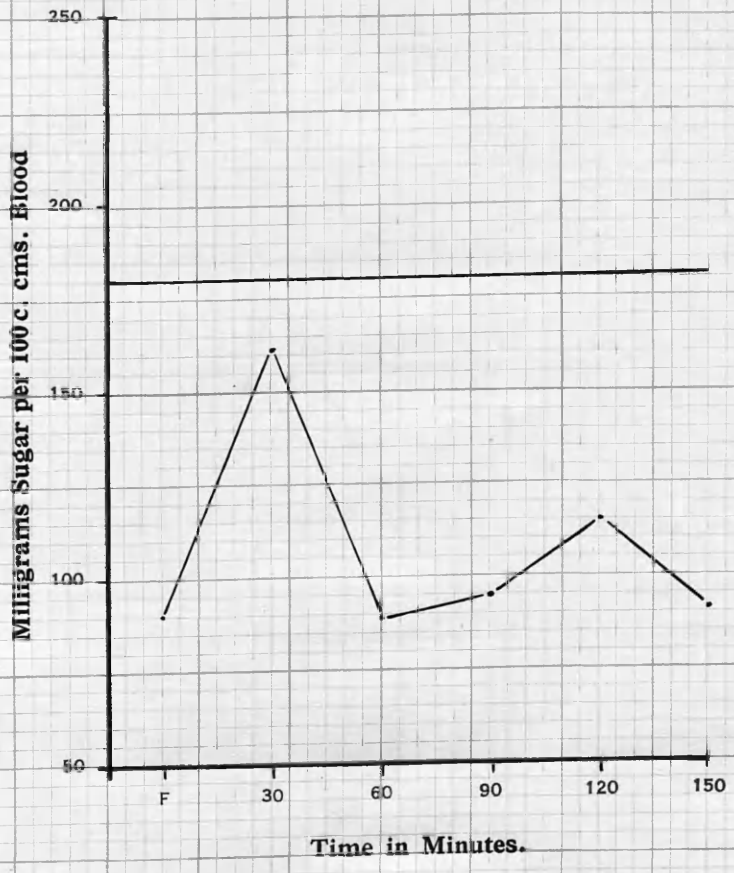

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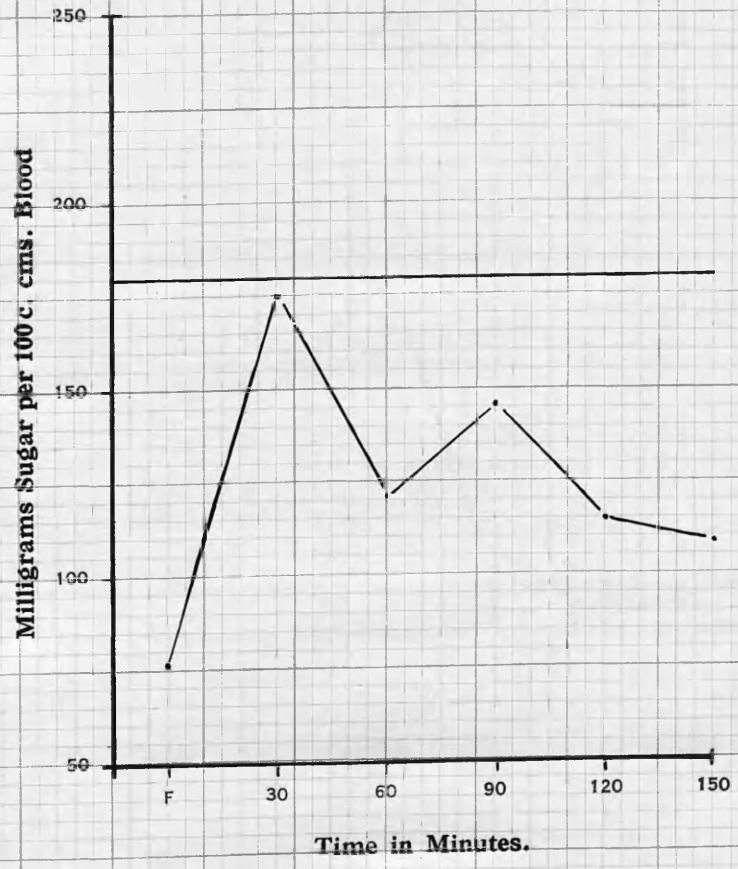

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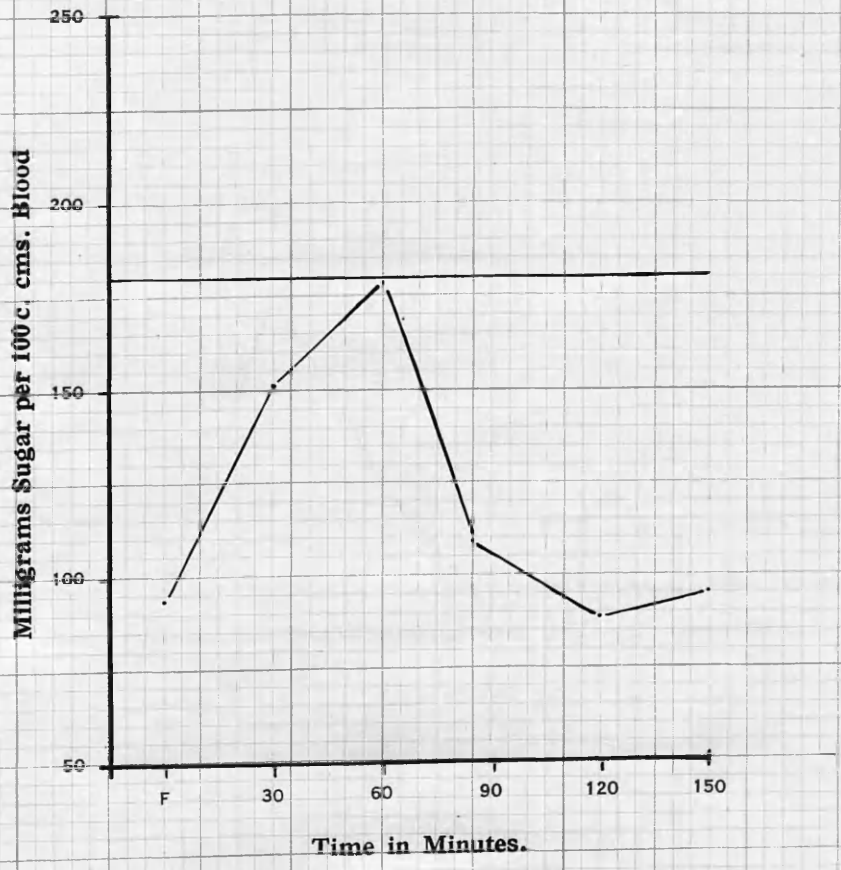

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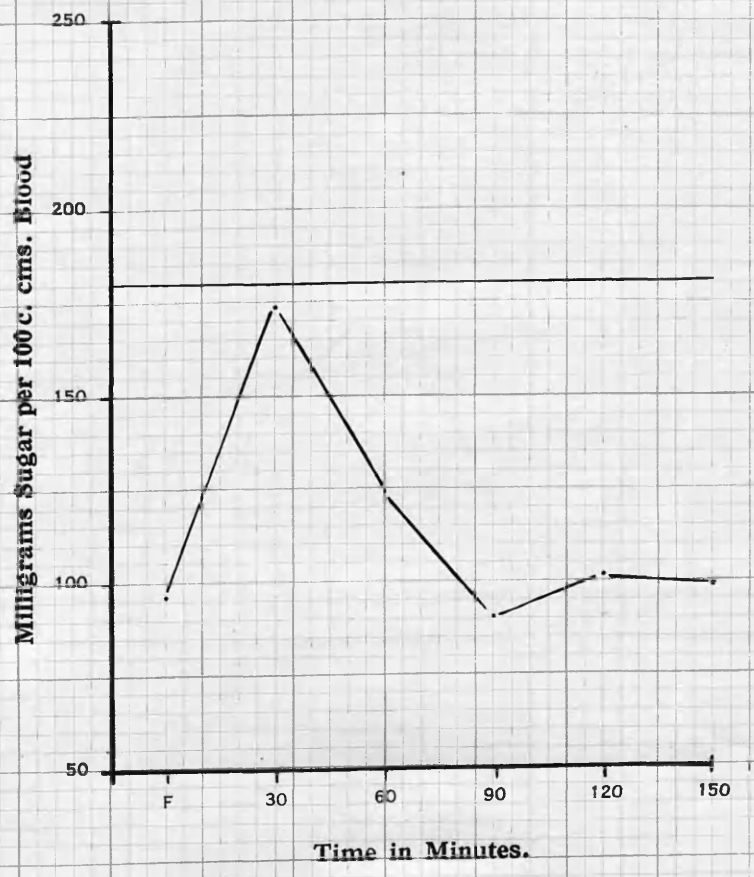

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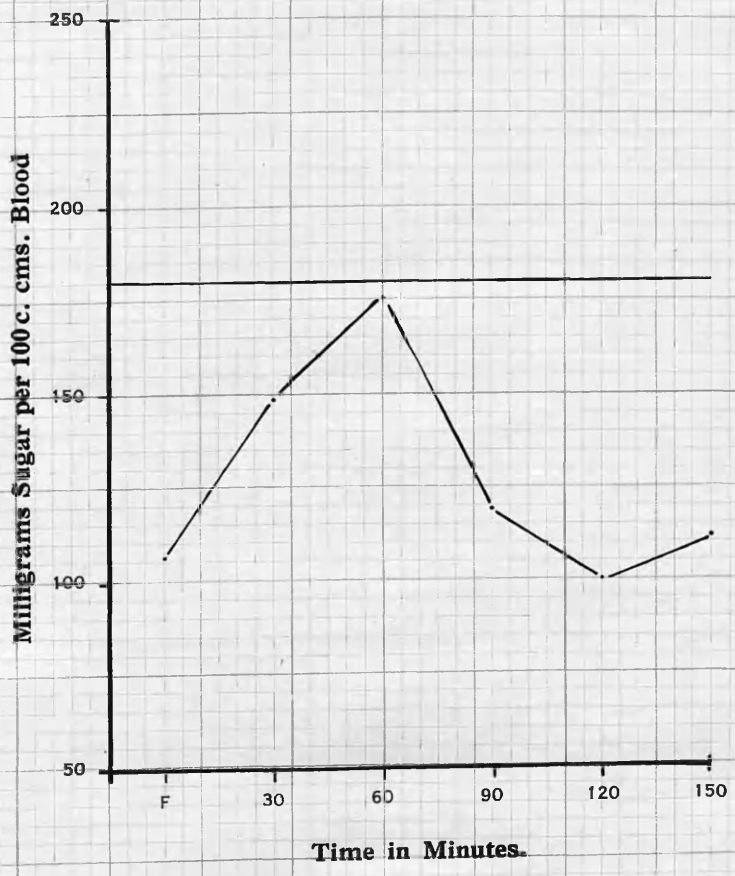

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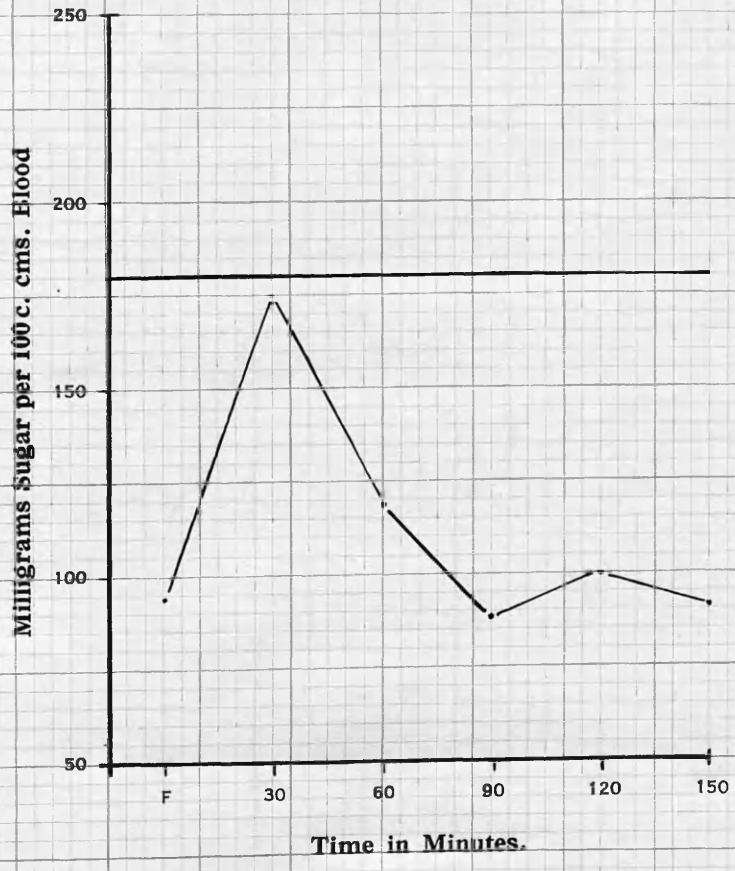
Chart 27.



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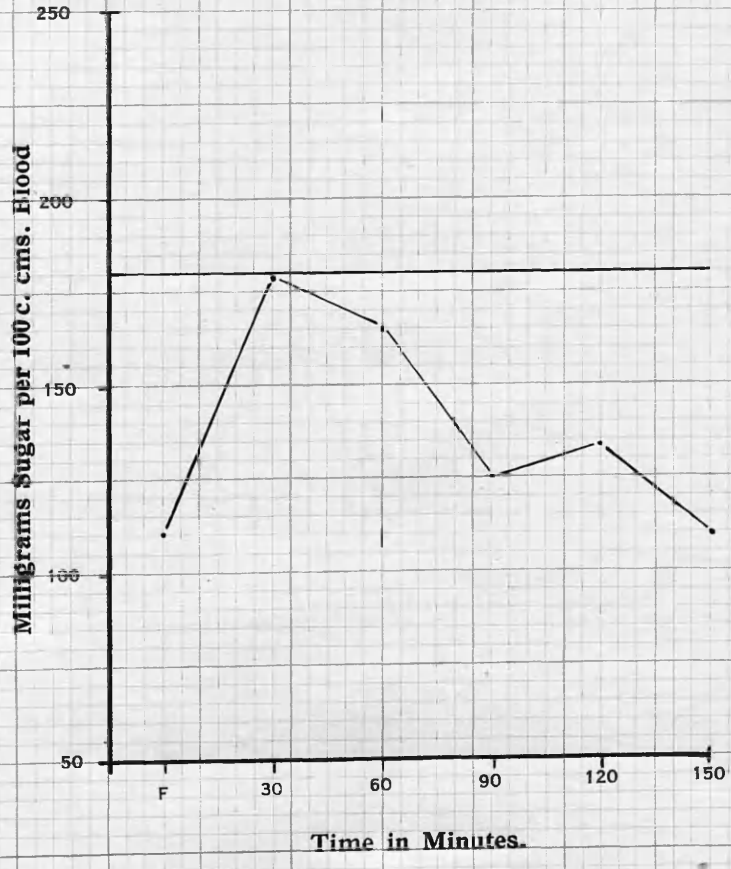

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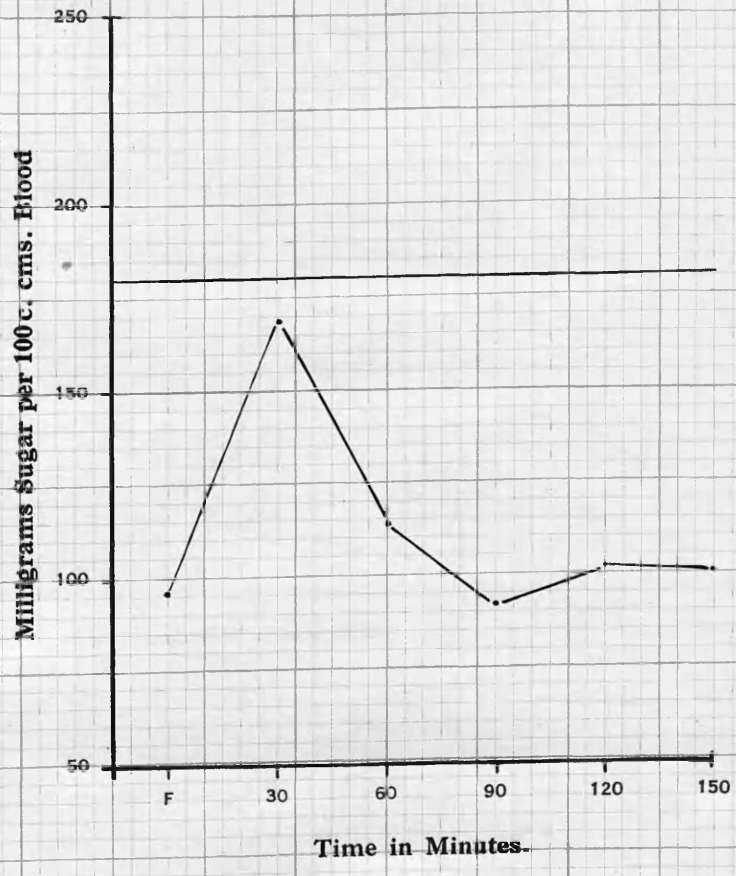

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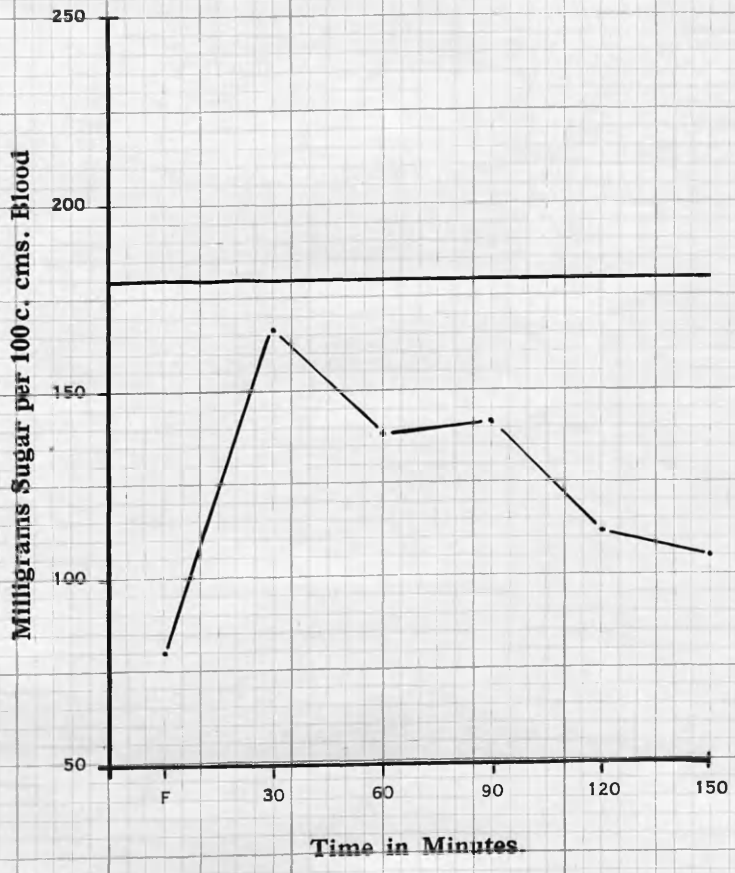

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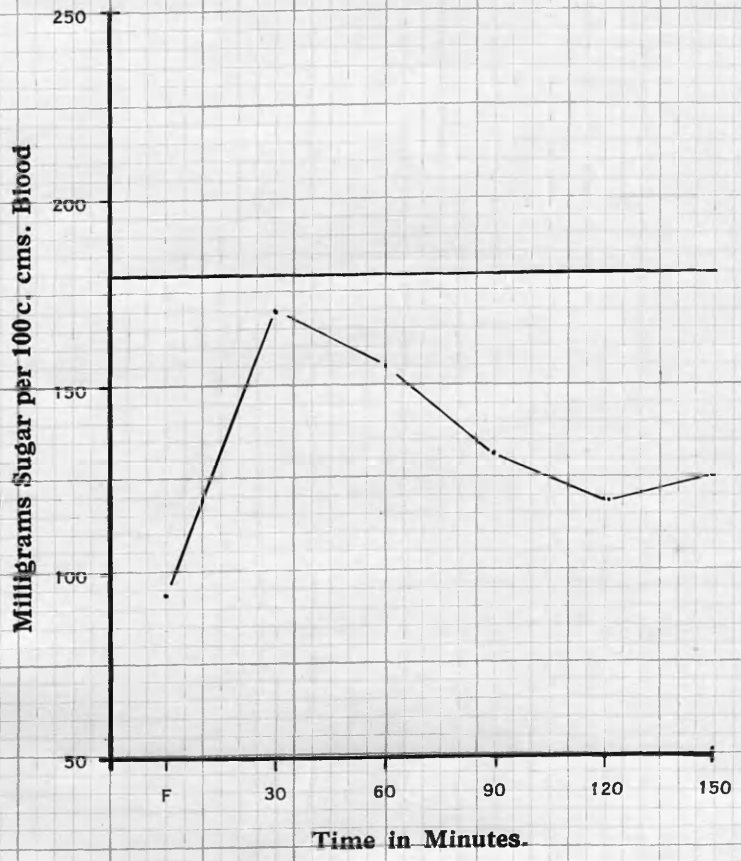

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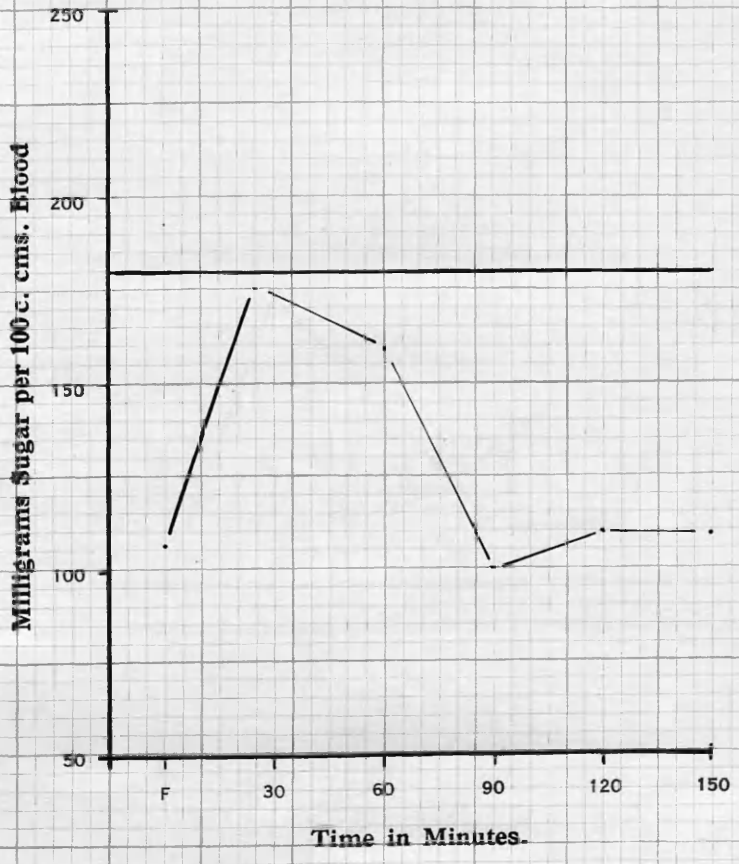

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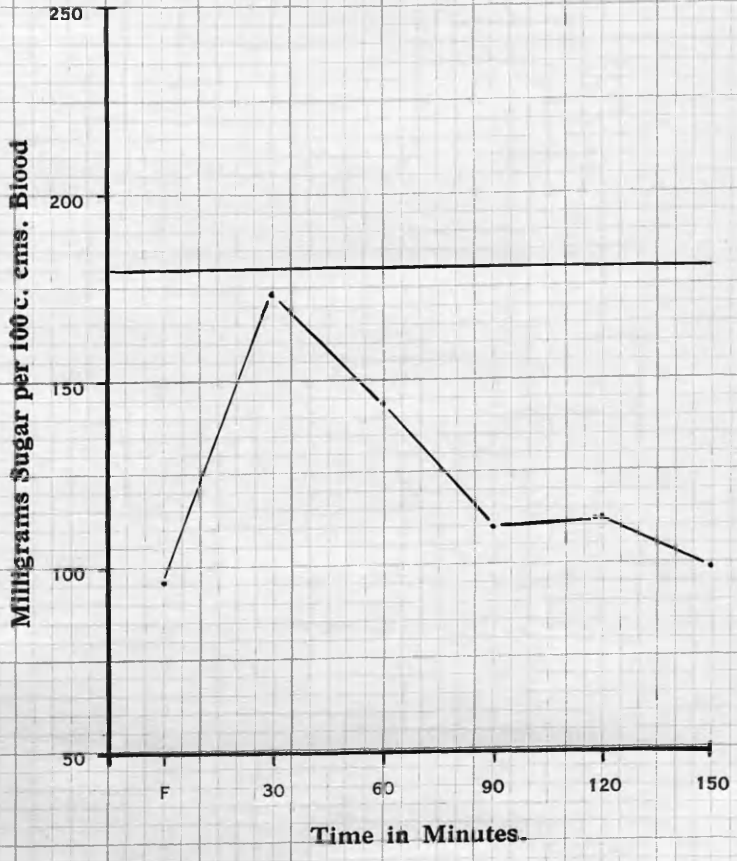

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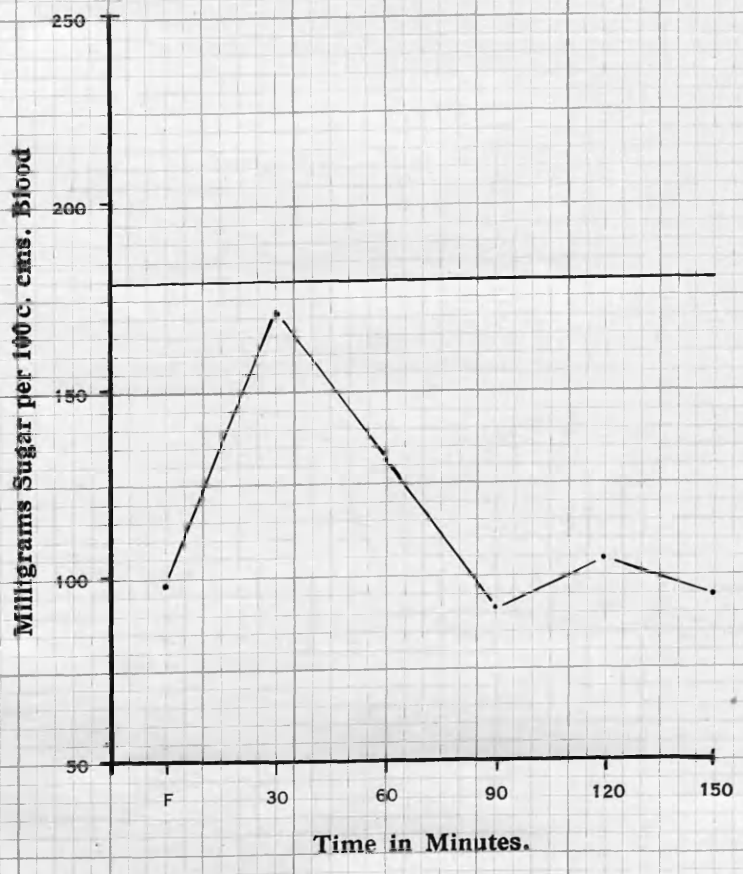

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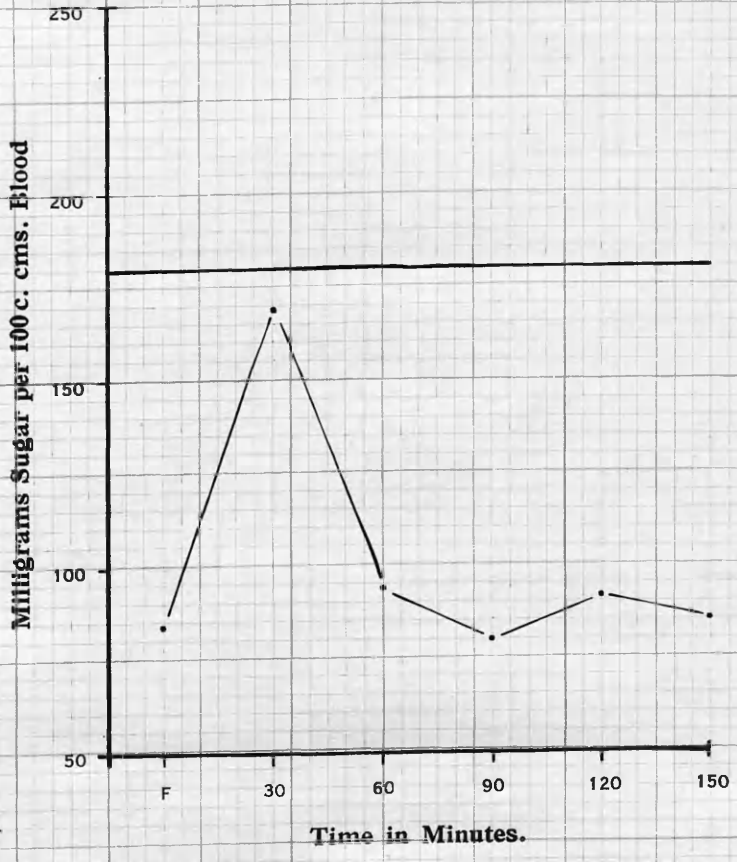

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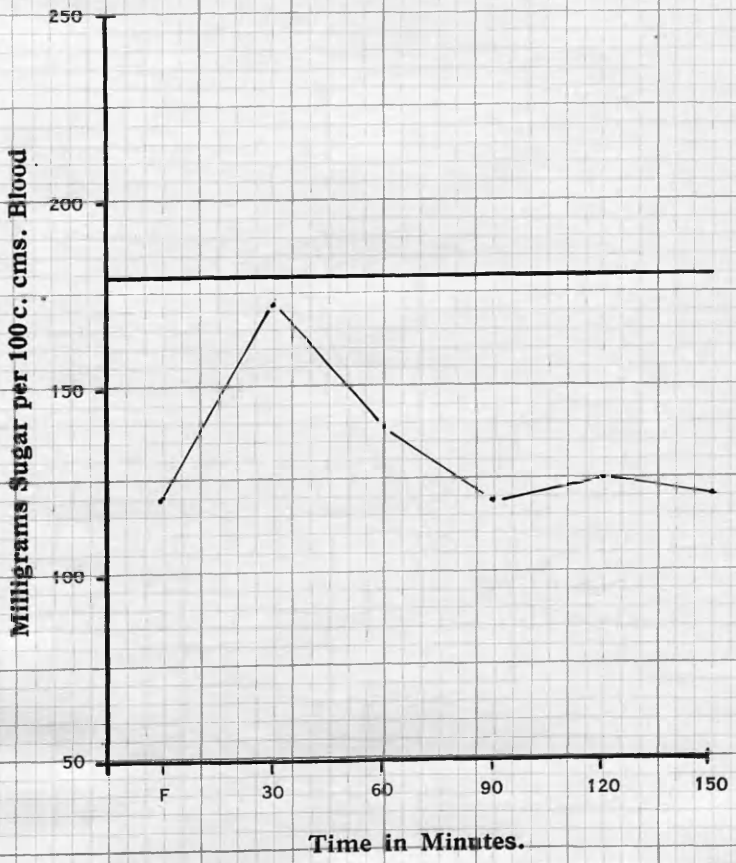

Case 18:
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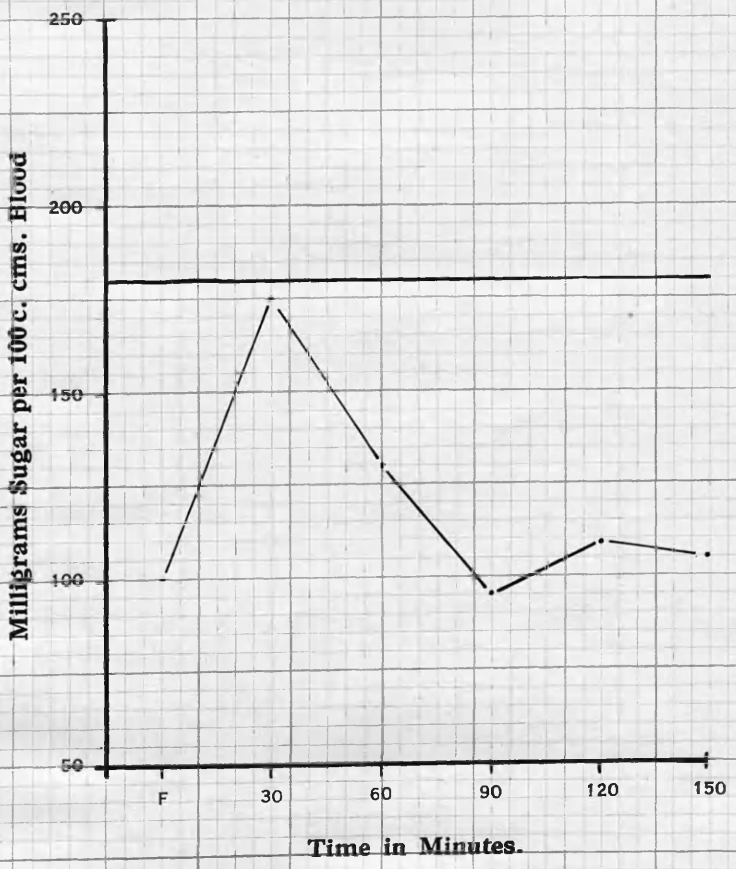

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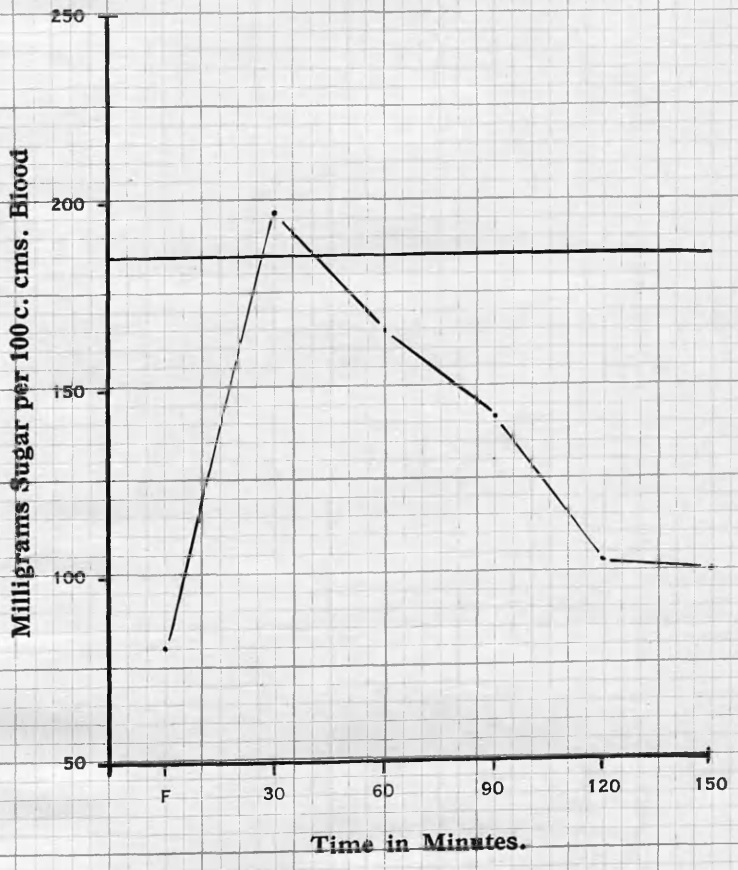

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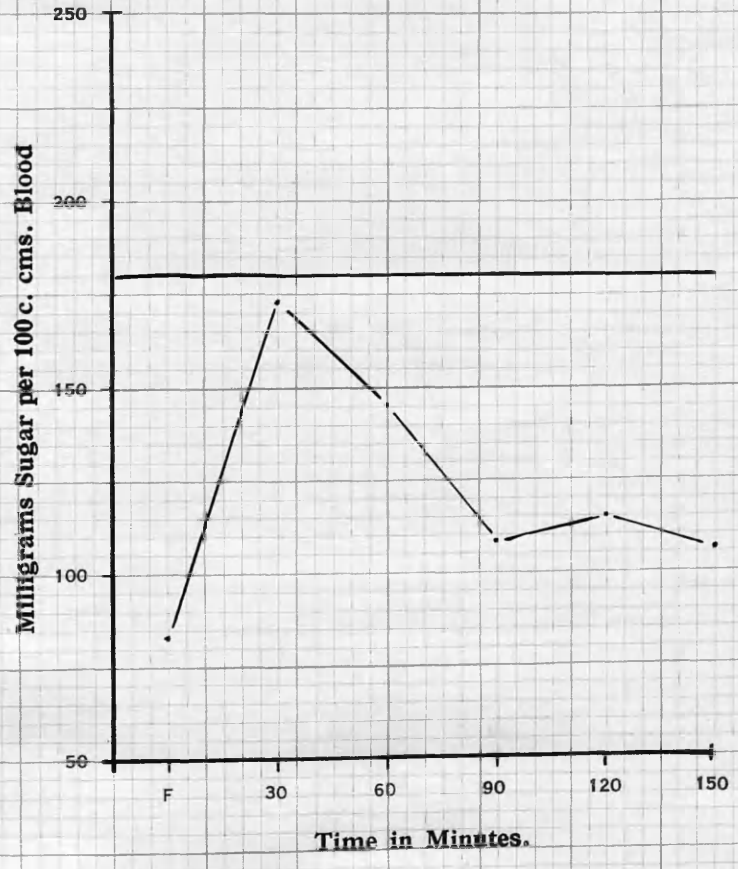
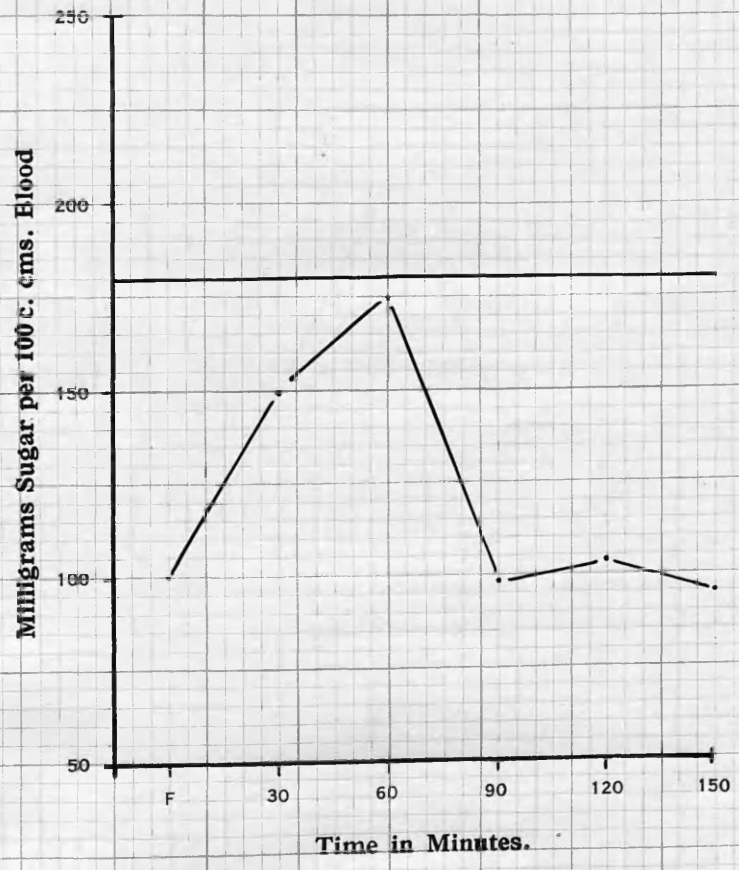
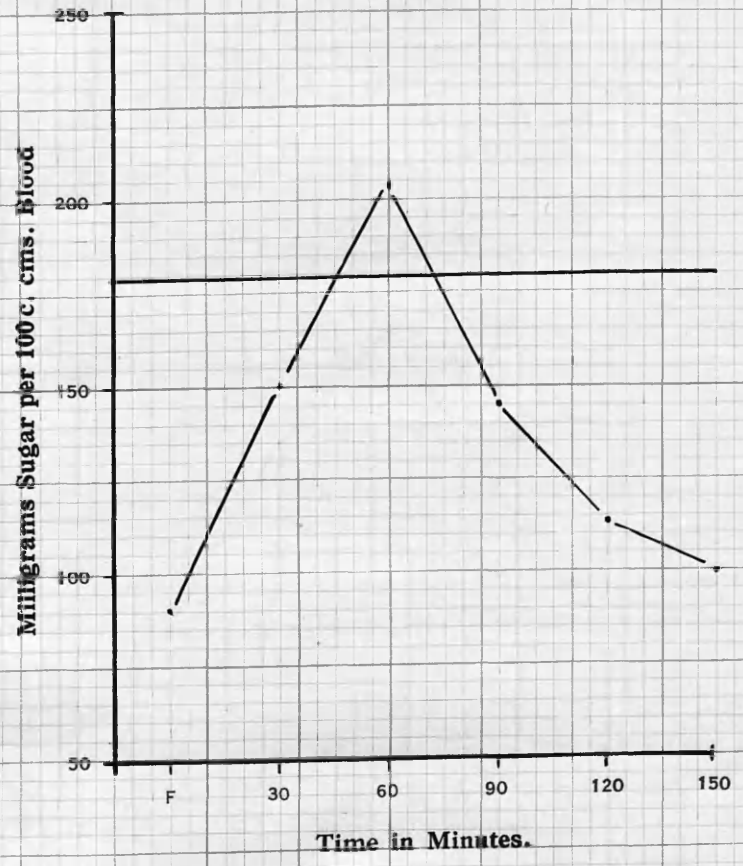


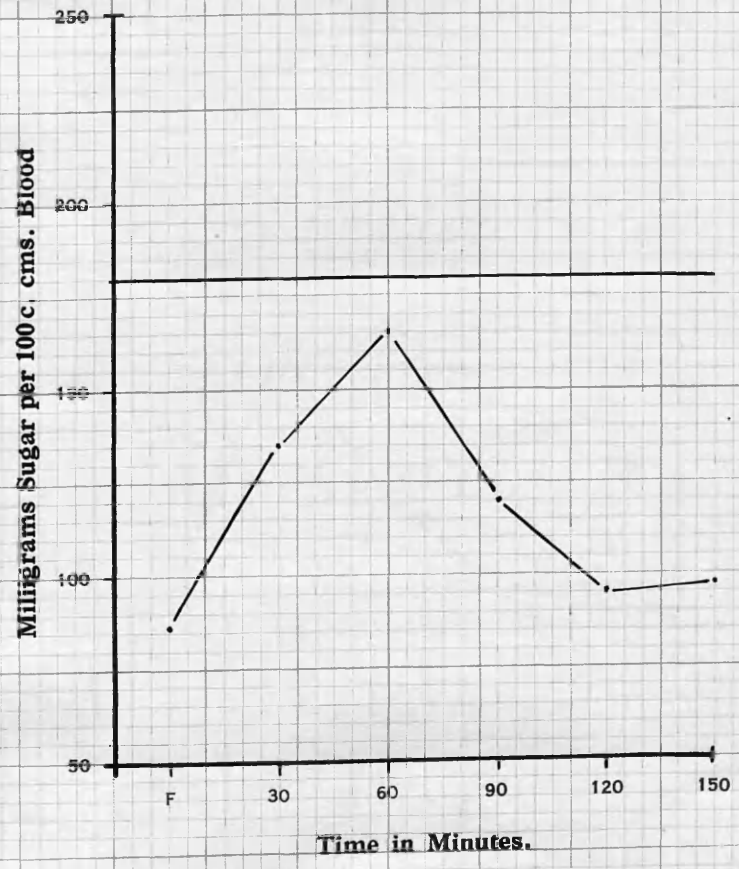
Case 19:
Chart 40.



Case 20:
Chart 41.



Case 20:
Chart 42.



Case 20:
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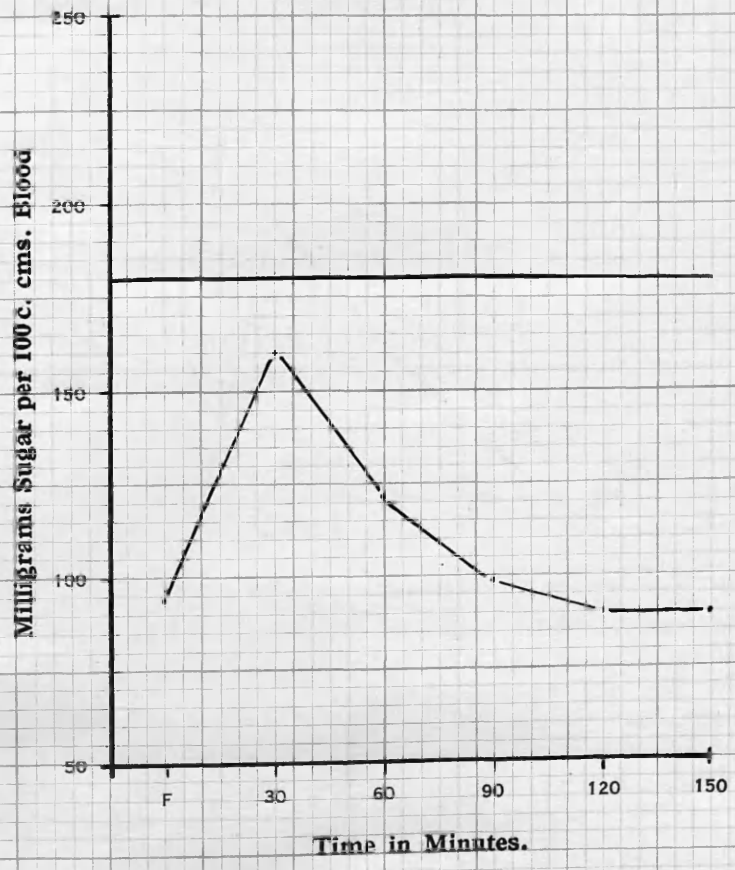
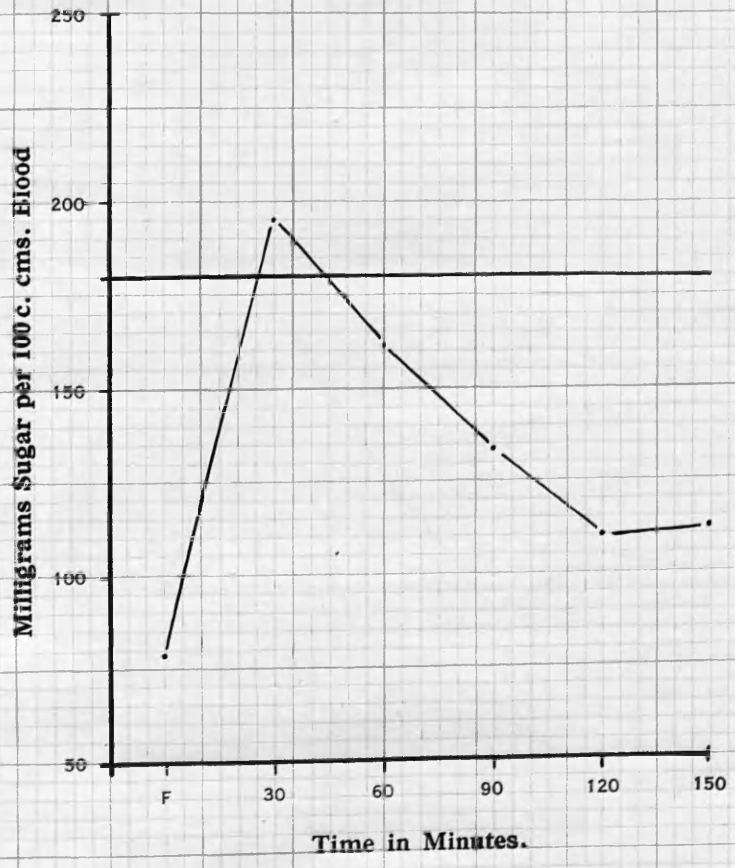


Case 21:
Chart 44.



Case 21:
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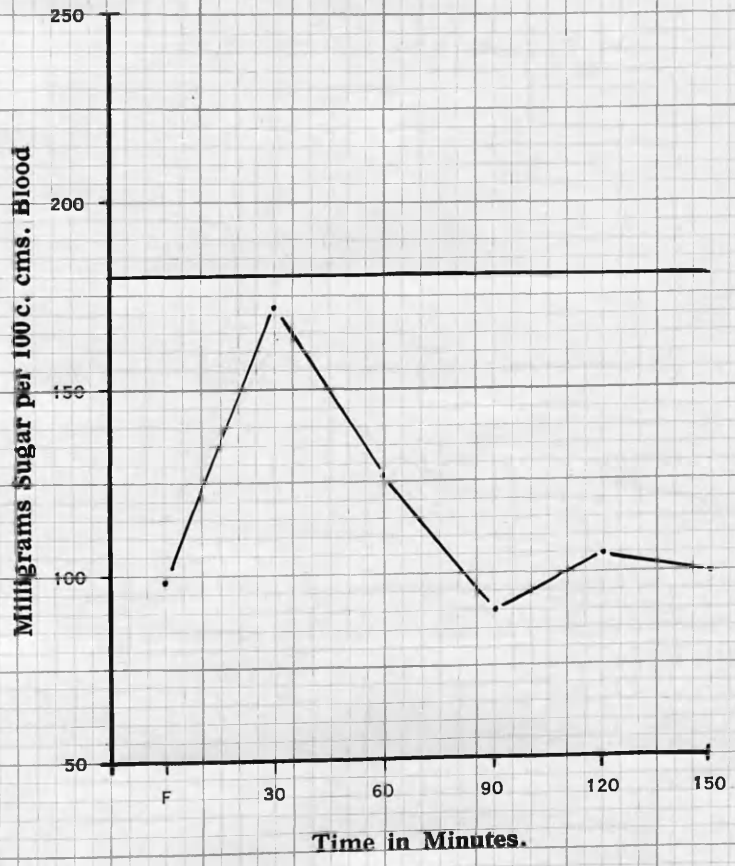
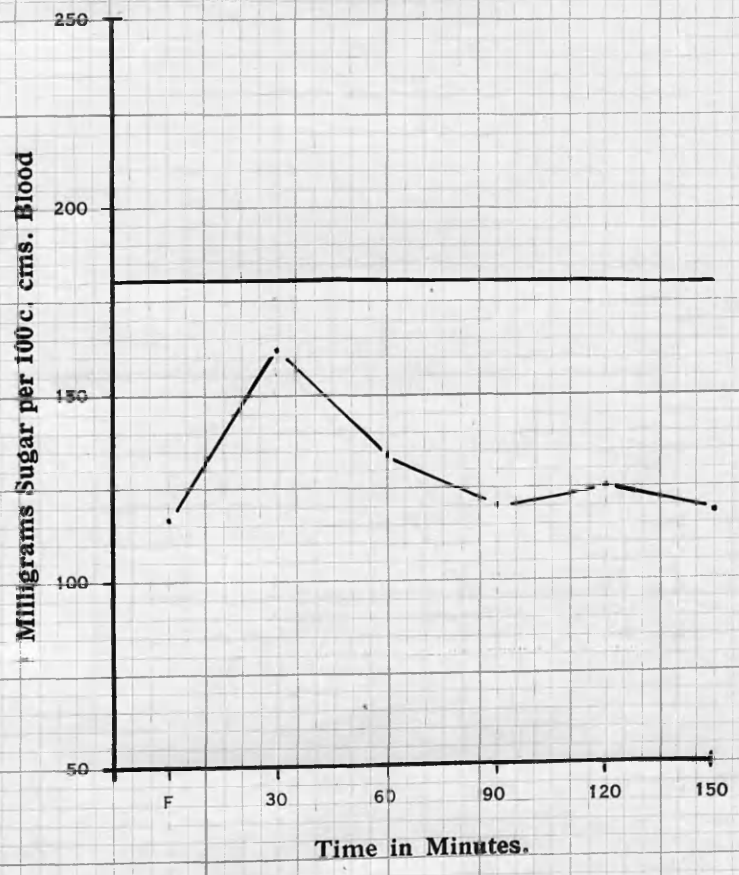


Case 22:
Chart 46.



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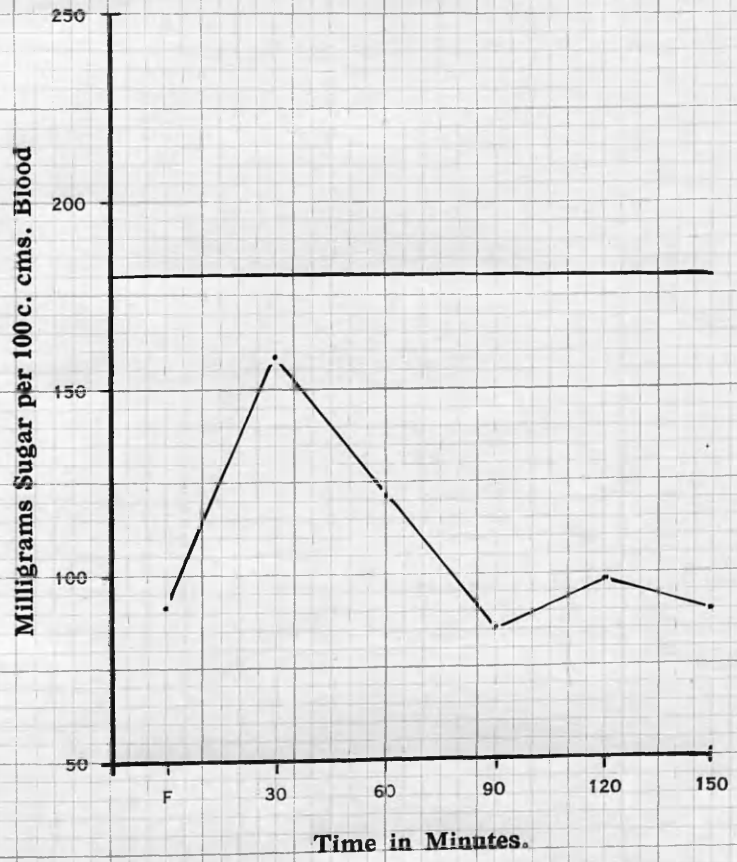
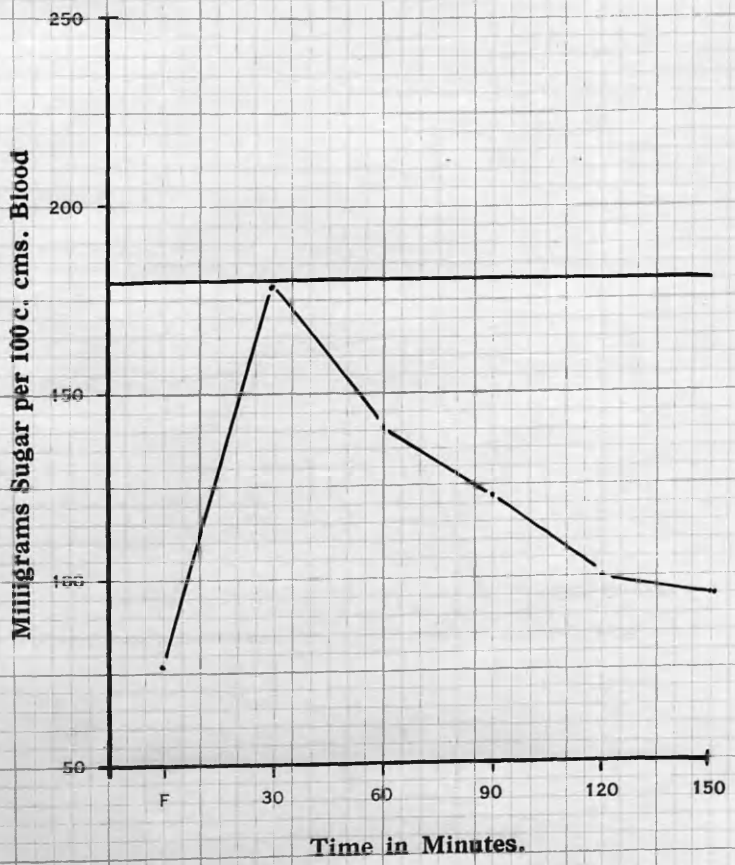
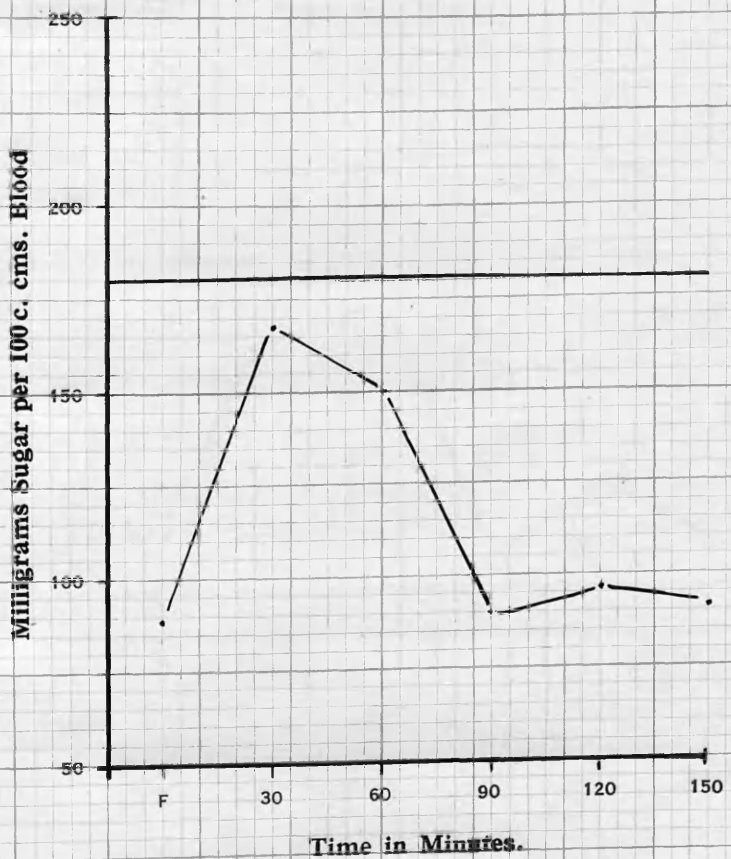


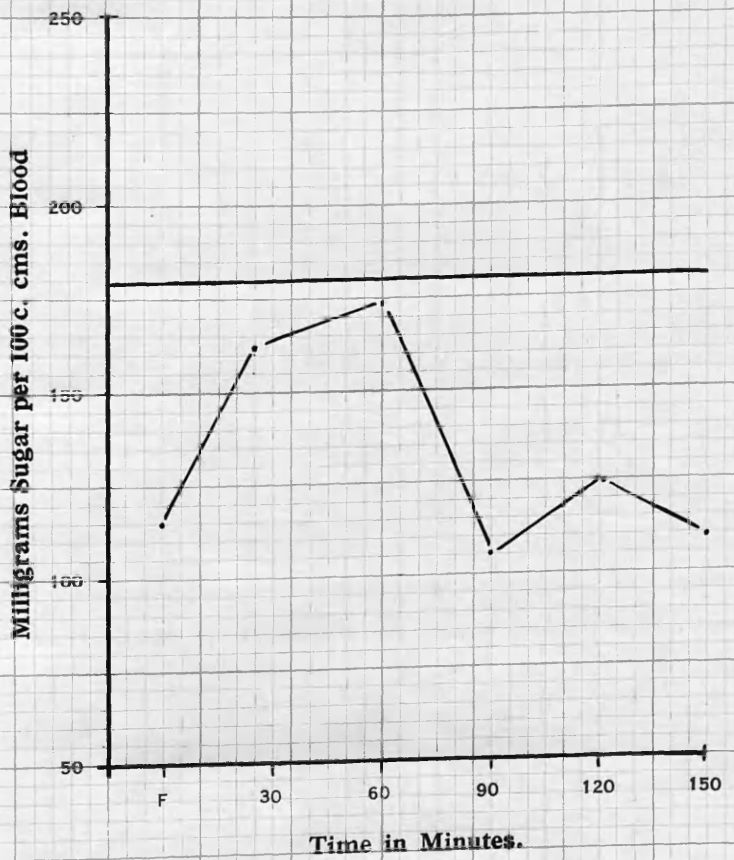
Case 23:
Chart 48.



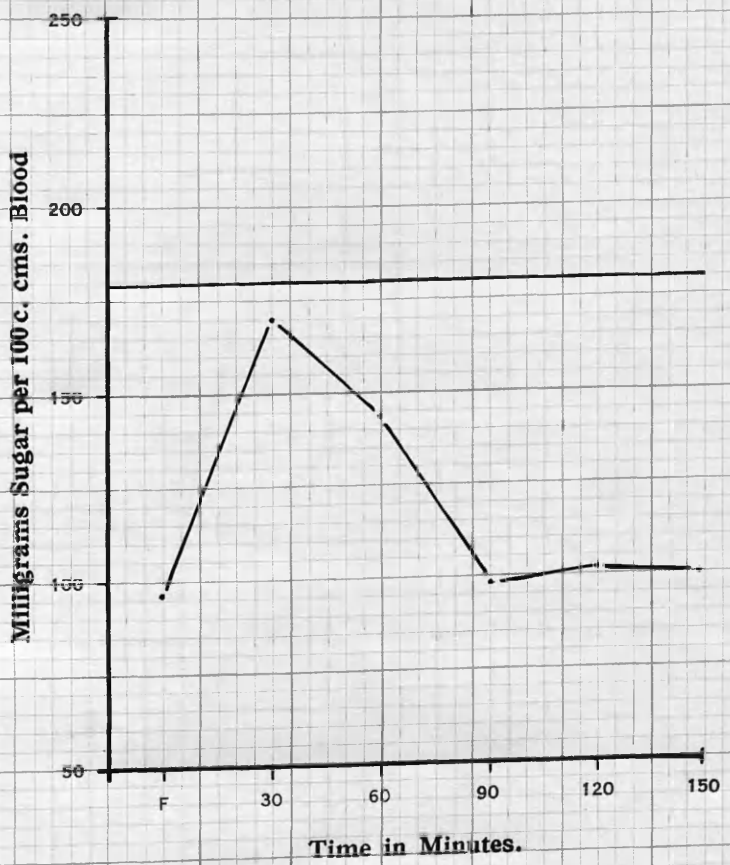
Case 23:
Chart 49.



Case 24:
Chart 50.



Case 24:
Chart 51.



Case 25:
Chart 52.

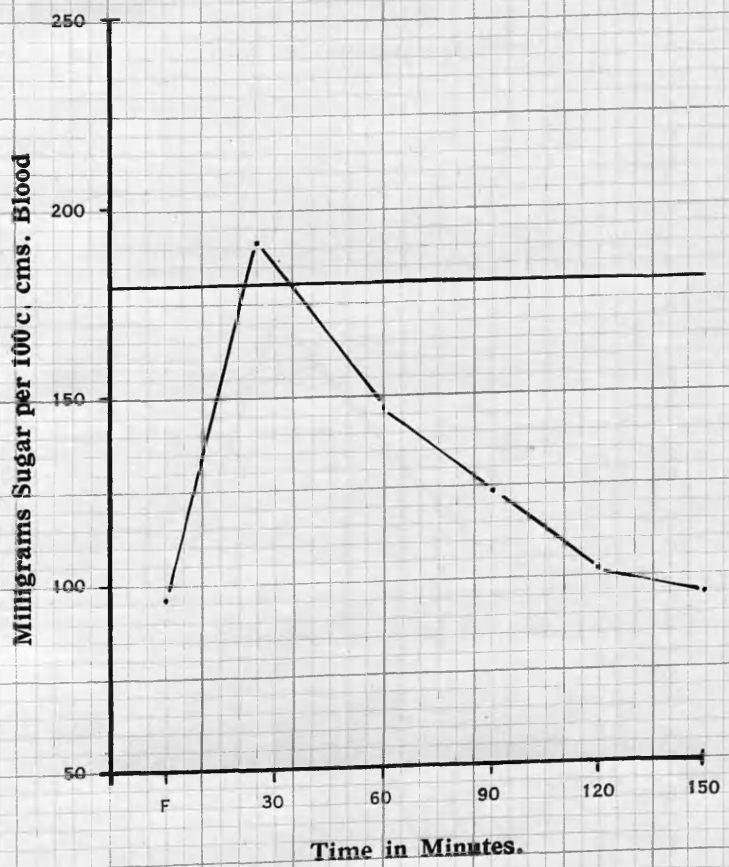


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Chart 53.

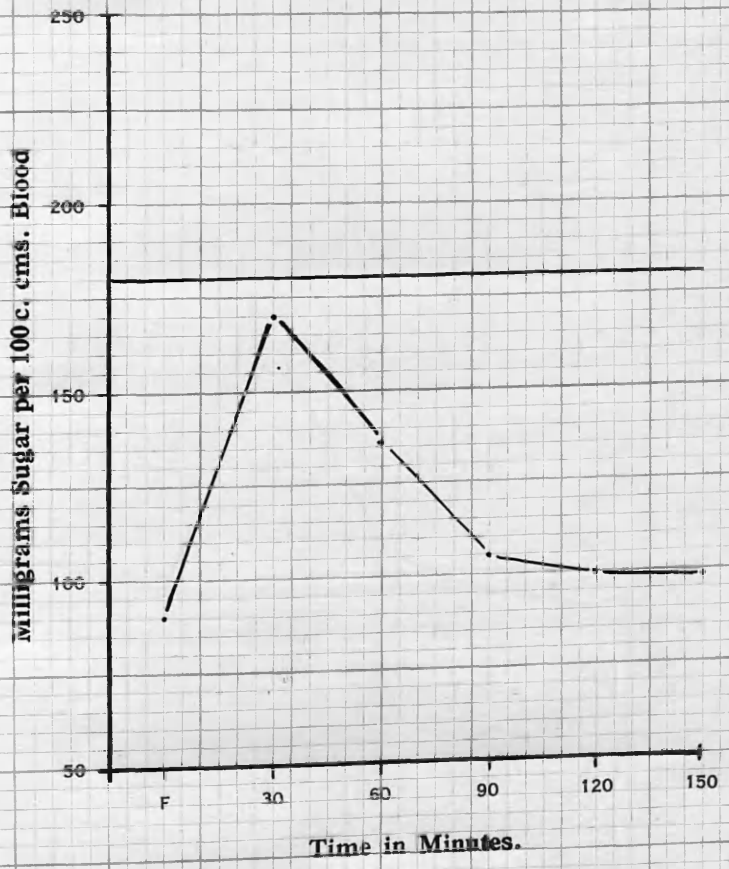

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Chart 54.

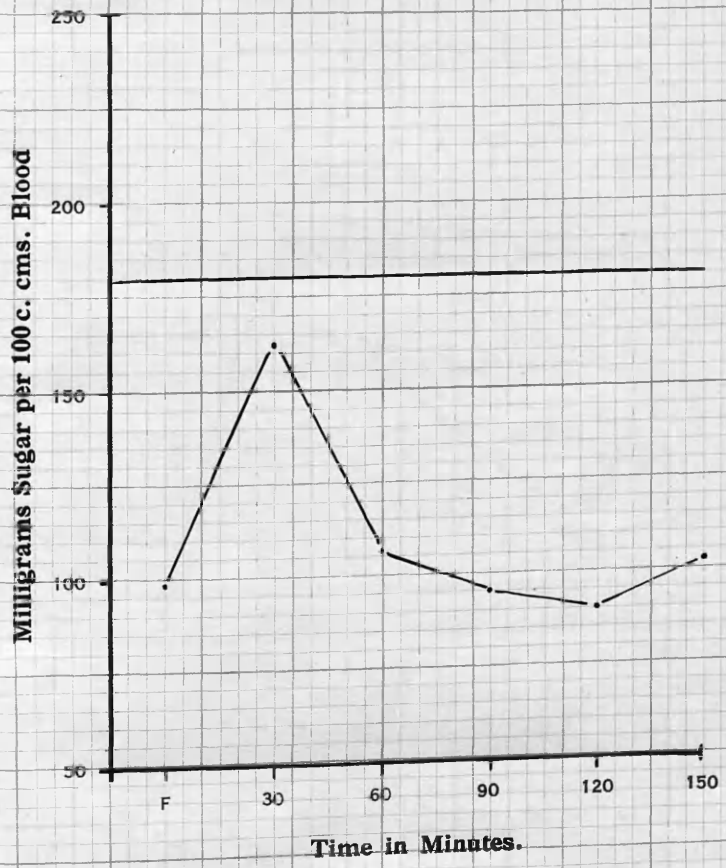

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Chart 55.

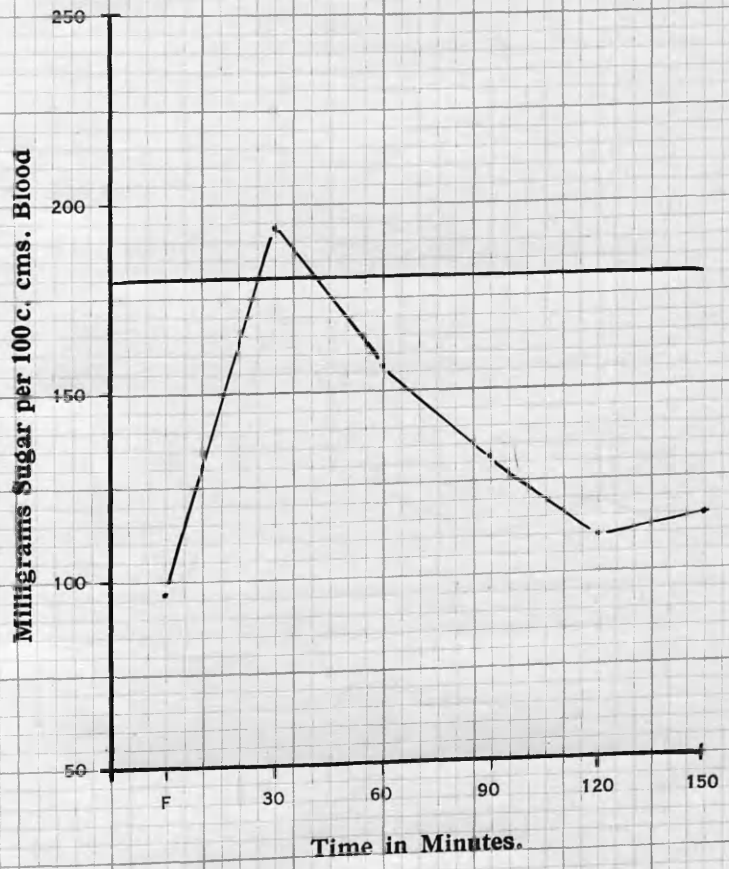

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Chart 56.

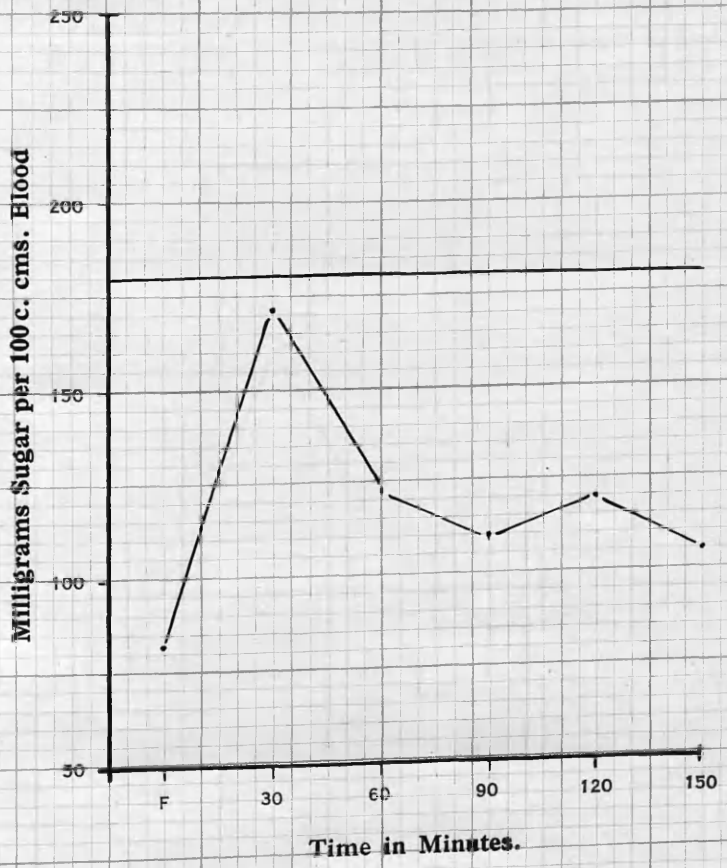

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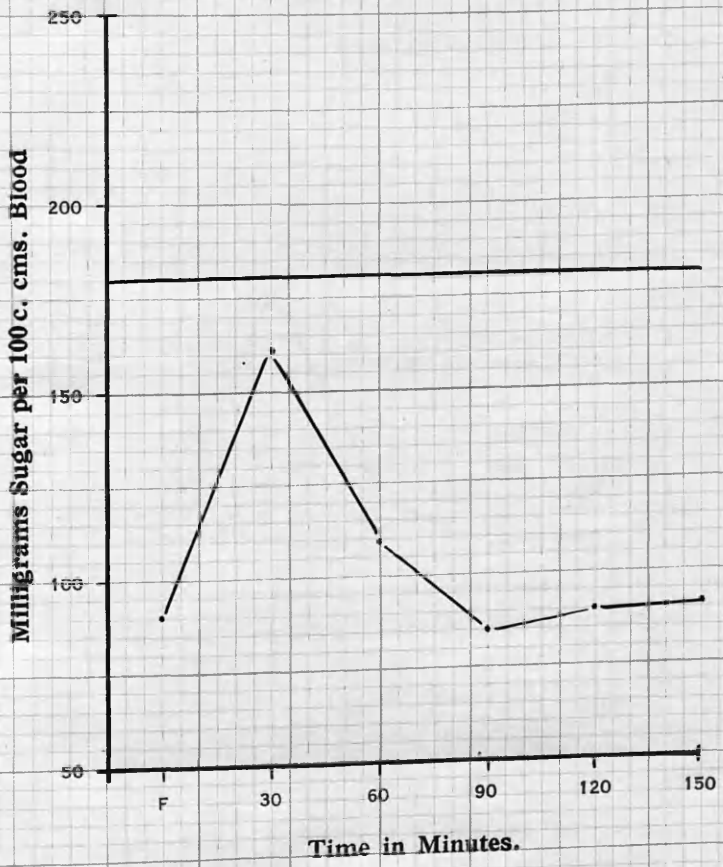
Chart 57.



Case 27:
Chart 58.

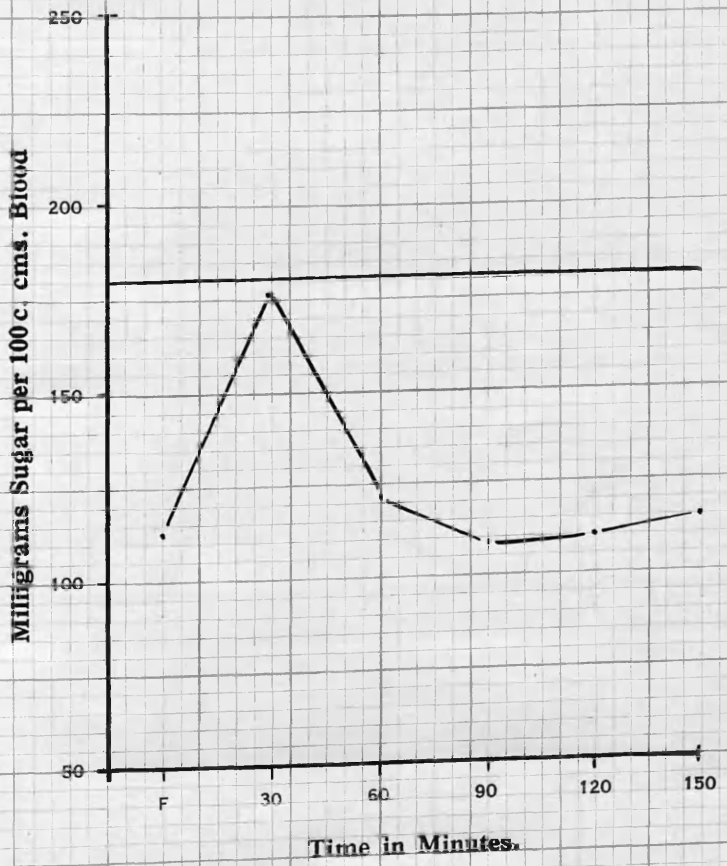


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Chart 59.

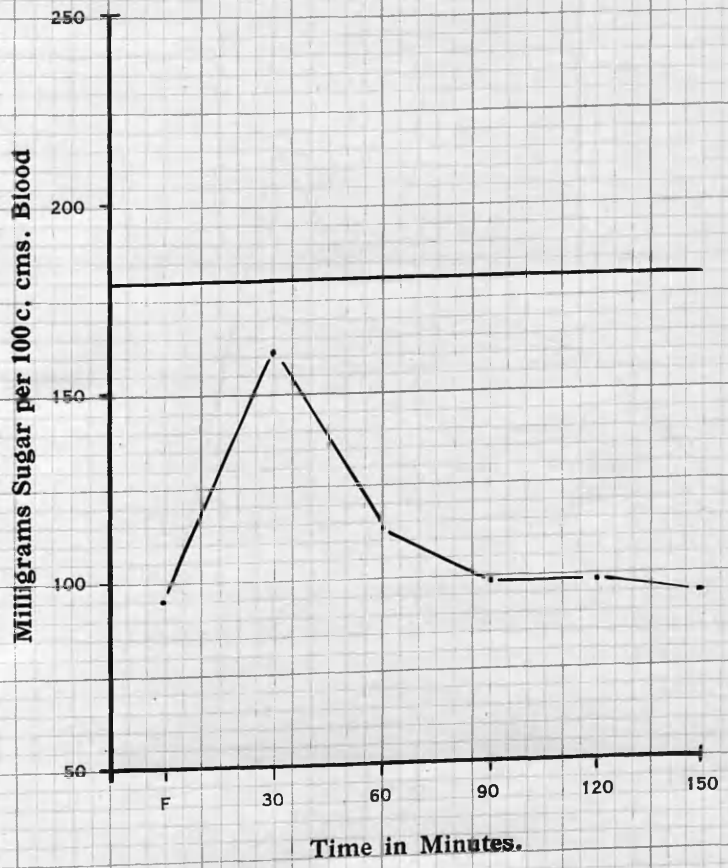

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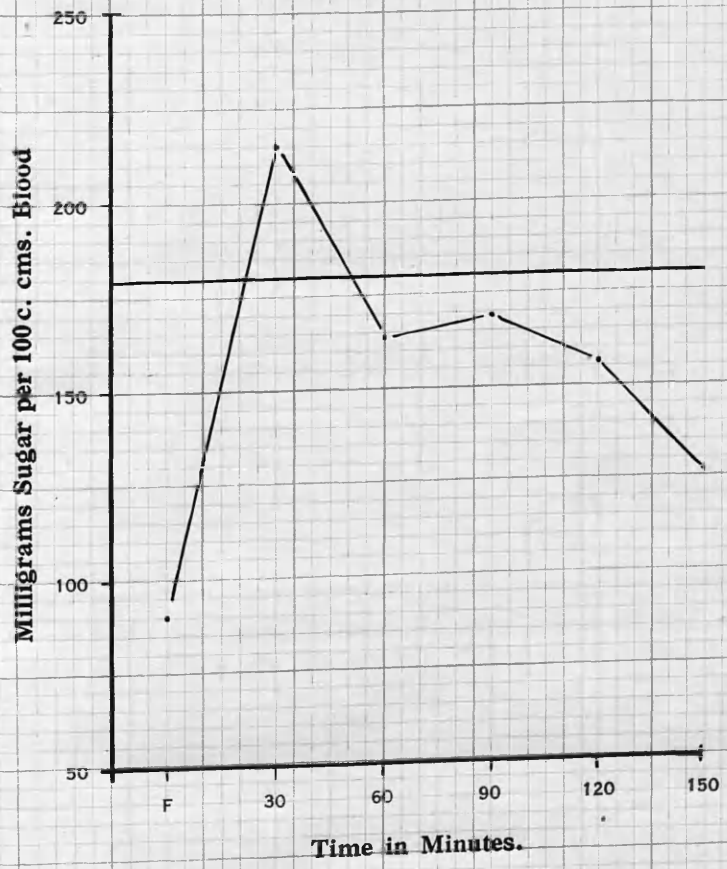
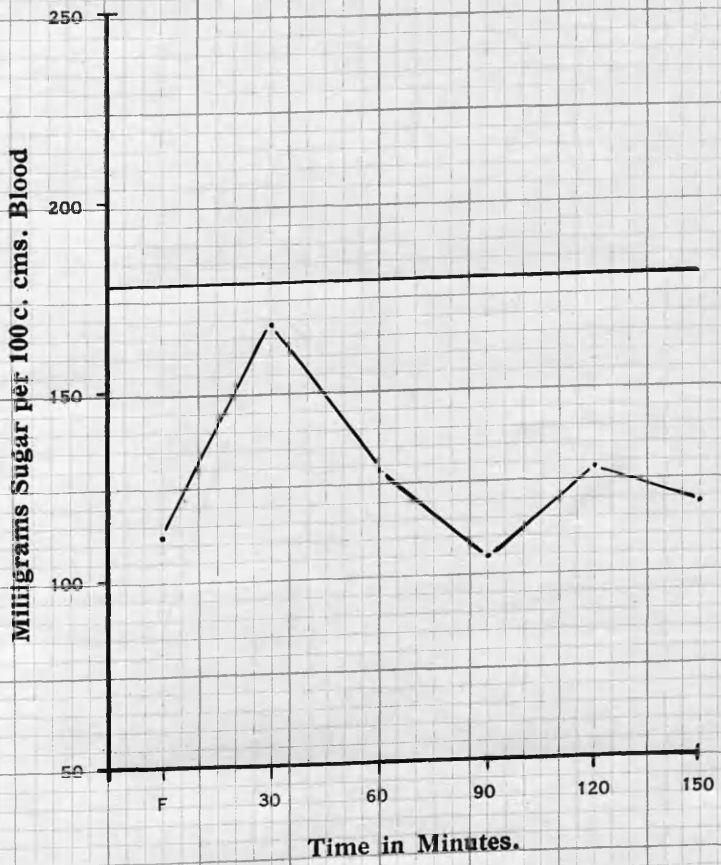
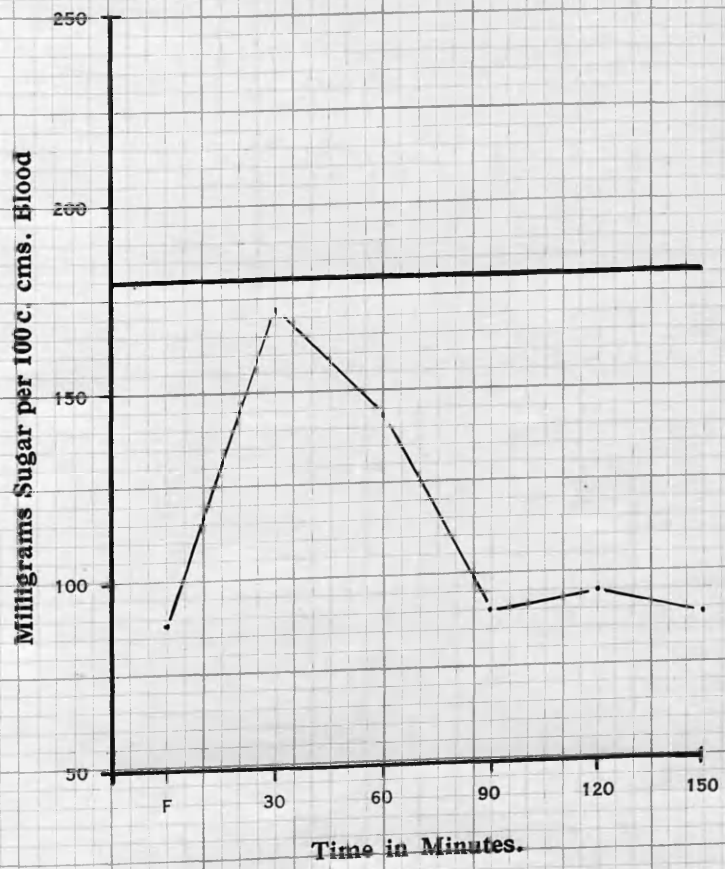
Chart 60.



Case 29:
Chart 61.



Case 29:
Chart 62.



Case 30:
Chart 63.

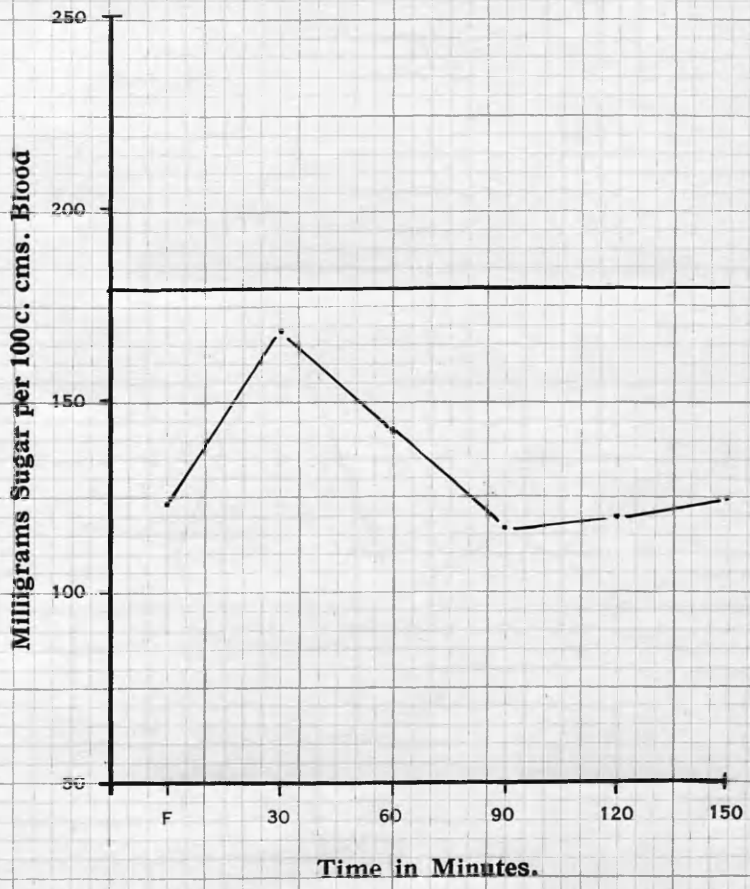


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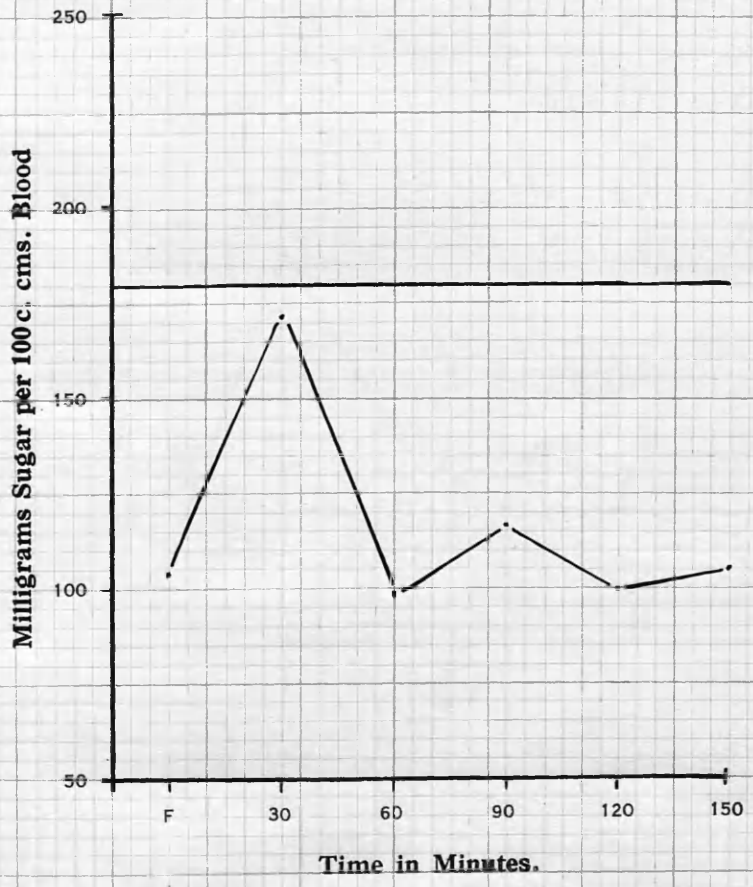
Chart 64.



Case 31:
Chart 65.

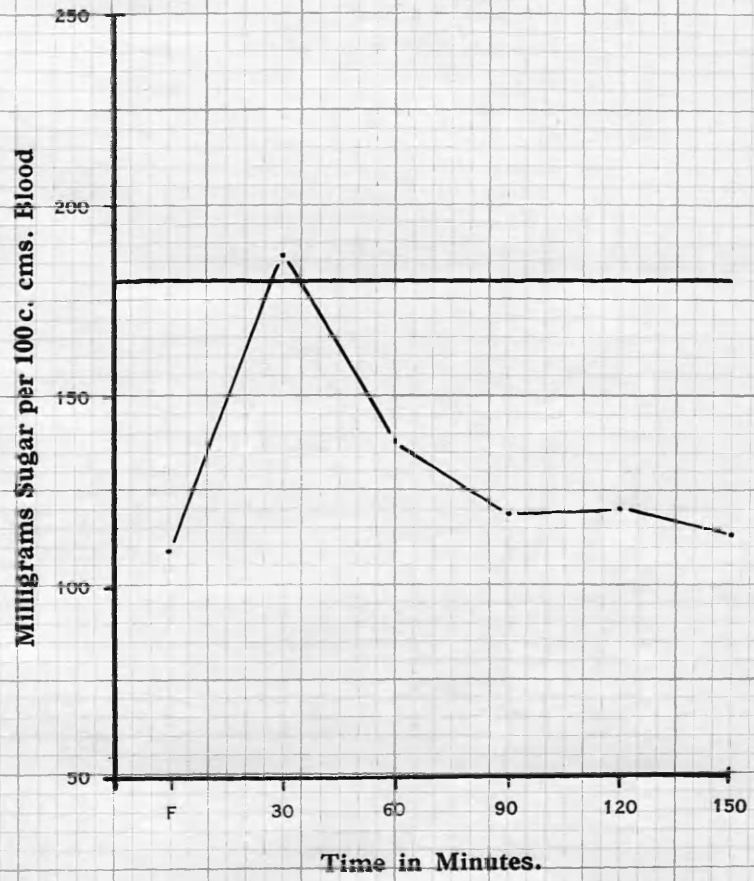


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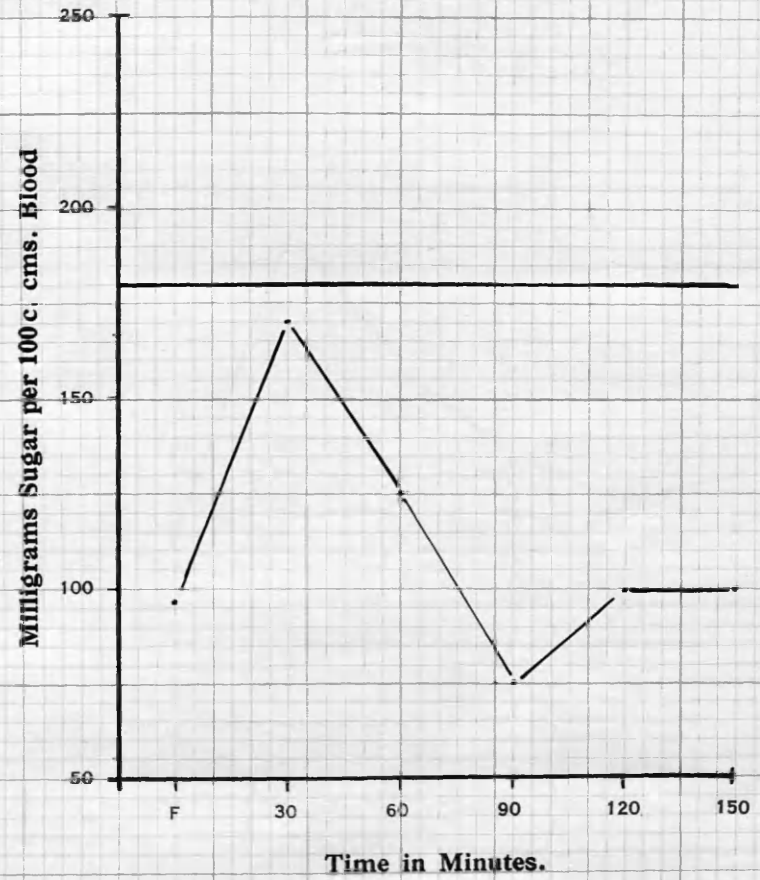
Chart 66.



Case 32:
Chart 67.

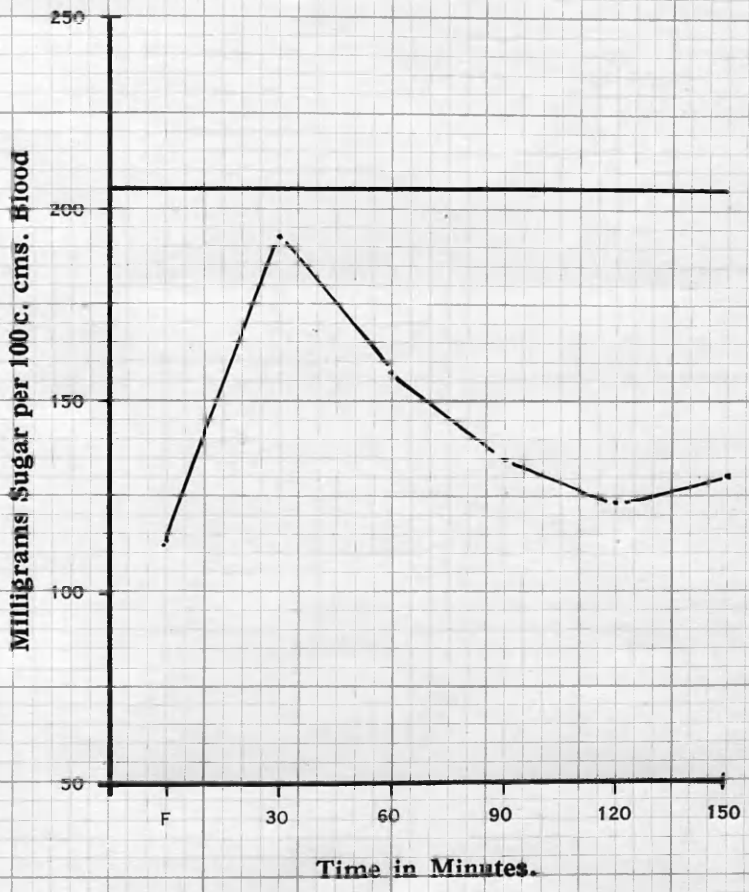


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Chart 68.

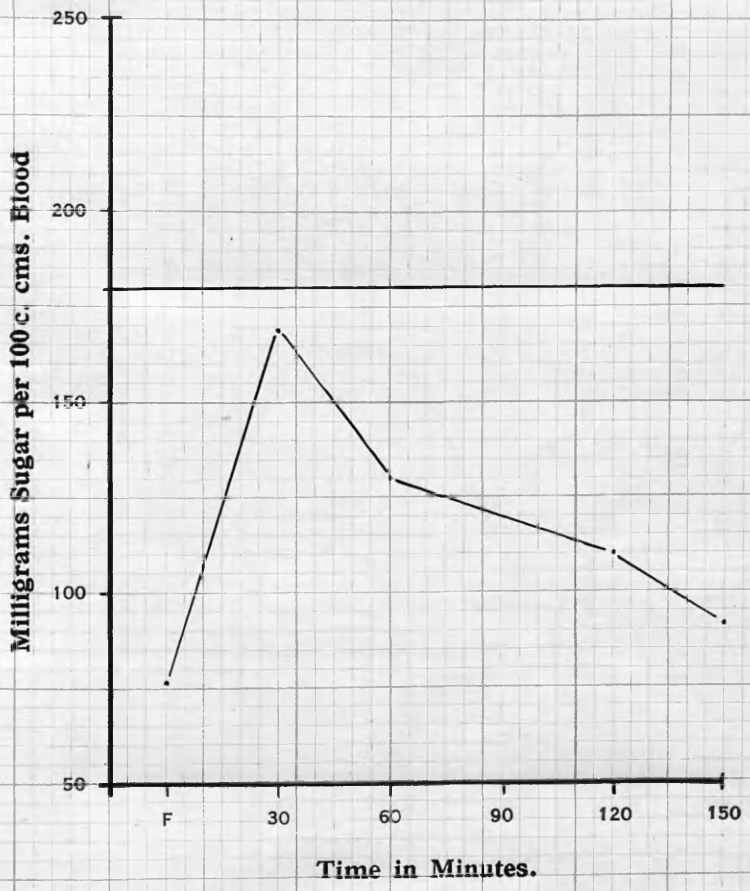

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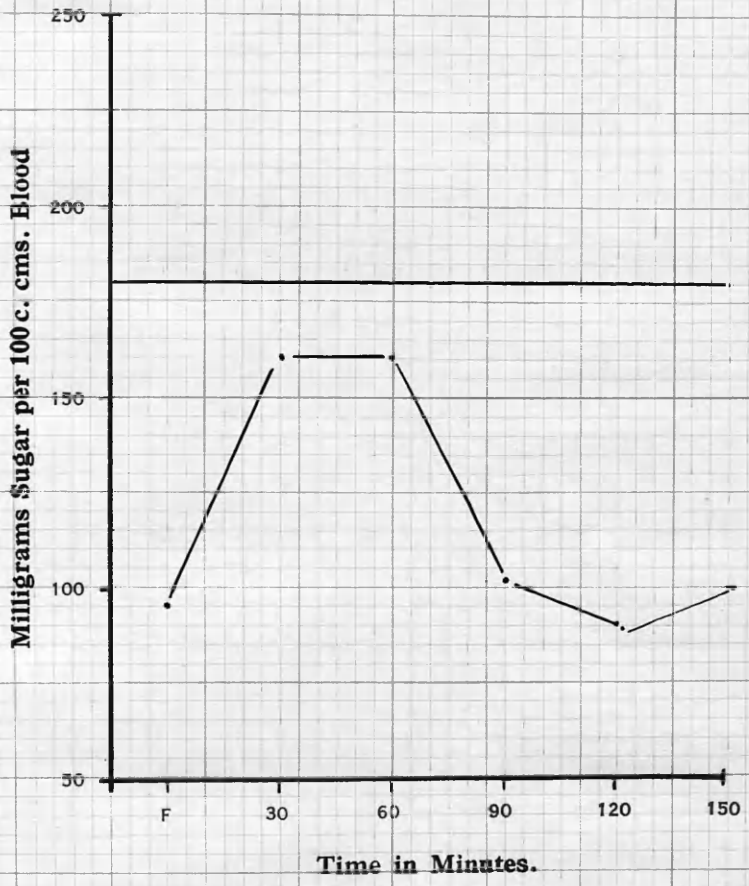
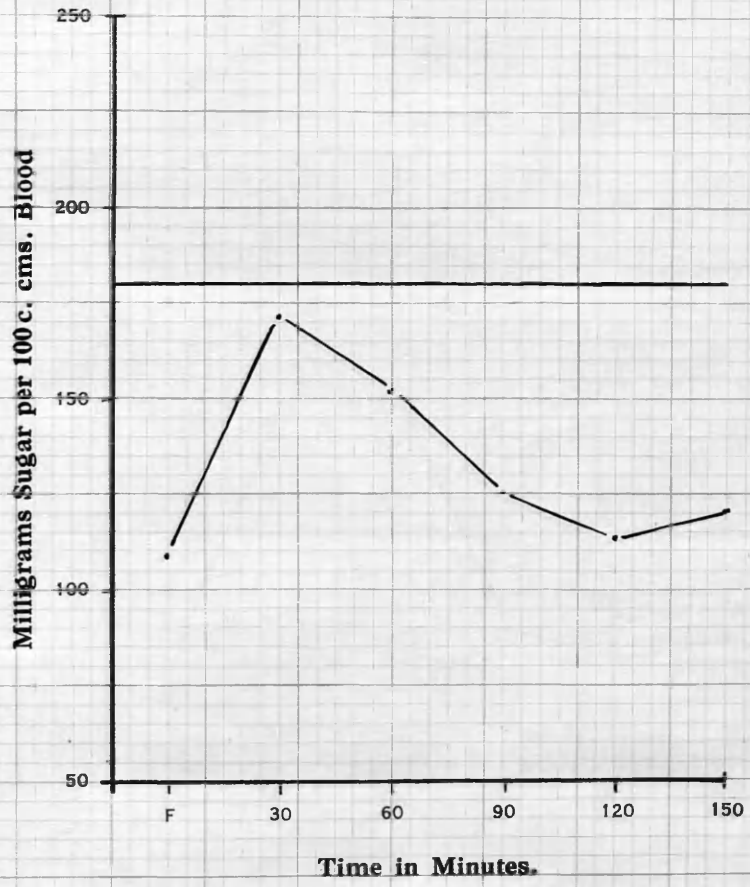
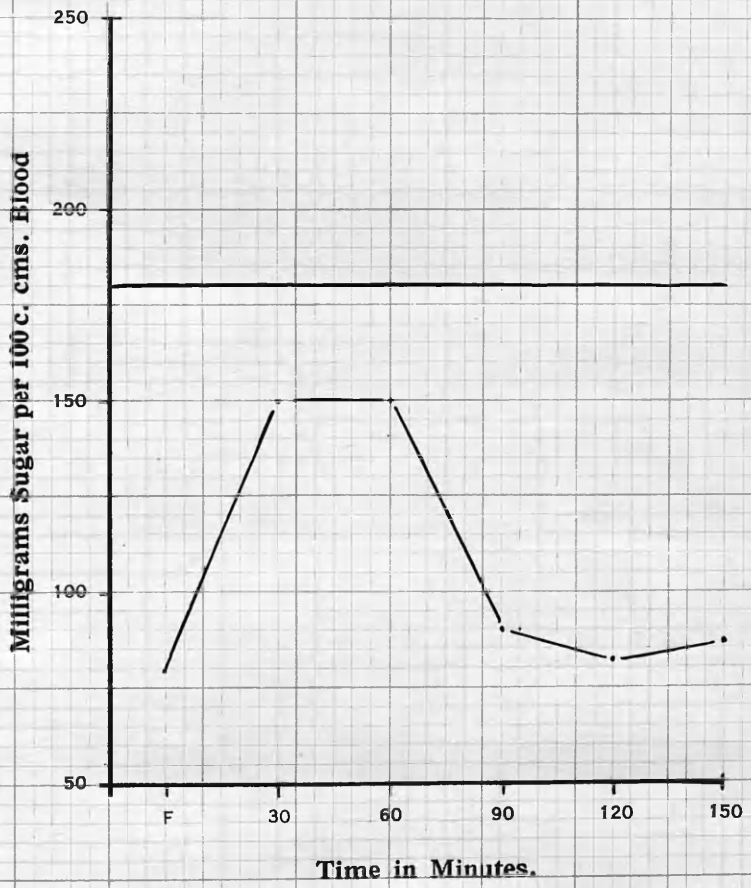
Chart 69.



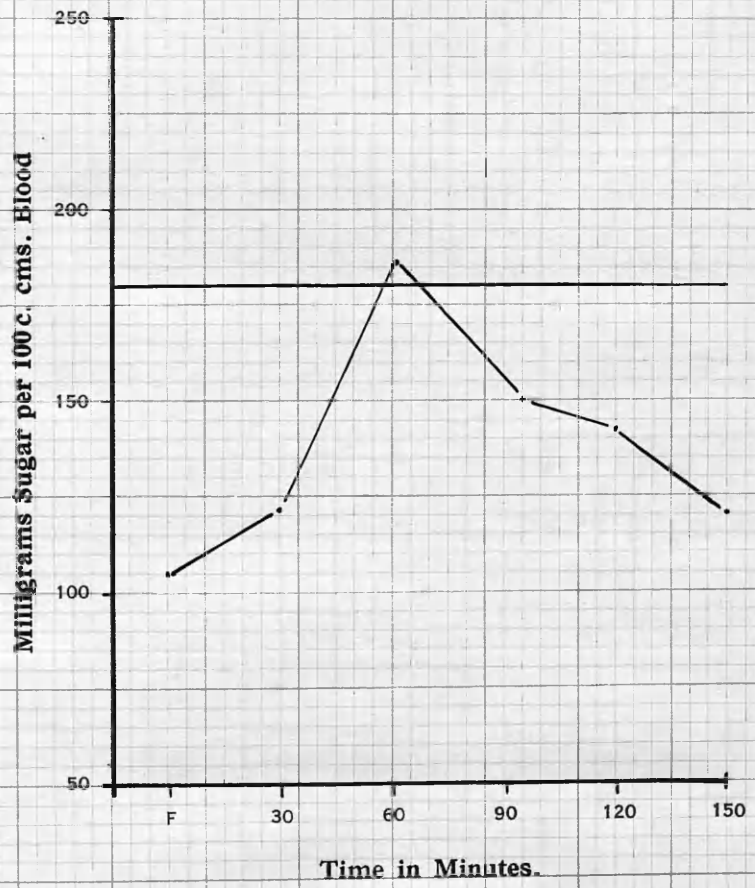
Case 33:
Chart 70.



Case 33:
Chart 71.



Case 34:
Chart 72.



Case 34:
Chart 73.

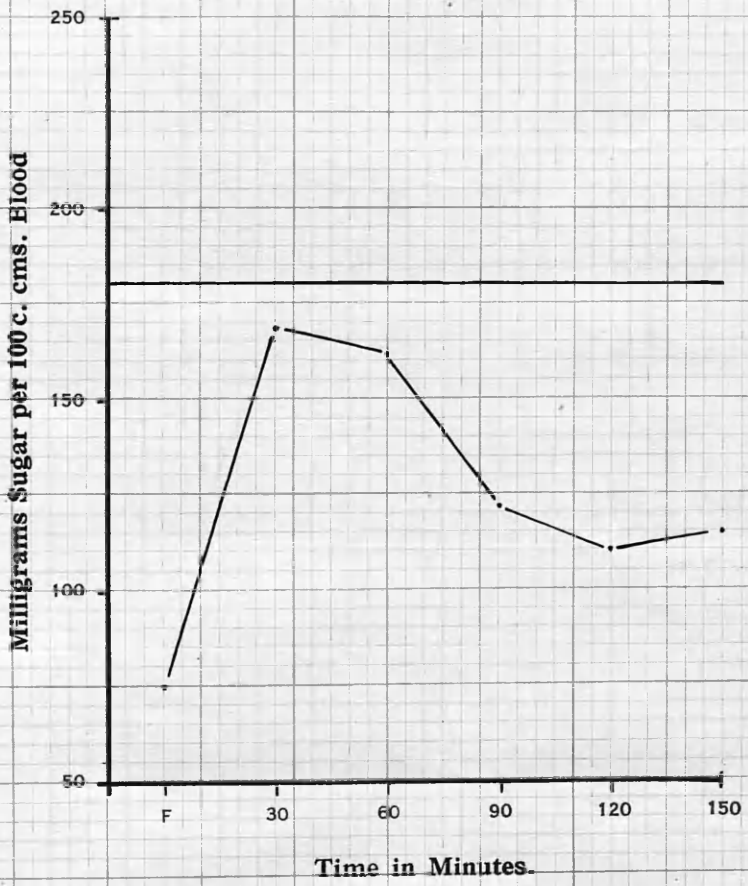


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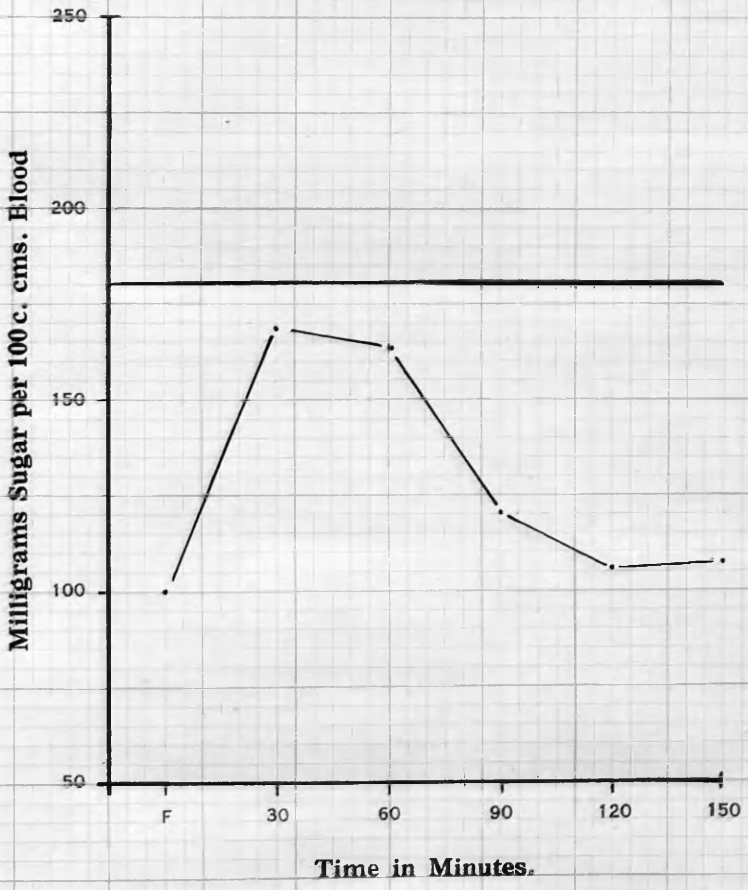
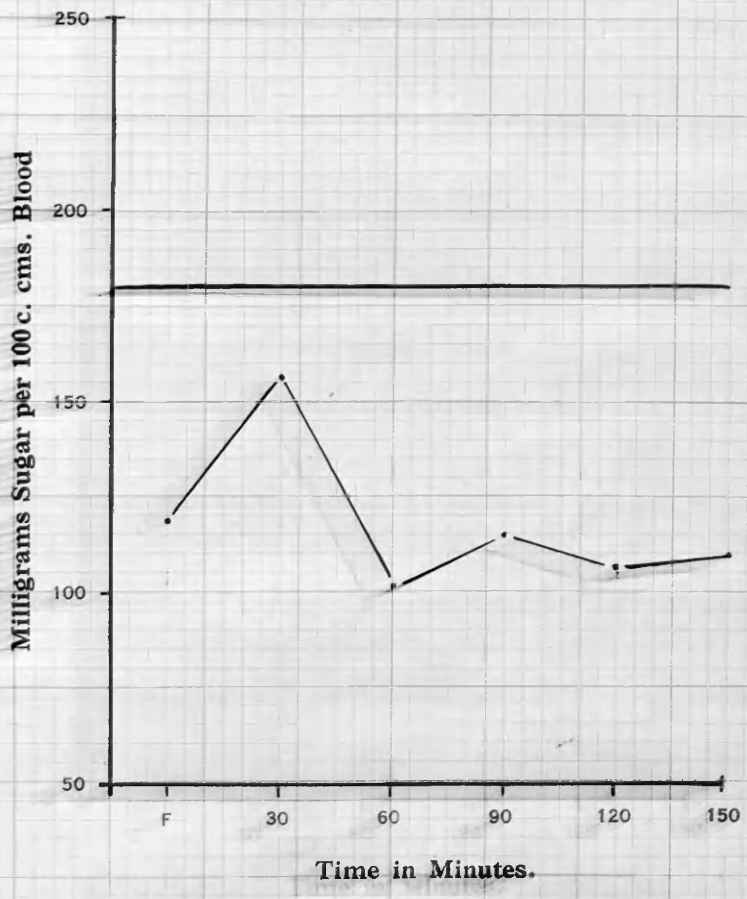
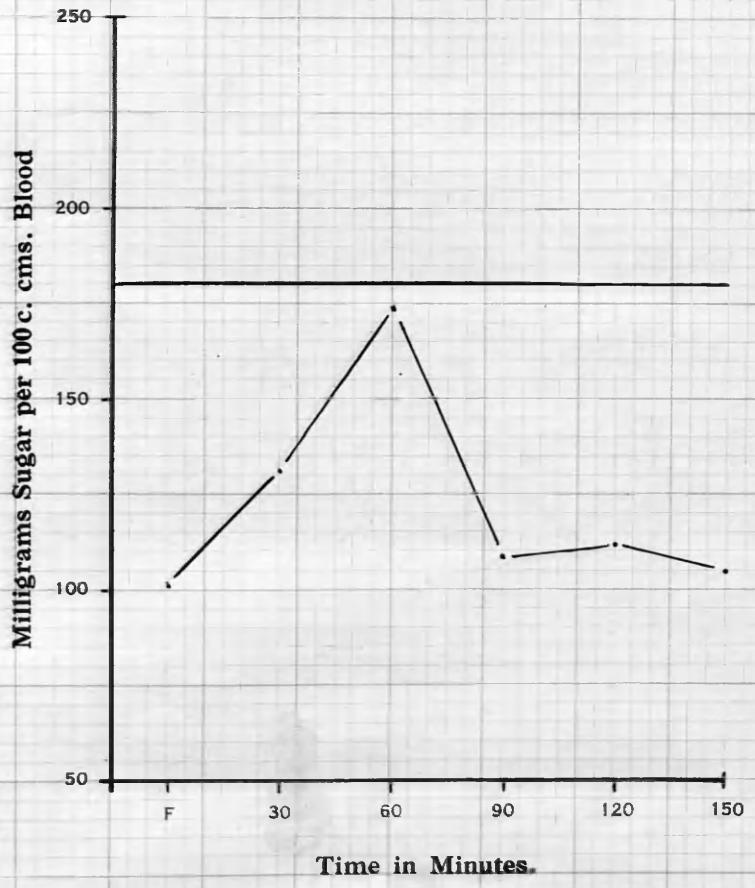
Chart 74.



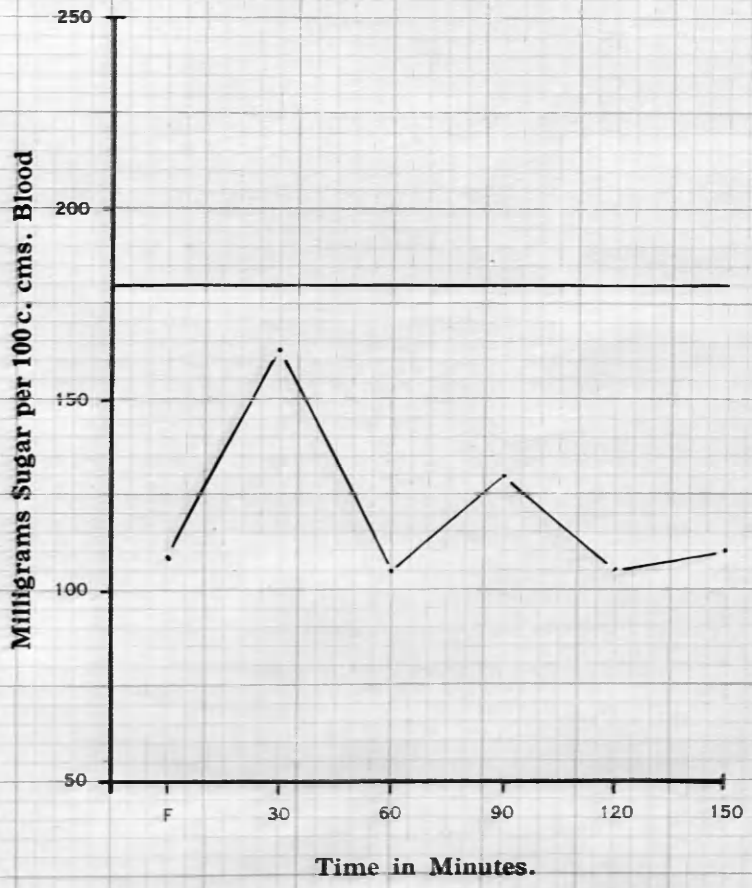
Case 35:
Chart 75.



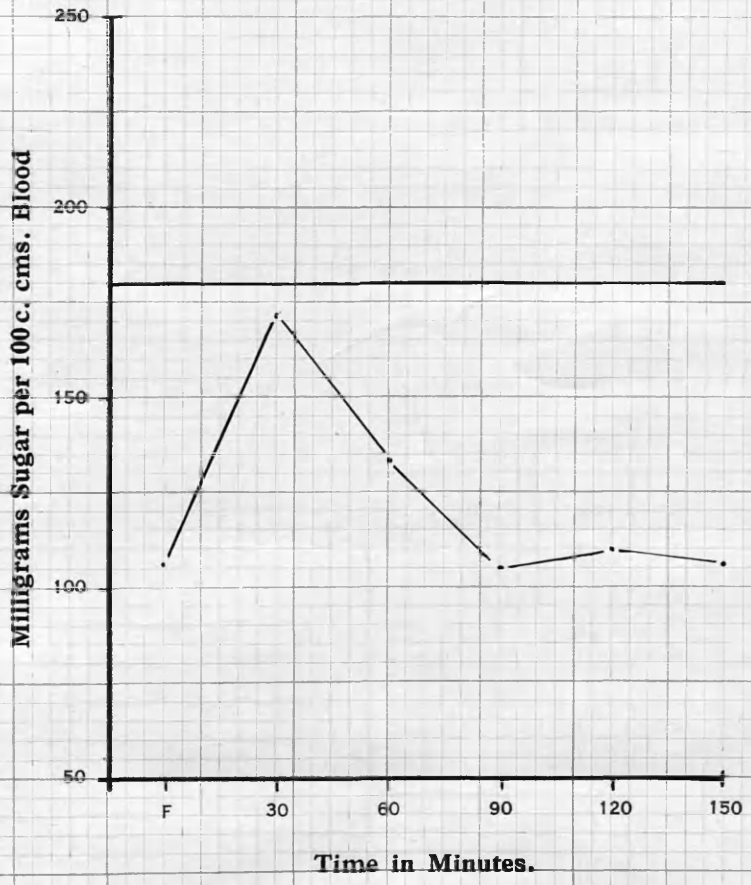
Case 35:
Chart 76.



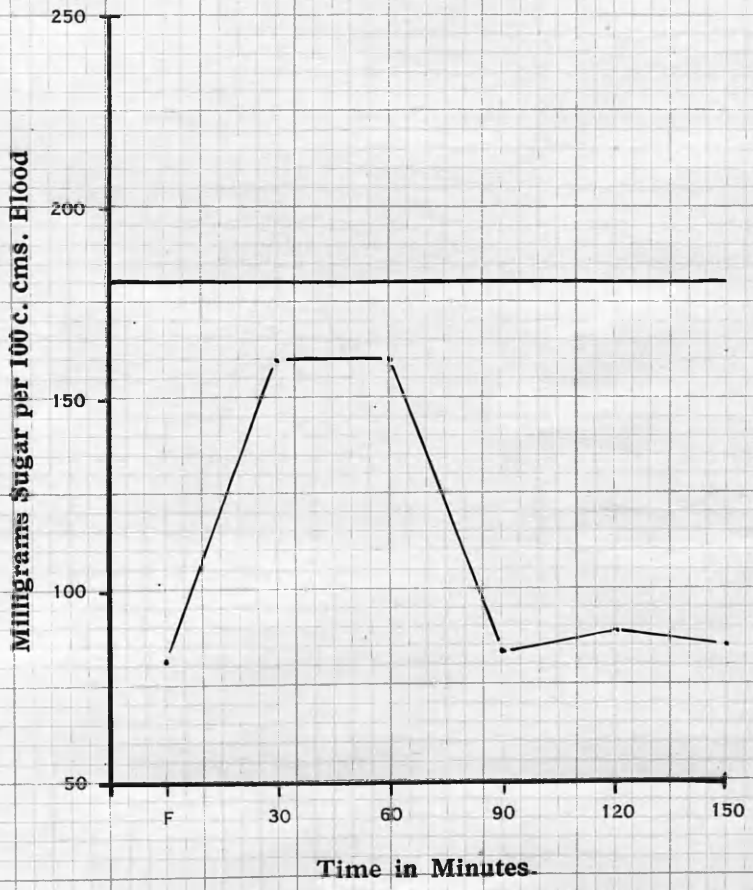
Case 36:
Chart 77.



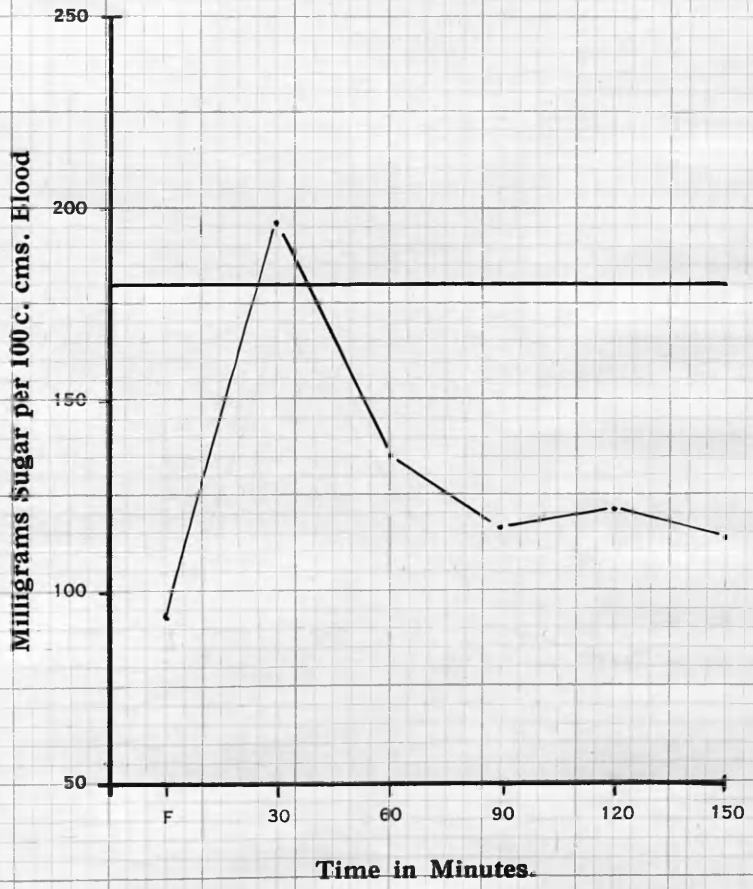
Case 37:
Chart 78.



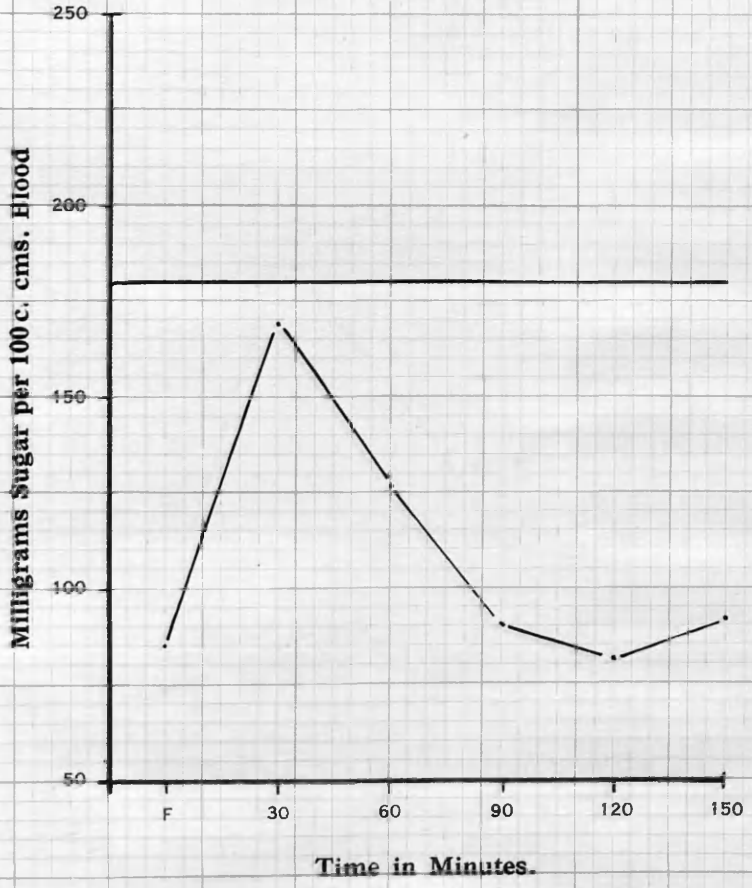
Case 37:
Chart 79.



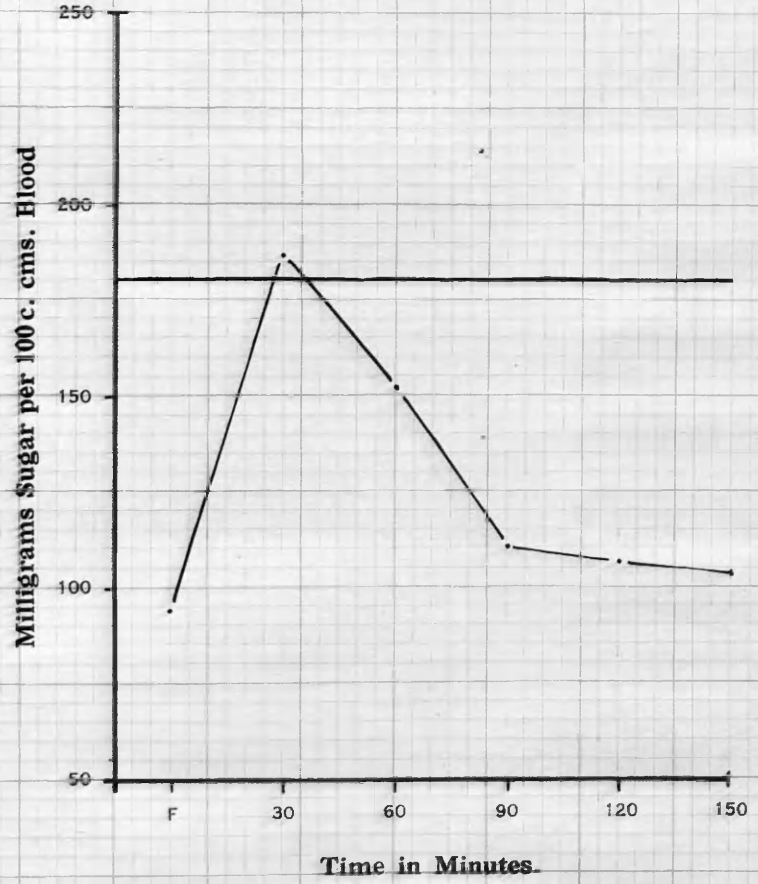
Case 38:
Chart 80.



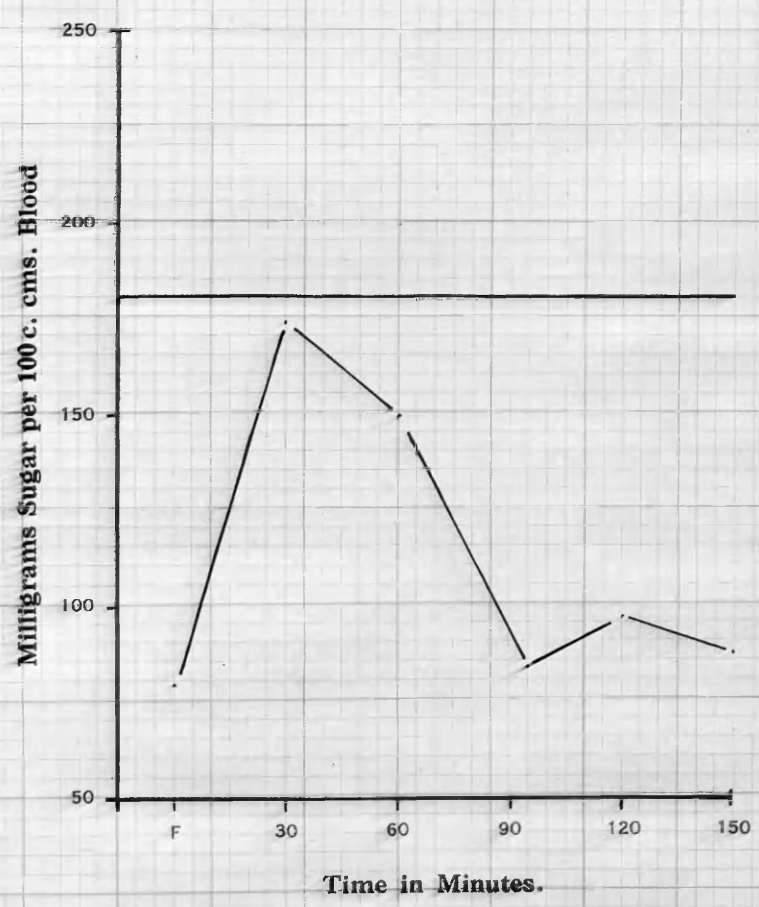
Case 38:
Chart 81.



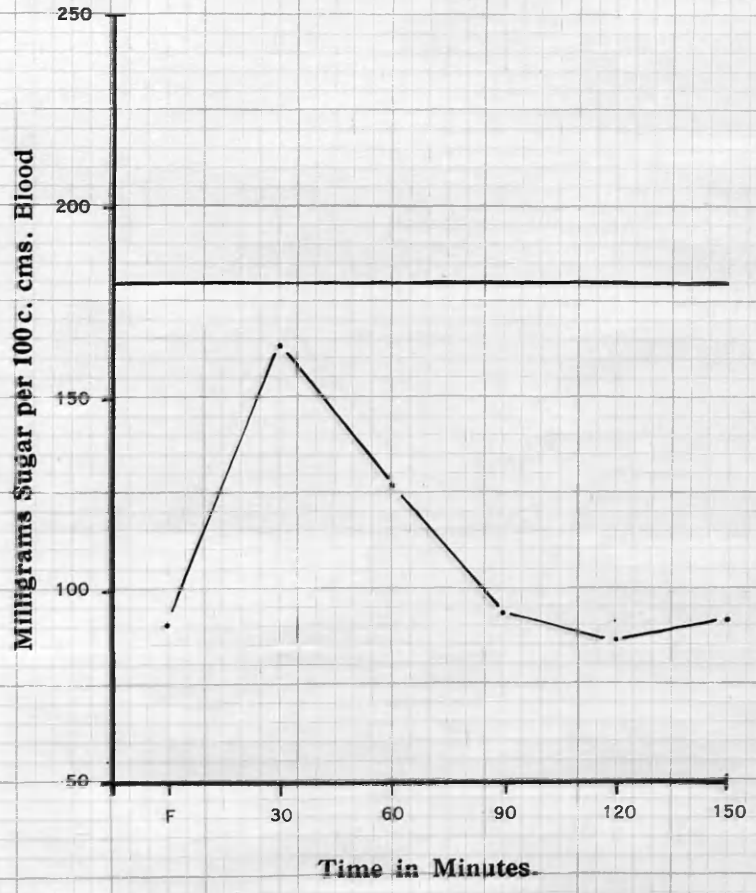
Case 39:
Chart 82.



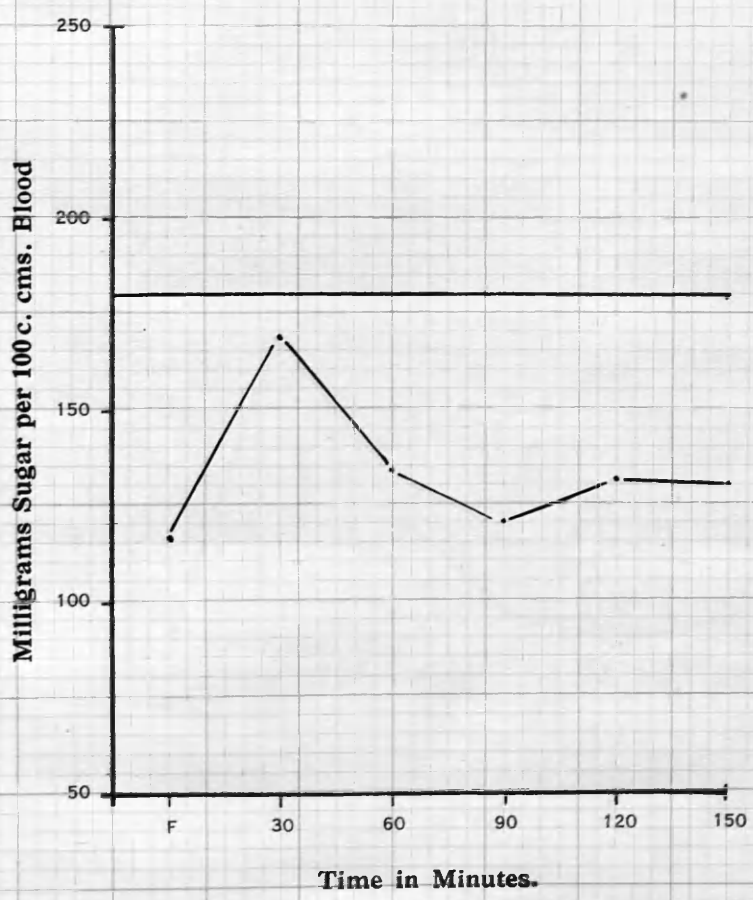
Case 39:
Chart 83.



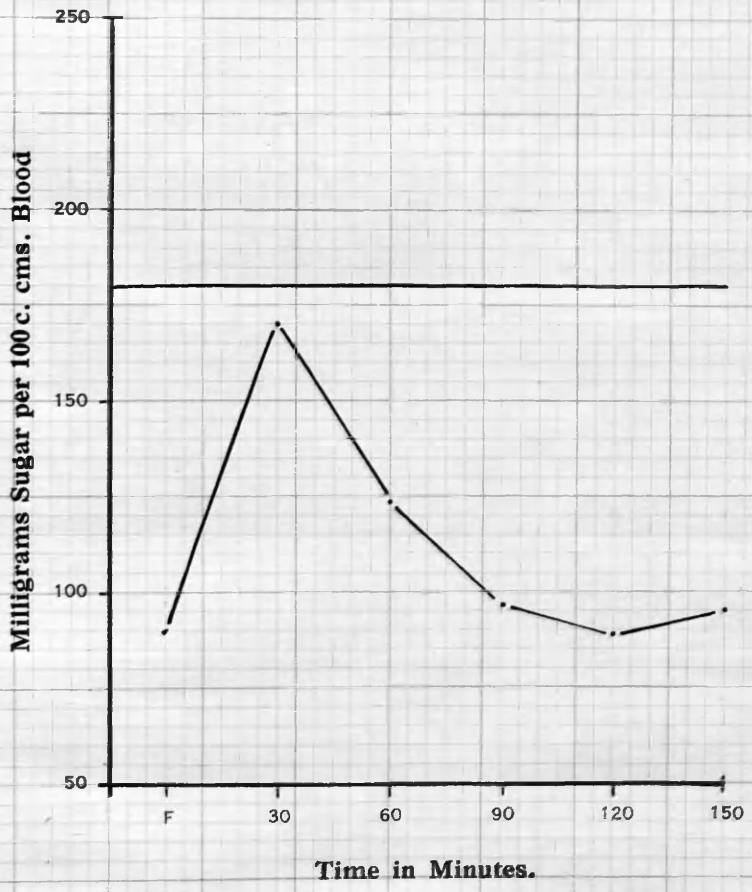
Case 89:
Chart 84.



Case 40:
Chart 85.



Case 40:
Chart 86.



Case 41:
Chart 87.

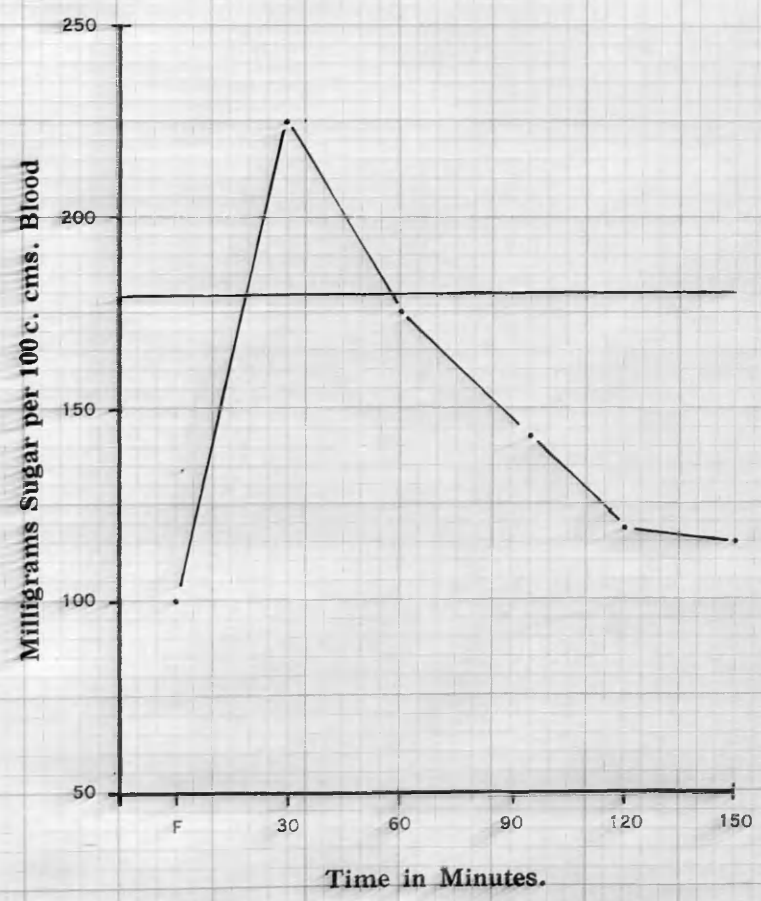


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Chart 88.

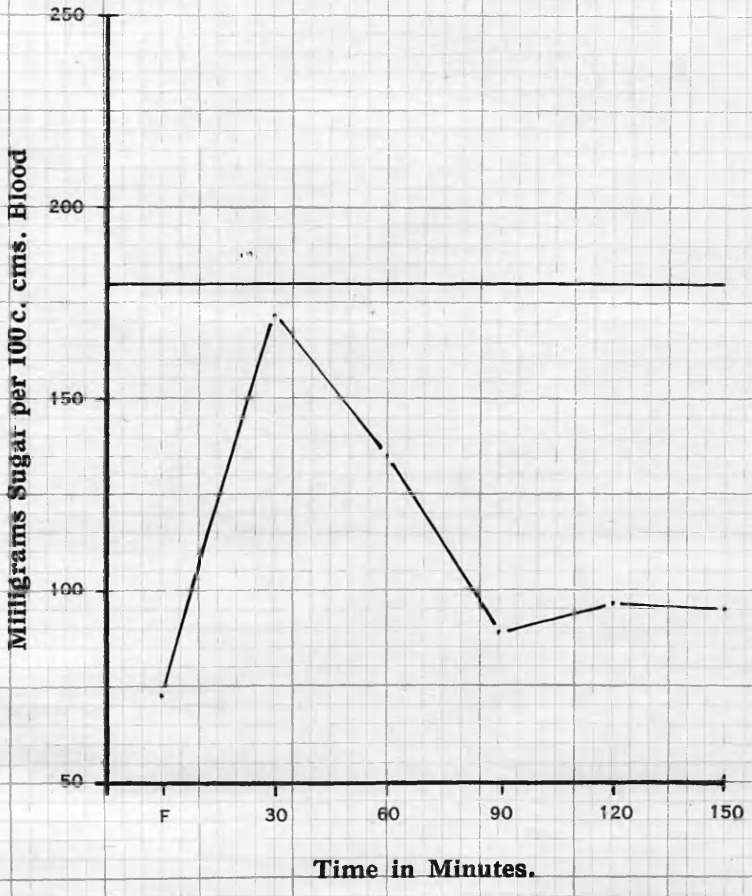

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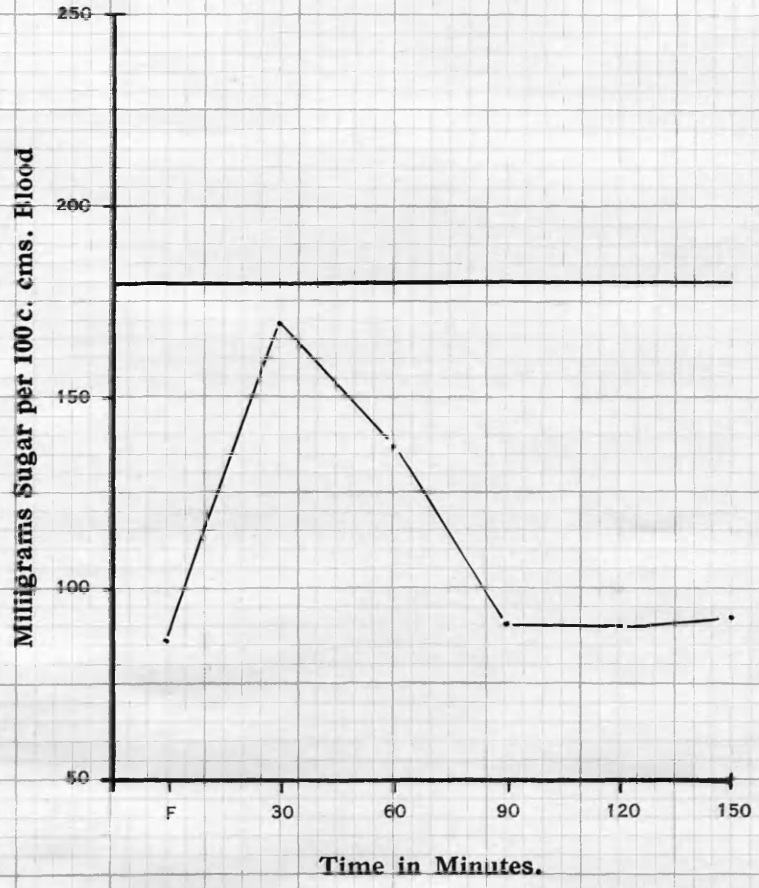
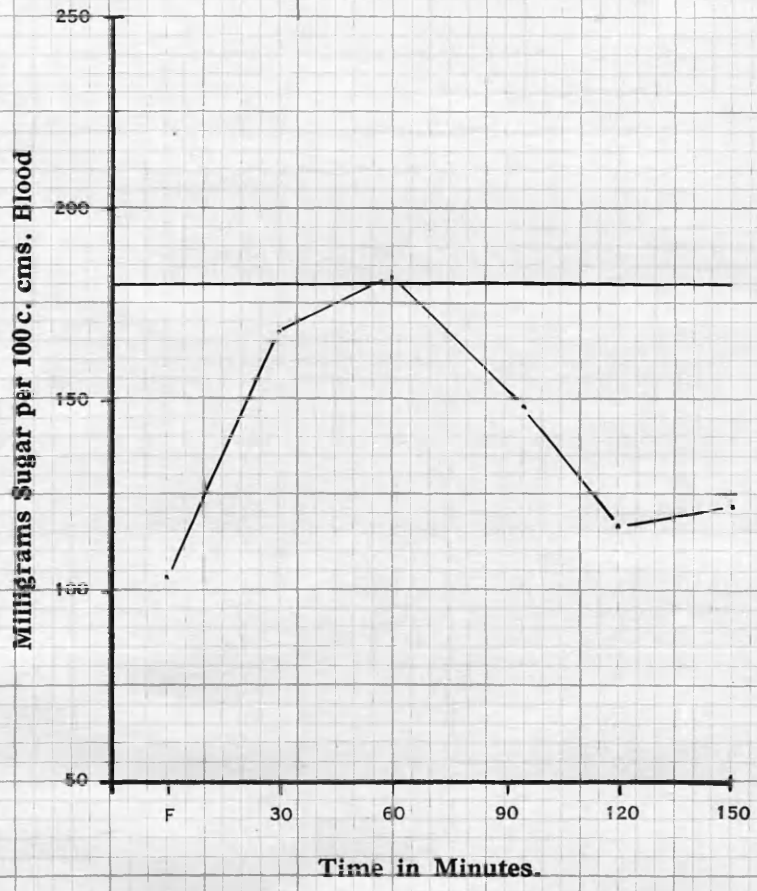
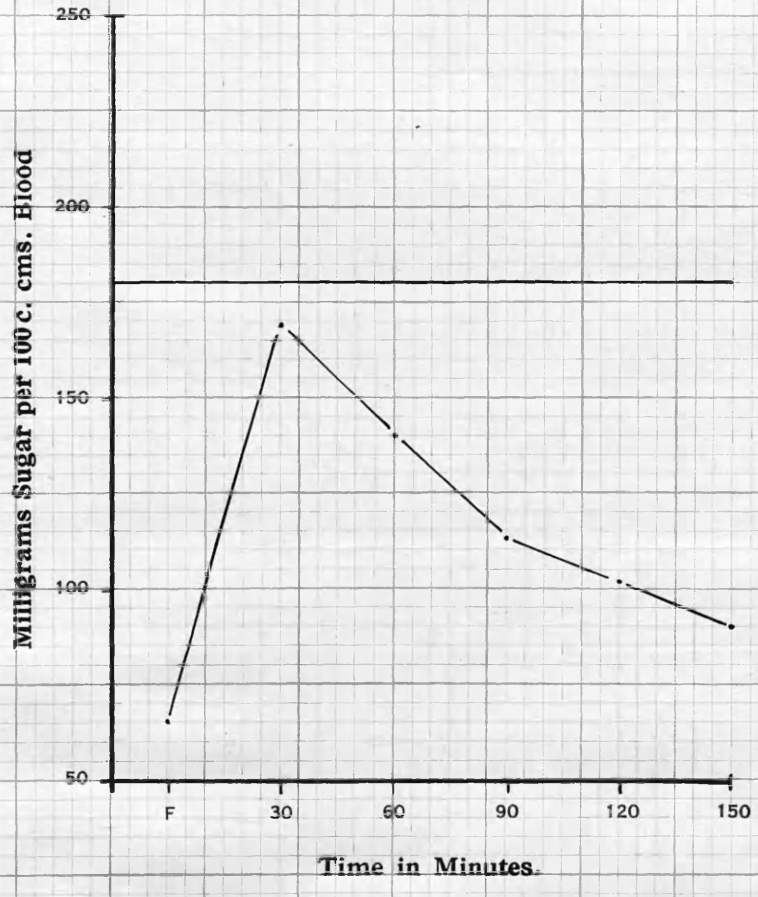
Chart 89.



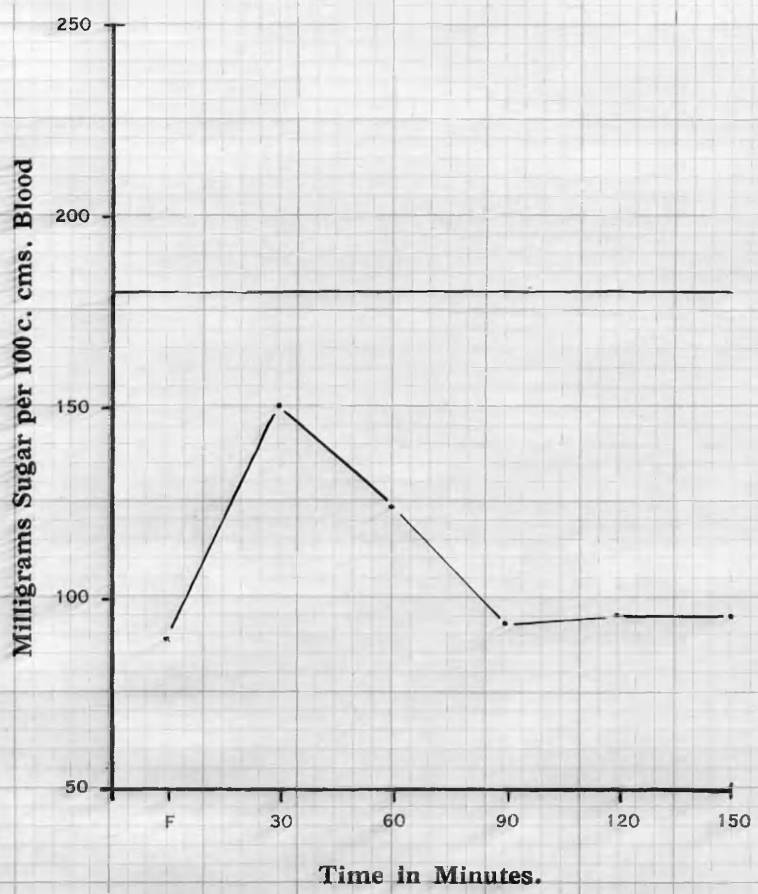
Case 42:
Chart 90.



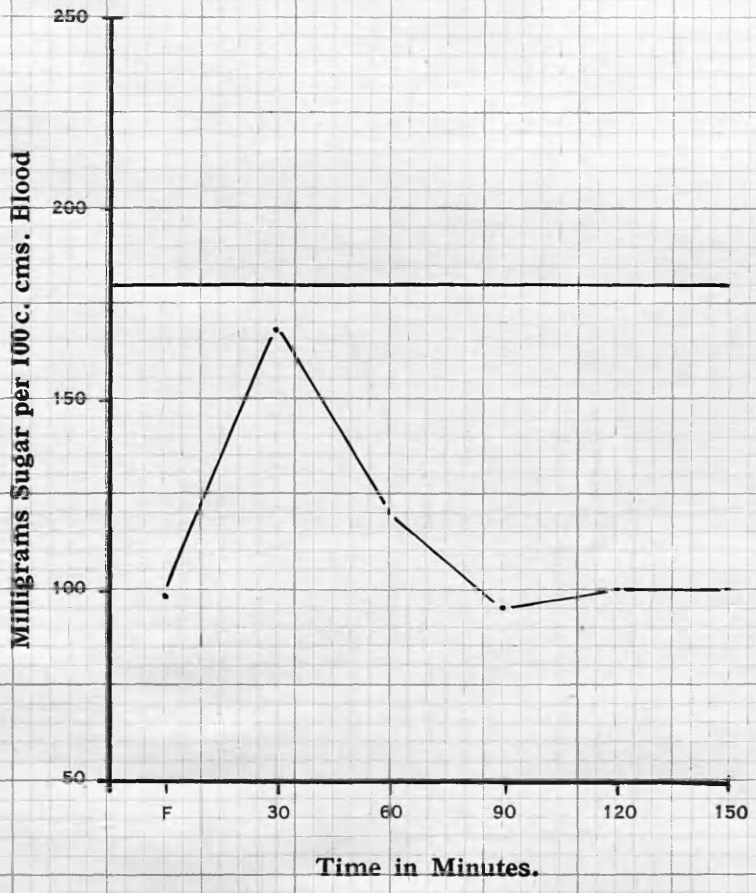
Case 42:
Chart 91.



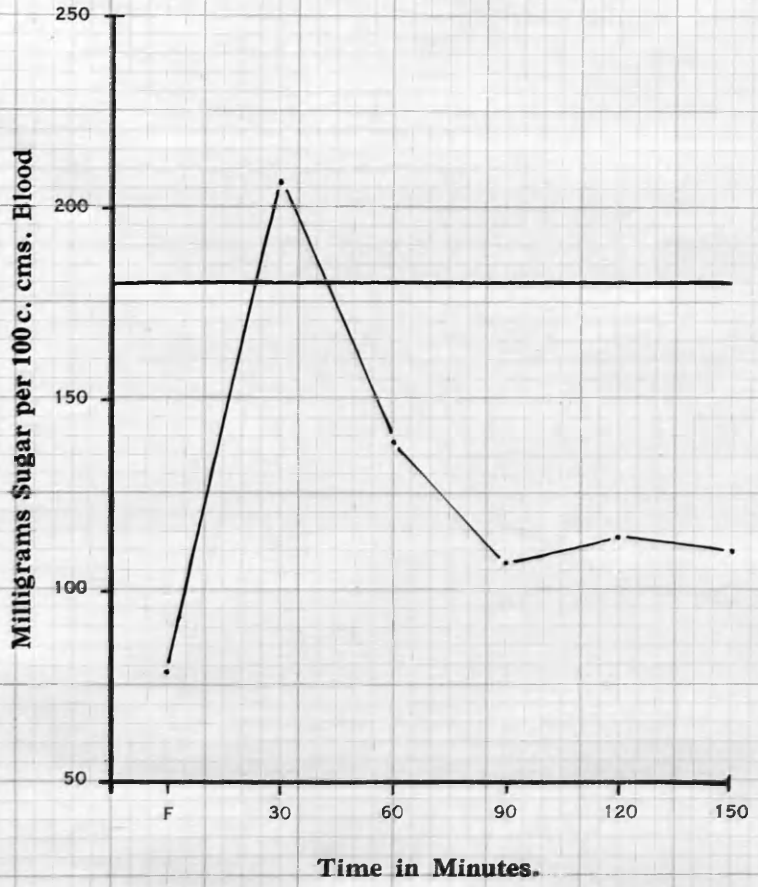
Case 42:
Chart 92.



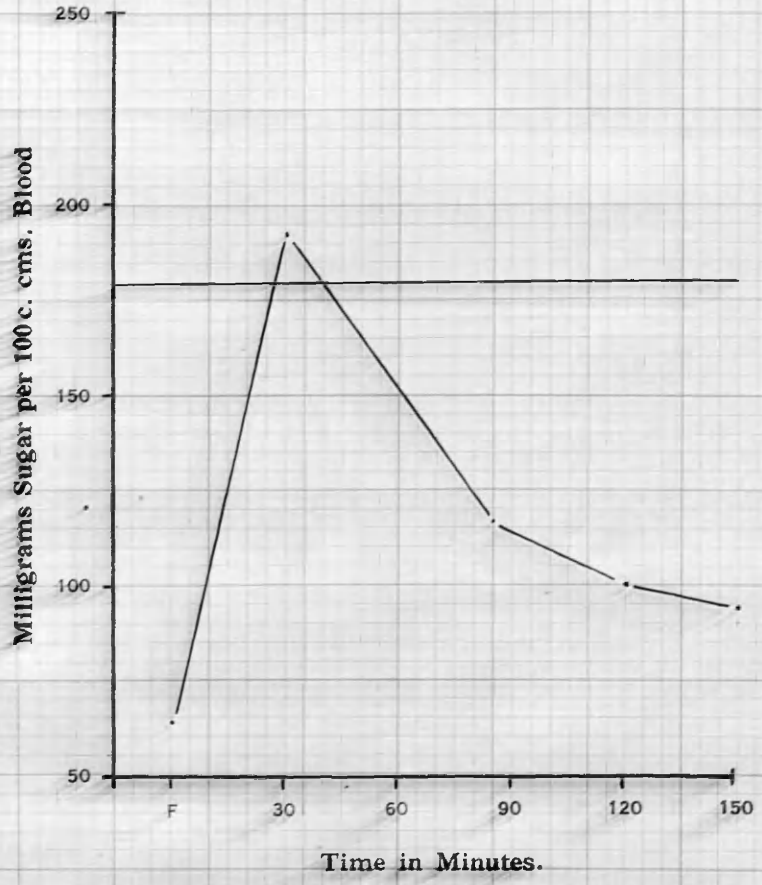
Case 43:
Chart 93.



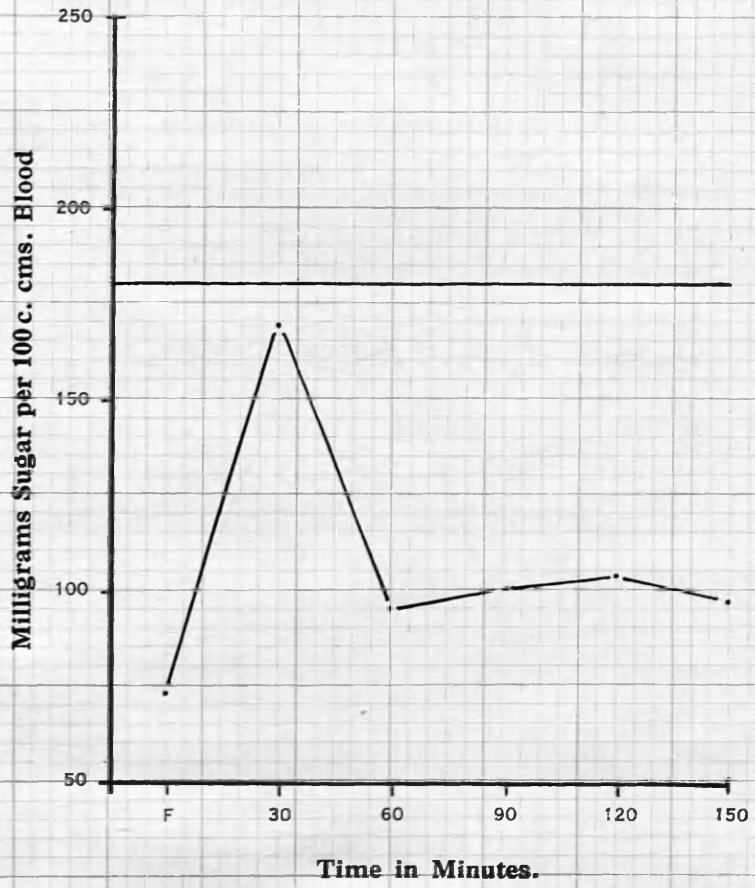
Case 44:
Chart 94.



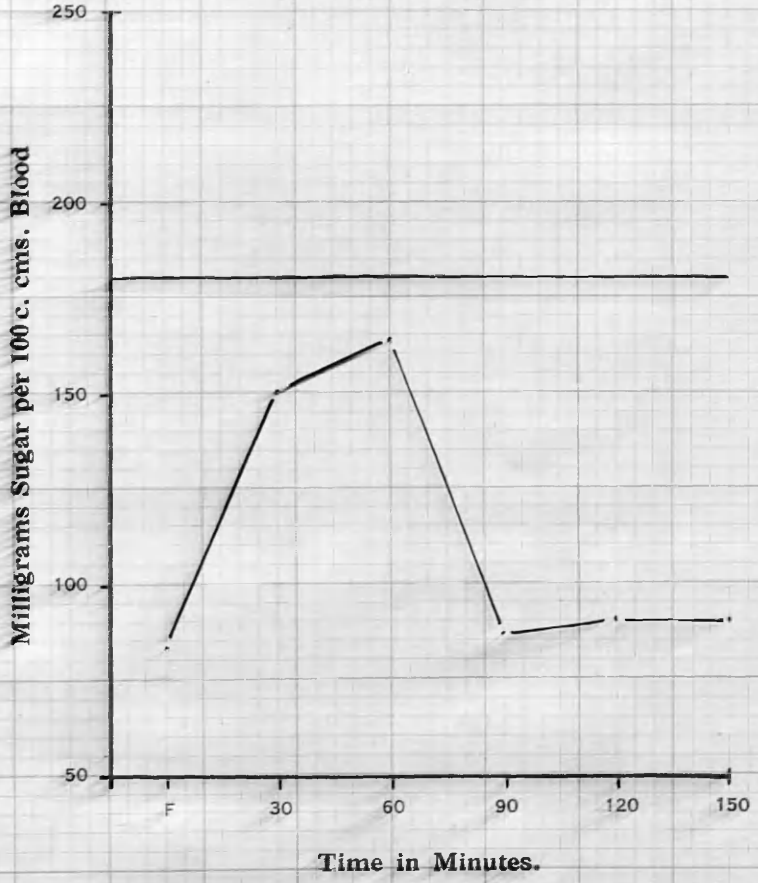
Case 44:
Chart 95.



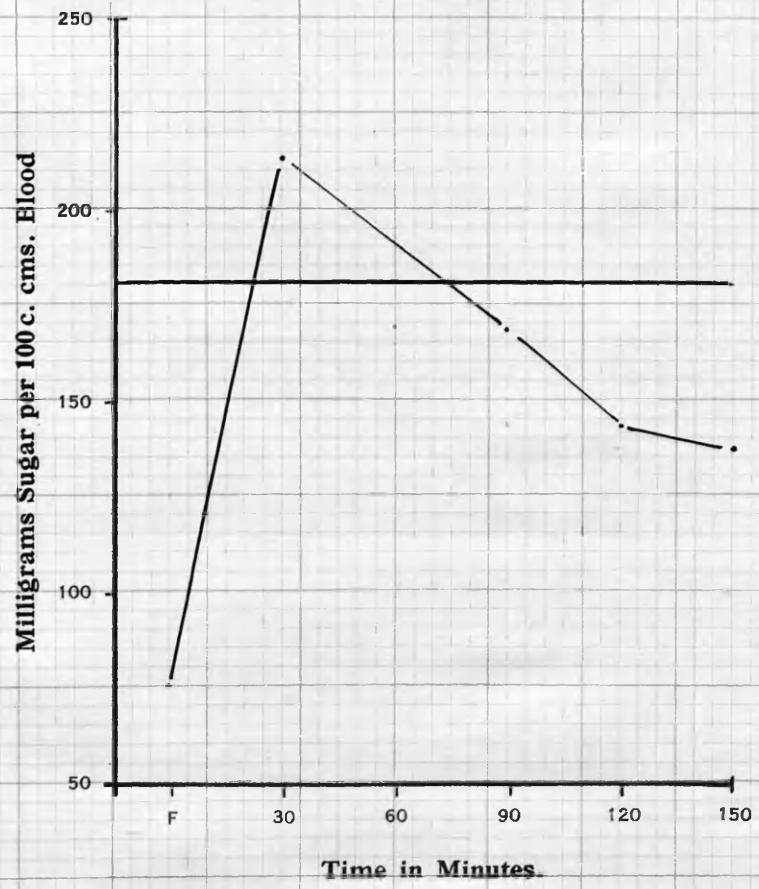
Case 44:
Chart 96.



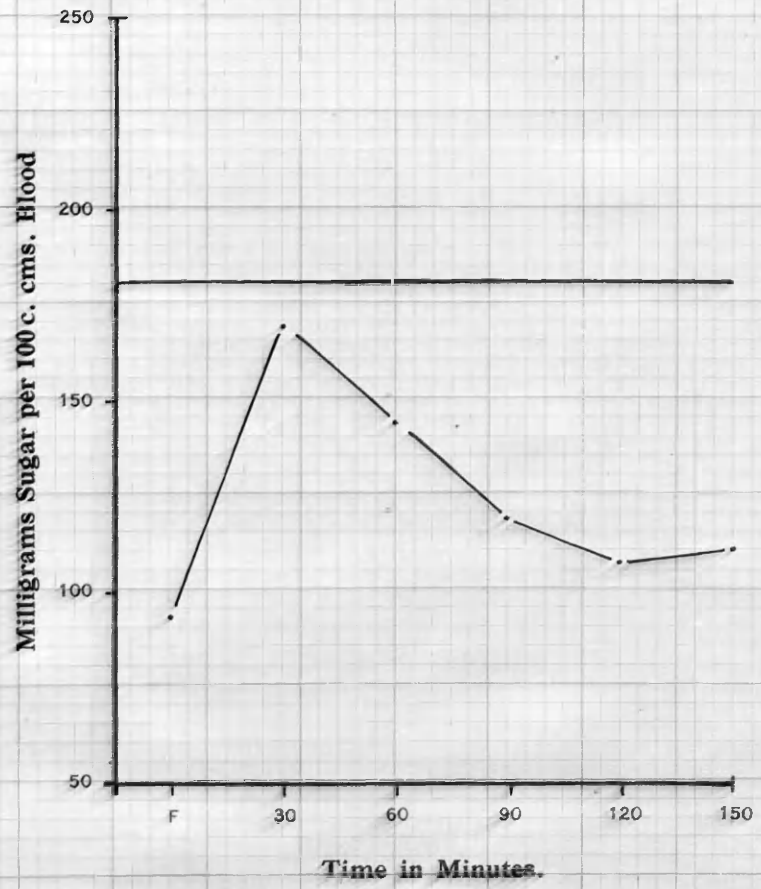
Case 45:
Chart 98.



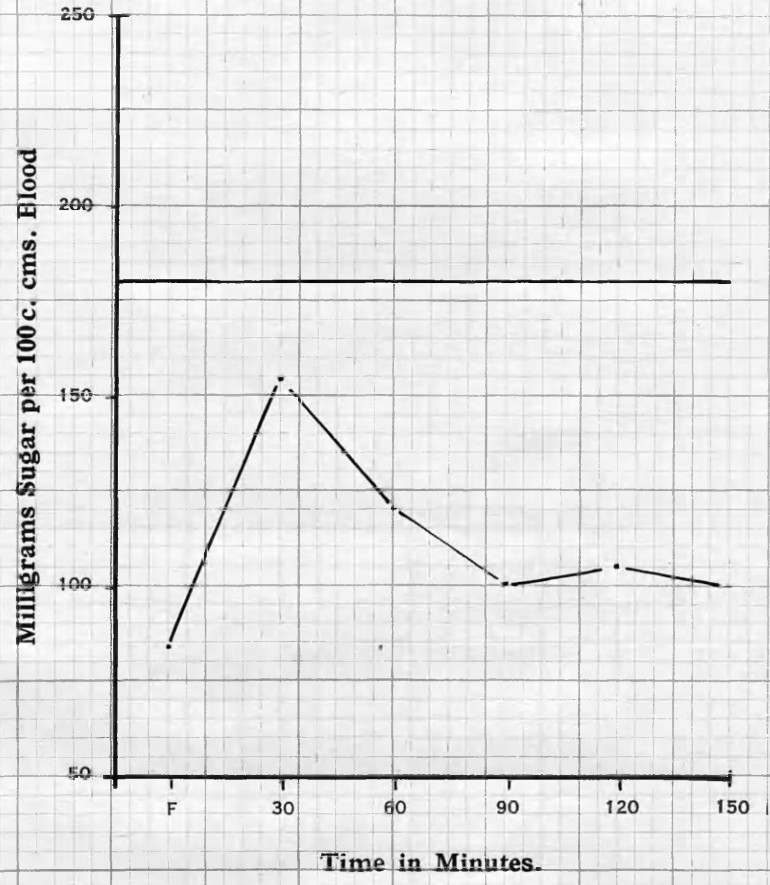
Case 45:
Chart 98:



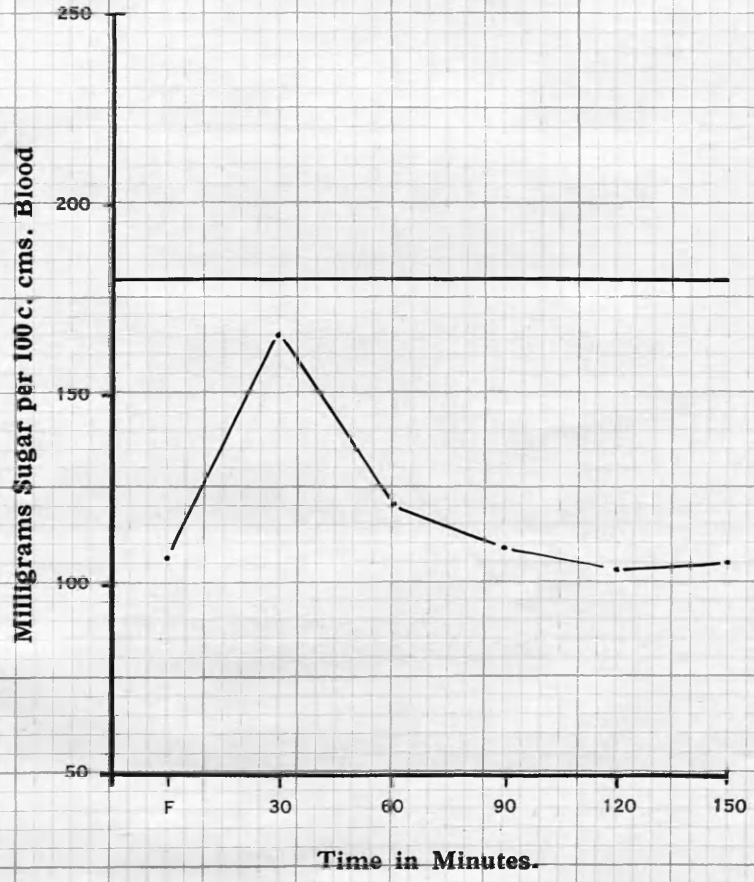
Case 45:
Chart 99.



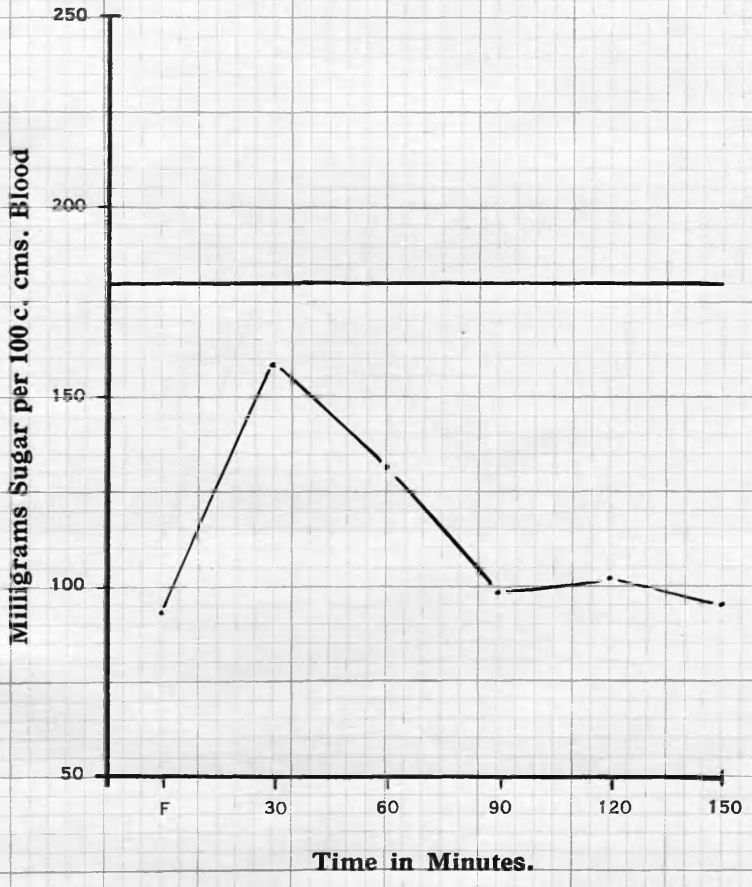
Case 45:
Chart 100.



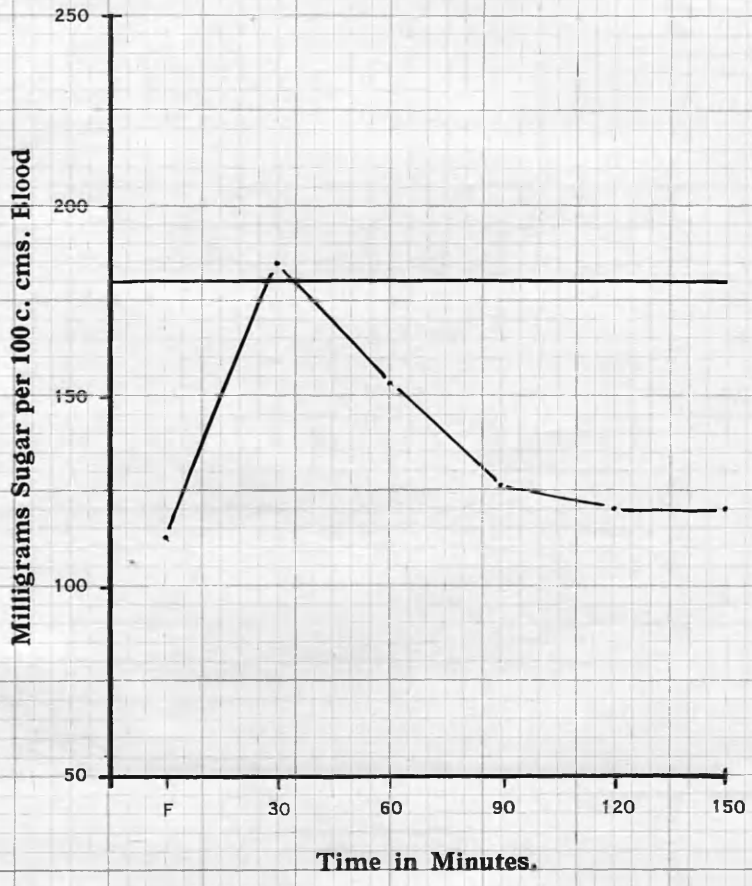
Case 46:
Chart 101.



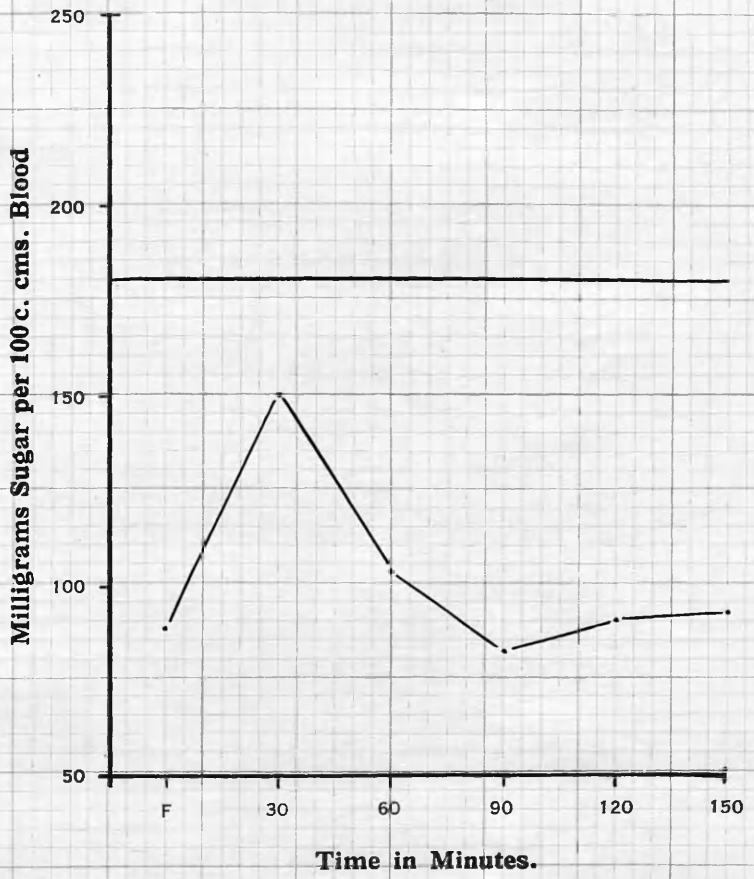
Case ~~46~~:
Chart 102.



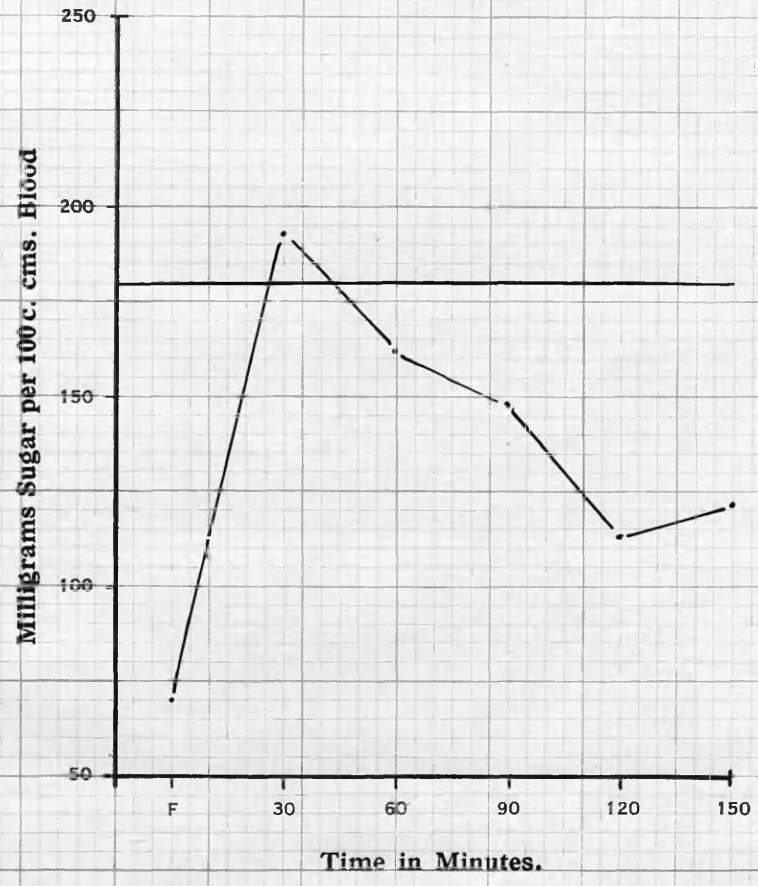
Case 47:
Chart 103.



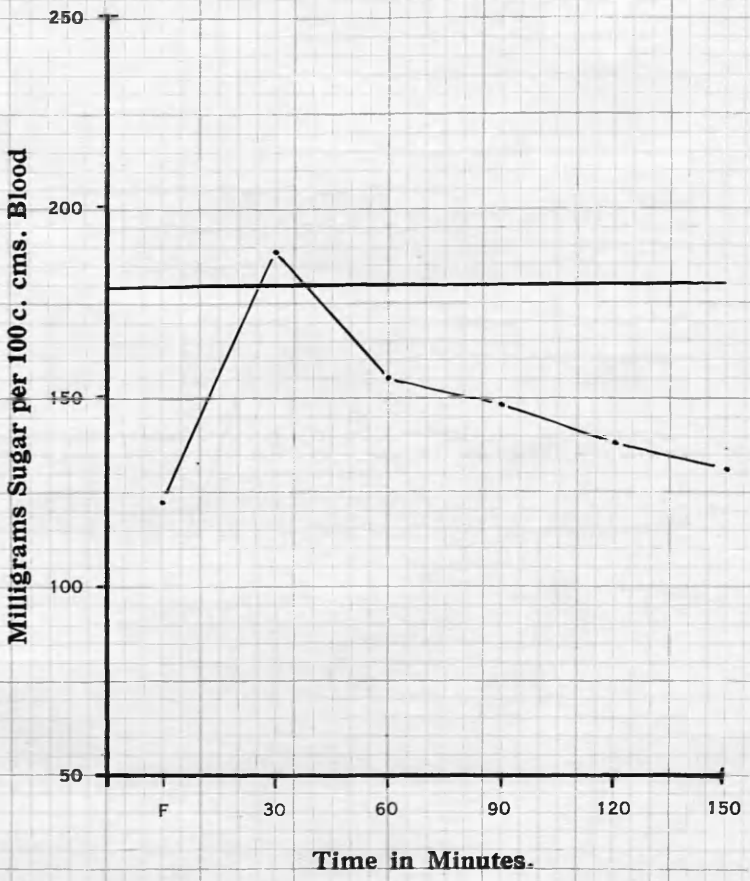
Case 47:
Chart 104.



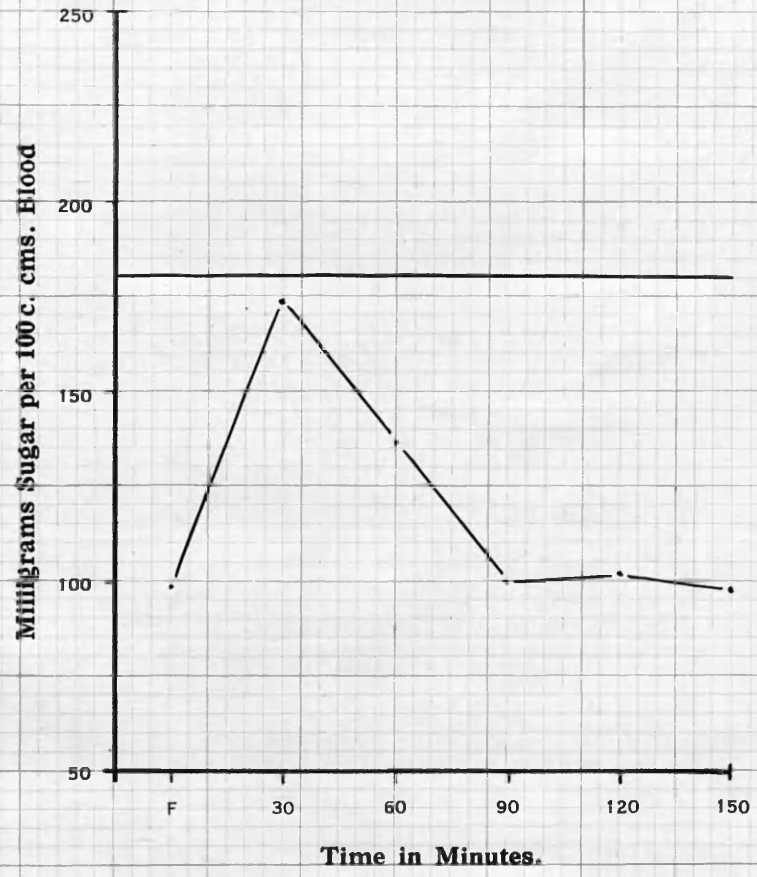
Case 48:
Chart 105.



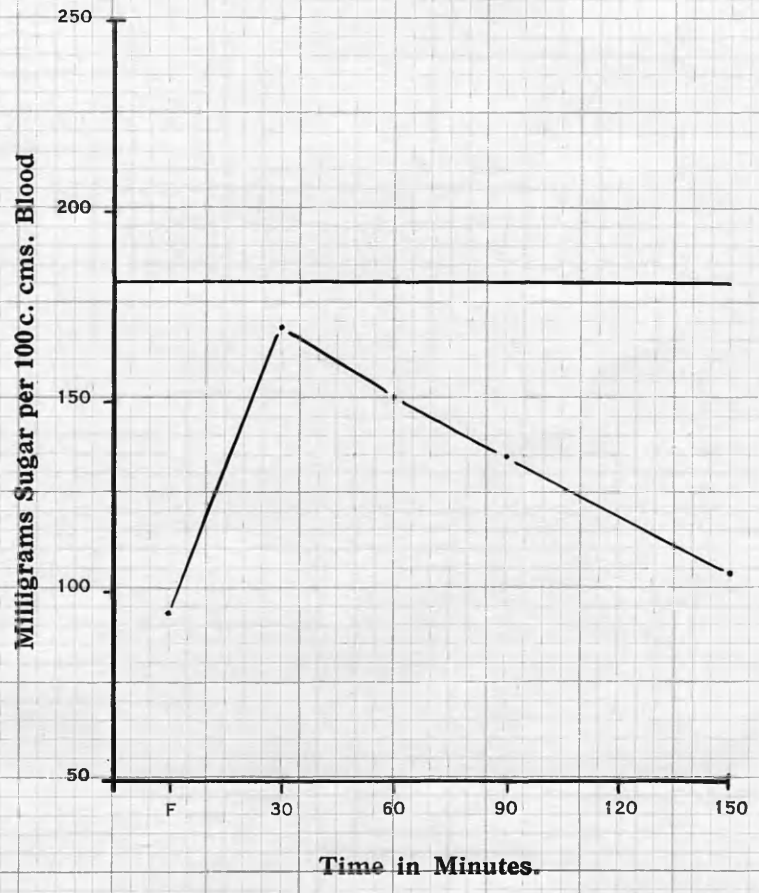
Case 49:
Chart 106.



Case 49:
Chart 107.



Case 50:
Chart 108.



Case 50:
Chart 109.