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MATHEMATICAL MODELLING AND CONTROL OF BLOOD GLUCOSE/INSULIN CONCENTRATION IN AN INSULIN-DEPENDENT DIABETIC SUBJECT.

BY

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CERTIFICATE OF APPROVAL

We the undersigned hereby certify that this thesis by Mbah, Godwin Christopher Ezike meet the requirements for the award of the degree of Doctor of Philosophy in Mathematics and that this thesis has not to the best of our knowledge been previously submitted for award of any certificate or degree in any institution.

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ABSTRACT

Mathematical models describing the variations in the plasma glucose and insulin levels over time in an insulin - dependent diabetic person (IDD patient) were formulated. We showed that these models can correctly describe these variations when we solved them simultaneously by analytical approach rather than the normal numerical approach employed for solving non-linear differential equations.

The effect of the various parameters involved in the model were tested and it was shown that even though the body cell response to the plasma glucose contributes to the determination of the plasma glucose level, the major determinants of the plasma insulin/glucose level are the pancreatic and liver cells respectively.

Furthermore, a control process of the plasma glucose and insulin levels in the blood of an IDD patient was demonstrated. It was shown that insulin infusion or injection (intra-muscularly) correctly reduces the plasma glucose level to normal state. The dose of the insulin to be injected into a patient depends on the level of severity of this disease. Similarly, the quantity of the sugar (glucose) to be taken by the patient and the time it has to be taken, depends on the level of severity. It was noticed that due to wrong diagnosis, over dose of insulin into a patient can result to HYPOGLYCAEMIA and this usually complicates the state of health of the patient.

The peripheral cell response (body cell level of response to the glucose and insulin quantities in the blood) does not markedly determine the plasma glucose level but affects the length of time required to return this level to the basal state.

CONTENTS

CHAPTER ONE

INTRODUCTION

This research work is based on the mechanism and the effect of the interaction of the glucose and insulin levels in the human system with particular interest on the insulin-dependent diabetic patients. The study is carried out by the use of Mathematical models which are built based on the knowledge of the glucose and the insulin. Hence, we shall consider the glucose and insulin under such sub-headings as glucose and its biosynthesis, Liver control of blood glucose, mechanism of glucose entry into the cells, insulin and its biosynthesis, e.t.c. We shall also introduce the disease, Diabetes Mellitus, method of diagnosing it and such other information that may be very necessary for the proper understanding of our mathematical model and the subsequent results and analysis.

GLUCOSE AND ITS BIOSYNTHESIS

Human food substances are mostly product of photosynthesis by plants of which carbohydrate is one. Thus, green plants in the presence of Sunlight uses water and carbondioxide to produce carbohydrates. It is in this form that much of the glucose in the human system is derived since the carbohydrates when taken as food undergo digestion in the stomach/intestines and thus are broken down into monosacharides, polysacharides and diasacharides. Glucose molecules incidentally are monosacharides and it is in this form that the body makes use of the carbohydrates. Examples of food substances rich in carbohydrate are cassava, rice, yam and corn. After the digestion of the carbohydrates and the subsequent breakdown to the various forms, the glucose diffuses from the digestive system into the blood. The blood then conveys it to the requiring cells

where it will be utilized by a mechanism to be explained later. Principally, much of the glucose in the blood passes through the liver before being taken to the tissues and peripheral cells. When in excess, it is converted to glycogen and stored in the liver by the appropriate enzymes. In extreme cases where the liver has stored to its maximum capacity, the excess glucose is converted to fats and then taken to the muscles and other tissues for storage.

Conversely, in case of dearth of glucose in the blood, these stored fats and glycogen are reconverted to glucose and sent back to the blood for onward transportation to the requiring cells. Much as the liver can store, the quantity of glucose stored as glycogen barely sustain life for 24 hours after which the stored fats and proteins are then being converted to supply the energy needed by the cells. In this situation also it is noted that the gate to glucose metabolism by cells other than the brain cells are shot. This happens due to basal level of insulin which do not interact further with the glucose. The reason for closing the door to glucose metabolisms is that the brain cells needed mainly the glucose for their sustenance while the other cells can make use of the fats and protein in obtaining the energy they need.

In general, the daily intake of carbohydrate varies considerably although this ranges from 250-800g. Most of these carbohydrates come in the form of plant polysaccharides, starch and with small amount of disaccharide's (table sugar) and lactose (milk sugar). Carbohydrates are compounds whose general chemical formula is $(CH_2O)_n$ where n is a positive integer.

BLOOD GLUCOSE REGULATION BY THE LIVER AND OTHER TISSUES:

From what has been said about the liver, we can say that it is an organ of glucose production and consumption. It is exposed to insulin concentrations in the portal venous

blood. The insulin concentration here are 3-10 folds greater than what obtains in the systemic circulation. The Liver also is the sole site of the blood glucoregulating action of the glucagon. In considering the regulation of the blood glucose level by the Liver, we consider the period following an overnight fast and preceding the ingestion of the breakfast meal. This period is generally referred to as "postabsorptive state". After the overnight fast, the concentration of hormones (insulin and glucagon) and substrates (glucose, amino acids, fatty acids) usually return to the base line concentrations which we call the basal levels. This reduction of the insulin to the basal level (10-20 μ U/m) results in virtually total cessation of glucose uptake by the insulin-dependent tissues such as resting muscles, adipose tissues and the Liver though its uptake continues by the non-insulin- dependent tissues such as the brain, the formed elements of the body and the renal medulla at a combined rate of about 2-3mg/kg/min. Under this state, the maintenance of the blood glucose is realised by the hepatic release of glucose at rates equal to tissue demands and utilisation. This addition process is made up of **glycogenolysis**- synthesis of glucose from the glycogen, and **gluconeogenosis**- the synthesis of glucose from the pyruvate, lactate, glycerol and amino acids. It is estimated that about 70-75% of hepatic glucose release is as a result of glycogenolysis while the remaining 25% is due to gluconeogenosis. For more detail of this, see **Vallence-Owen (1975)**. In as much as the fall in the plasma glucose giverrise to hepatic glucose output, the relative contributions from glycogenolysis and gluconeogenosis are influenced by the following:

(a). total glycogen stored in the Liver which is usually not less than 70g and about 450g in a 70kg man.

(b). stored protein-derived amino acids.

Now, the daily glucose requirement by the brain is about 150g so that if the liver stored say 70g daily, then this store will get depleted in less than 24 hours period of fasting. When this stored glycogen is depleted, the splanchnic uptake of alanine gets stimulated. This stimulation has been shown to be a consequence of starvation, the kidney becomes an important source of glucose synthesis and at such a time, this accounts for approximately half of the total glucose release into the blood stream. This is suspected to have come from the conversion of nitrogen substances that would have been excreted in the urine since experiment has shown a reduction in the urinary nitrogen excreted (10-12g/day to about 5g/day or even less) after some long period of starvation. For such long period of starvation, glucose utilisation has reduced to as much as 50%. This is because at such periods, the brain uses ketone acid as its main oxidative fuel in place of glucose. Also one of the functions of the liver is the conversion of the excess glucose to glycogen which is the storage form. However, this action is possible in the presence of insulin. Hence, the recognition of the liver as the site for insulin action on glucose. Also the peripheral muscles and adipose tissues take part in the disposal of oral glucose. The level of glucose in the systemic circulation (blood plasma) measures the amount of glucose that escapes from the splanchnic bed. Also the basal rate of glucose utilisation represents consumption by non-insulin-dependent tissues particularly, the brain and blood cellular elements. **Felig et al (1975)** showed that only about 15% of the ingested glucose load is available for disposal by the peripheral insulin-dependent tissues. They further showed the disposal of the 100g ingested glucose over a 3 hour period as:

Glucose remaining in glucose space (unmetabolised)	< 5%
Increased peripheral glucose utilisation (insulin-dependent)	15%
Hepatic disposal	
Glycogen -spacing (non-insulin dependent peripheral uptake)	25%
Hepatic retention	55%

Glycogen synthesis

Triglyceride formation

glycolysis

Fats are produced in the liver of which only some small amount is stored there and the rest released into the blood and taken to the adiposed tissues for storage. The catabolism of adipose-tissues triacylglycerol liberate fatty acids into the blood which are picked by all these tissues (excluding the nervous system), which enters the krebs circle and are oxidised to release the required energy by the cells. This as earlier said, helps in the reservation of the glucose for the brain cells and the nervous system.

MECHANISM OF ENTRY OF GLUCOSE INTO THE CELLS

The study of the cell structure shows that the cells are separated from the extra-cellular fluids by the surface membrane called the **plasma membrane**. This membrane provides barrier to the movement of molecules in and out of the cells and equally provides scaffolding to which the cell compartments anchor. Movement of molecules across cell membranes is not constant and this regulates the cell functions. On the outer surface of the plasma membrane are located the receptors to hormones and chemical messengers so that the plasma membrane acts as a signal-receiving device for the detection of chemical signals that regulate the cell activities. These receptors are protein. Also in the plasma membrane are the junctions which serve as channels for cell-to-cell communication. Certain enzymes also anchor on the cell membranes rather than dissolving in the intra-cellular fluid so that chemical reactions occur only in association with particular organelle. This is because mediating reactions are either bound to the membranes of the organelle or are located within the organelle and thus unable to penetrate the surrounding membrane.

In general, the cell membranes are composed of bimolecular lipid matrix in which proteinsare embedded. The lipids and proteins are present in approximately equal proportions. The lipids form the barrier to movement of molecules through the membrane while the protein provide selective means for the transfer of certain molecules through the barrier and constitute the binding sites with enzymes associated with the membrane. Majority of the membrane lipids are phospho-lipids which are amphipatic molecules having a charged region at one end (negatively charged phosphate group which is usually attached to another small group) while the other end is neutral and consists of two long chain fatty acid. For more information on cell polarity, see **Vander et al (1980)**.

Having looked at the cell structure we consider now the forms of molecular transport across cell membranes. Such forms of transport are **diffusion, mediated-transport system, osmosis, endocytosis and exocytosis.** However, we shall only discuss those forms that are of importance to us here. Thus, we note that the exchange of molecules between cells occurs in part by diffusion. By diffusion, we mean the movement of molecules from one location to another (possibly across a membrane) by random molecular motion. Thus when the glucose is got as one of the products of digestion, it is absorbed into the blood from where it diffuses into the extacellular spaces surrounding the cells. Since diffusion is an extremely slow process, the blood circulation helps in taking the glucose very close to the cells so that time needed for receiving the nutrients is minimised. Though the sugar (glucose) diffuses into the extracellular surrounding of the cell from the blood, it does not actually diffuse into the cells. The movement of these glucose molecules into the cells requires a special mechanism that are built into the cell membrane structures. This special mechanism through which the glucose molecules move into the cells is called the mediated transport mechanism. In this mechanism, the glucose molecules bind to specific protein on the membrane surface and this leads to their movement through the membrane.

The membrane actually determineswhich molecules should enter the cell by mediated transport or diffusion. The major characteristic of mediated transport are specificity, saturation and competition. In mediated transport, the flux constant changes in the extracellular nutrient concentration unlike in diffusion, although there is maximum rate the nutrient can enter the cell by this means.

The transporters are carrier protein and they facilitate the transport of these glucose molecules from the extracellular spaces to the intracellular space of the cells **(Simpson and Cushman, 1965, 1986).** About six of such carrier proteins hawebeen identified. However, not all of the glucose transporters are responsive to insulin stimulation. As earlier stated, there are protein receptors on the cell membranes which receive those glucose molecules when the transporters bring them . These receptors are evenly distributed in the membrane when not influenced by the insulin. However, the mechanism by which these carrier proteins enable the solute to pass through the molecules is not quite known though it is thought to involve conformational changes in the carrier molecules resulting from the binding action of the solute.

Though we said that mediated transport system is the mechanism of transport of glucose molecules into the cells, this mechanism is further subdivided into facilitated-diffusion system;

---leads to equal concentration of solute at area of higher concentration across the membrane. Thus, the actual movement of glucose molecules across the membranes of the cells occur mainly by facilitated-diffusion system since the polar molecules do not easily diffuse through the lipid or pore regions of the membrane. This process is possible in the cells because the binding sites on the carrier proteins are accessible to solute molecules in both the extra and intracellular region of the cells.

For IDDM patient, this process still holds but at a reduced level due to non-availability of sufficient insulin in the blood plasma.

INSULIN AND ITS BIOSYNTHESIS

Insulin is a protein hormone secreted by the islets of Langerhans clusters of endocrine cells, in the pancreas. This hormone has wide spectrum of activities among which is the enhancement of the conversion of glucose to glycogen which is the storable form of glucose in the body. There are three distinct types of the islet cells namely: the alpha, beta and gamma cells. The alpha cells secret the glucagon, the beta cells secret the insulin while the gamma cells secret the peptides named Somatotastin. Insulin acts directly or indirectly on most tissues of the body though it has no action in the brain cells (**Vander et al 1980**). The presence of insulin induces on its target cells an alteration of either the membrane transport or the enzyme function.

On biosynthesis of insulin, this takes place in the beta cells in the islet of langerhans of the pancreas. The study of the process involved and controlling the biosynthesis, storage and release of insulin was done by studying the insulin-producing tumours and insulinomas that abound in the pancreas. **Stainer and Oyer (1967), Stainer (1967)** through their studies showed that their is a precursor insulin called the proinsulin in insulin biosynthesis. This pathway thus suggest that limited proteolytic might play a more general role in protein biosynthesis. It has also been shown that proteolytic conversion of this precursor to the hormone (Insulin) proper prior to its storage takes place in the β -cells . In the proper sense of it, insulin synthesis begins at the ribosomes bound to the endoplasmic reticulum (**Sorenson et al, 1970**) . This synthesis has been shown to be enhanced by the presence of glucose. The presence of glucose leads to proinsulin production and this is conceptrated at the golgi body cisternae where it is packaged in the secretory granules, though some remain in the cytoplasmic microvesicles. This is the stage where proinsulin is converted to insulin and C-peptide (**Steiner et al, 1974**). For the conversion of the proinsulin to

insulin, two types of proteolytic activity are necessary: a tryptic-like activity to cleave at the dipeptides located at the ends of the C-peptides and a Caboxypeptidase B activity - to remove the arginine dipeptide from the Caboxyl end of the B-chain leaving the B-30 residue intact. Research has also shown that although enzymes are thought to be responsible for the conversion of the proinsulin to insulin, only one such enzyme has so far been discovered and this takes place in the secretory granules . This suggests that the more mature a granule is, the less it will contain proinsulin, since newly formed granules contain mainly proinsulin. The proteolytic conversion of proinsulin to insulin is strictly an intracellular process and this is not inhibited by Cyclohaximide or other inhibitors of protein synthesis, indicating that transformation of proinsulin to insulin is not necessarily due to continuous protein synthesis.

INSULIN RELEASE

Glucose presence is not the only pre-eminent stimulus for insulin secretion. It is also one of the major regulators of insulin biosynthesis. The stimulation of the cells for insulin synthesis and release by the presence of glucose is thought of as being a kind of signal by the glucose or one of its metabolites. It has been shown that replica stimulation of insulin synthesis and release is possible in a low calcium medium though the extrusion of granules is inhibited under these conditions. Another stimulant for insulin release is the sugar called manose. Similarly, the glucose metabolites formed in the liver and the blood/tissue insulin level are thought to influence insulin secretion. **Lacy et al (1968), Howell and Lacy (1971), Malaise et al (1972), Gomez-Acebo and Hermida (1973)** showed that insulin release is by the process of exocytosis which is the movement of the secretory granules to the cell membrane where they fuse with it and

then the extrusion of their contents to the extracellular fluid. For detailed information on this mechanism, see **Ashcroft and Randle (Vallence -Owen) (1975).** While the above mentioned factors initiate insulin release, there are other factors that inhibit the release. There are mannoheptulose, absence of external Ca^{2+} (blocks secretory responses to all agents except Ba^{2+}) and other chemicals. On timely release of insulin, it is seen that its secretory response to glucose stimulation is biphasic where increased glucose concentration elicits within 0.5 - 1 minute, a rapid rise in the rate of the release, which returns to basal level within 5 - 10 minutes and this is followed by a more gradual increasing rise in the rate of insulin **(Glodsky, 1972).**

Similar biphasic release was seen when insulin release was stimulated by more of tolbutamide. These observations thus suggest the storage of insulin in two compartments, - the smaller being particularly labile to stimulants so that the limited phase of the insulin release is the emptying of this liable compartment; while the second phase release is from the larger storage compartment **(Grodsky, 1972)**

Insulin produced by the islet of langerhans of the pancreas are usually stored in case of need by the body mechanisms. In a normal person, the average basal insulin level in the blood is about 20μU/ml **(Arnold**, 1966). The daily insulin requirement is about 30-50μU while about 200 units are stored in the pancreas **(Campbell et al**, 1977). As earlier stated, the produced proinsulin is stored in the secretory granule and this is where its conversion to insulin takes place. This suggests that insulin is stored in the secretory granules and thus ever ready for release.

However, in the case of insulin-dependent diabetes Mellitus (IDDM), the insulin available to the cells for usage is very low so that amount released when the glucose concentration increases is low. It might also be that when the level is a bit high, there may be poor cell response to this

insulin even at high level of blood plasma glucose. This has been demonstrated in our analysis of the mathematical models.

When the insulin is used up, the replacement is possible by conversion of the produced proinsulin although it has been shown that this replacement is not based on a linear relationship. This means that the amount of insulin degraded is not at all times equal to the amount produced. Hence for long period of glucose charge, insulin response usually attain a peak and will not show any further appreciable increase in the plasma level. This means that after a long period of glucose charge, only the recently produced insulin is being released where the former stored quantity has been fully utilised as it is being released. Hence, continued glucose charge may eventually result in high blood plasma glucose level since the quantity of insulin produced and releasable may not be enough to take care of this high level.

INSULIN DEGRADATION

Since insulin is a hormone, it has to be degraded like any other one. Apart from its degradation as it helps in the conversion of the excess glucose to glycogen, it is being used for other bodily activities and these activities degrade it. It has been shown that the level of degradation of insulin varies from person to person and from man to woman. Even in women, the pregnant women degrade insulin more than the non-pregnant ones. However, in our model, we simply assumed an average and this has proved quite good in our analysis.

In general insulin degradation occurs in two ways;- reduction and proteolytic. The reduction process is encountered when insulin takes part in reaction or used up by cells as they act as enzymes in reactions in the body. This has been demonstrated by **Misky and Broh - kahn (1949)** as insulin is involved in enzymatic activity. This activity therefore reduces the amount of the insulin available for further reactions. Also certain enzymes in the body inactivate the biological

activity of the insulin. Such enzymes are called **"INSULINASE"** and they are considered to be proteolytic in nature.An example of such inctivating enzyme is "protein-disulphide-reductase ,(glutathione)". It inactivates the insulin by catalysing the reduction of the disulphate bonds of insulin and thus splitting of the insulin molecules. **Tomizawa and Varandani (1965), Varandani and Nafz (1969)** and **Chandler and Varandani (1974)** have isolated this glutathione in the liver, kidney and the leukocytes respectively. This glutathione also inactivates proinsulin and at the same time is involved in the reactivation of reduced and randomly oxidised proinsulin **(Varandani and Nafz, 1970a)**. However, excess inactivation of the insulin is controlled by another enzyme called the glucagon. Also, other growth hormones contribute in the control of insulin degradation. These enzymes help in the adjustment in the rate of insulin degradation to changing rate of insulin secretion and requirements.

MECHANISM OF INSULIN ACTION ON GLUCOSE LEVEL IN BLOOD

It has been said that the increase in the plasma glucose concentration induces insulin release and this insulin released in turn helps in the reduction in the level of this glucose in the same plasma. Also, to properly understand how this happens we will consider the action of the released insulin on the proteins (which form barriers to molecule entry into cells) in the plasma membrane.

Now, as the glucose concentration increases in the blood plasma, the pancreas are activated to release insulin. As this insulin is released into the extracellular fluid in the pancreas by exocytosis, it diffuses out into the blood stream and therefore is taken along to the appropriate sites, most especially the liver, for the required actions. At the liver, it diffuses into the extracellular fluids surrounding the liver cells where the insulin binds with the appropriate protein on the plasma membrane and gets aggregated thereby clearing the inhibiting actions of these

receptors to glucose transporters, which are also protein-like. Thus, the insulin binds with these receptors either in the phosphorylated form or the unphosphorylated form. This autophosphorylation of the insulin is what causes the agregation of the protein-receptors on the plasma membrane (**Quon & Campfield**, 1991) which we know are evenly distributed at the membrane surface when not activated by glucose charge ,(**Gavin et al, 1974; Lonnroth & Smith, 1983; Kosmakos & Roth, 1980**). This might mean that the level of entry of glucose into the cell depends on the insulin action since the area of the plasma membrane to be cleared of the inhibiting actions of the plasma membrane-protein depends on the insulin and its binding actions (**Jarett and Smith, 1979**). This action so treated is for the case of a normal person with normal insulin release and high glucose concentration in the blood plasma. However, if the individual is fasting, we have just the basal level of the insulin as always required in the body. This insulin level is such that it does not act on the glucose being converted from glycogen to glucose in the liver. Hence, we may say that if the glucose level in the blood plasma is of basal value, then the gateway to insulin action on plasma glucose level gets shut. Recall the earlier information that in the dearth of glucose in the blood plasma (and glycogen in the liver), the cells use the lipids in the production of the required energy and the converted glucose from the liver (from glycogen) are solely used by the brain and the nervous system. We recall also that insulin has been identified to have no effect on brain cell metabolism of glucose.

For the diabetic patient (**IDDM**), this binding action of the receptor-proteins is impaired. This impaired action negatively affects the amount of glucose that enters the cells and thus the high concentration of glucose in the blood plasma. Also in IDDM patient, there is reduction in production and release of insulin although the amount released follows the above described process in reducing the blood plasma glucose level.

Going by the result that insulin infusion into an IDDM patient corrects the high blood plasma glucose concentration, one may be tempted to say that the reduction in the available quantity of insulin affects the plasma membrane action on the glucose transporters. This has been considered in our analysis by varying the plasma membrane action. Result of this analysis is as shown in the discussion part of this thesis.

DIABETES

This is a term used to described a disease characterised by chronic high blood plasma glucose concentration (hyperglycaemia) and other disturbances of carbohydrate and lipid metabolism which are often associated with the development of specific microvascular and macrovascular complications. The most affected parts of such a patient are the eye and kidney as well as other vascular and coronary tissues.

This disease is characterised by passage of sweet urine, excessive urination and thirst, excessive hunger and weight loss. These complications usually result to death if left untreated for some period of time. Diabetes mellitus constitutes a group of disease with aetiologies and causes that are much more diverse than simple insulin deficiency. The detection of diabetes is based on the measurement of the fasting glucose level.

Diabetes mellitus are classified into many types and this classification is based on the classification of the group of disorders which constitute the disease, that is, it is based on the pathogenesis of the disease. One of the most acceptable methods of classification of this disease is the one based on the verification method. Diabetes mellitus is classified into three major subclasses: insulin-dependent, non-insulin dependant and others. In this our work, we shall strictly be interested in insulin-dependent diabetes mellitus (IDDM). In this type of the disease, the high

blood plasma glucose concentration is usually due to low level of insulin in the blood plasma. This low level of the insulin is as a result of diminishing rate of insulin production and secretion by the beta-cells of the islet of langerhans of the pancreas. This low level of insulin in the blood plasma causes reduction in the insulin action on the high glucose level so that instead of converting this excess glucose to glycogen for storage in the liver by the cells, it is excreted in the urine. **Czech and Massagne** (1982) stated that the concentration and regulation of the insulin receptors which are distributed on the surfaces of cells of chordates are influenced by the blood plasma insulin level, catecholamine as well as the glucocorticoid levels. This high level of blood plasma glucose has effects on the body of which the major ones are:

(a) Exerts large amount of osmotic pressure in the extracellular fluid which can cause cellular dehydration.

(b) Loss of glucose in the urine thereby reducing the available quantity of glucose to the cells of the body.

(c) The cause of the disease called Diabetes Mellitus.

However, the pathological physiology of all types of diabetes mellitus are:

(i) decreased utilisation of glucose by the cells in the body and hence an increase in the blood glucose concentration which may be as high as **300mg/100cc**.

(ii) acute metabolism and mobilisation of fats from the fat storage sites and thus causing abnormal fat metabolism and deposition of liquids in the vascular walls.

(iii) consequent depletion of proteins and fats in the tissues of the body.

(iv) detection of glucose in the urine and

(v) dehydrating effect.

As already stated, the IDDM is our concern in this study and it is characterised by the abrupt onset of symptoms, insulinopenia, proneness to ketoacidosis and dependence on injected

insulin to prevent ketosis and to sustain life. We have various levels of this disease such as juvenile, juvenile-onset, ketosis-prone and brittle diabetes. For more information on this , see **Ellenberg and Rifkin (1983).**

DIAGNOSIS OF DIABETES MELLITUS

There are many ways of diagnosing diabetes mellitus although an internationally accepted method, the glucose tolerance test, is always preferred. However, when diabetes mellitus is detected, further tests need to be carried out to know when it is IDDM or NIDDM (non – insulin dependent diabetes mellitus). In this method it is still not foolproof since it is usually based on abnormal carbohydrate tolerance and again this disease occurs even in conditions beside sugar diabetes. Thus, to clearly demonstrate that a given case is caused by abnormal carbohydrate tolerance, an abnormal standard oral glucose tolerance test has to be demonstrated and further shown that no other factor contributed to this abnormal result. The severity of Carbohydrate intolerance is instantly revealed by the height of the fasting blood sugar. The severity of the diabetes can thus be determined depending on this categorisation:

SEVERITY	RANGE OF FASTING BLOOD SUGAR
Normal Person	60---100 mg/100cc
Mild diabetic Person	60---105 mg/100cc
Moderately diabetic Person	106--200 mg/100cc
Severely diabetic Person	above 200 mg/100cc

Usually as can be seen from this table, the abnormal oral glucose tolerance curve of mild diabetes is indistinguishable from those found in many non-diabetic conditions. Hence, to correctly interpret a given tolerance curve requires awareness of the patient's total metabolic make-up.

Factors arguing for diabetes are those of positive family history or some specific clinical clues that gives a tip-off to its existence.

In analysis of the blood for its glucose level, the following facts must be known by the analyst:

(a) the actual method used

(b) whether it measures true sugar

(c) whether the blood being used is whole blood, plasma or serum and

(d) the fasting glucose levels for normal person when any of these blood sample types are used.

The knowledge of these facts is important because fasting glucose levels are not the same in the above three samples and again, the methods in use have also varying fasting blood glucose levels. An example can be shown by the table below:

	TRUE SUGAR AFTER OVERNIGHT FAST:	
CLINICAL STATUS	WHOLE BLOOD	PLASMA OR SERUM
Prediabetes	60---100 mg/100cc	70---115 mg/100cc
Mild diabetes	60---105 mg/100cc	70---120 mg/100cc
Moderate diabetes	106---200 mg/100cc	121---230 mg/100cc
Severe diabetes	above 200 mg/100cc	above 230 mg/100cc

However, the recommendation by the American National diabetes data group criterion is that diagnosis of diabetes requires fasting plasma glucose level of **140 mg/100cc** at least twice or the fasting blood glucose level of **120 mg/100cc**, although the renal glucose threshold rises with increase in age. Hence, we have cases of blood glucose being as high as **200 mg/100cc** though the person is not diabetic. This further suggests that the age of the individual in question need be taken into consideration when diagnosing diabetes. In diagnostic procedure, it is recommended that when

feasible, the blood should be taken from an **antecubital vein** within seconds of placing the tourniquet so as to avoid falsely high or low blood sugar value. The sample taken should be analysed the same day preferably. If the sample has to be taken from the **capillaries**, this has to be from the **heel, earlobe or finger tip** and this is equivalent to arterial blood sample. The capillary and venous blood levels are same after an overnight fasting. The capillary blood sugar is usually higher for the first two hours after meals since the tissues utilises postprandial hyperglycaemia. Also the plasma glucose levels are shown (as in the table) to be usually higher than those of the whole blood for an overnight fast. However, the plasma glucose level is preferred in determining the level of diabetes instead of the whole blood, for the following reasons:

(i) changes in plasma glucose level more accurately reflect the absorption, production and uptake of glucose than whole blood whose value is affected by dead space of red cell solids,

(ii) The plasma value is independent of the hematocrit where as the whole blood glucose rises by 3-4 mg/100cc for every each 10% fall in hematocrit and vice versa.

(iii) Plasma is more suitable than whole blood for analysis by the automated methods that are now replacing the manual methods in the laboratories.

METHODS FOR DETERMINING BLOOD GLUCOSE LEVELS

There are many methods used in the determination of the blood glucose level among which are; **Folin-wu, Somogyi-Nelson, Hoffman, Benedict, Hagedorn-Jensen, Folin-Malmros** and **glucose -Oxidase.** In determining this glucose level, they all use two basic reactions, namely; chemical reduction of the copper or ferricyanide by glucose or the interaction between glucose and

the glucose Oxidase which is an enzyme that reacts only with the specific form of the glucose found in the body fluids. The Folin-Wu method, even though clinically disqualified, is being widely used in the diagnosis of diabetes . However, acceptance of result of diagnosis performed by this method by a Clinician automatically indicates his not being interested in diagnosing mild diabetes. The details on the methods and also other factors contributing to diagnostic results are found in **Ellenberg and Rifkin (1983).**

CHAPTER TWO

LITERATURE REVIEW

Experimentally, it has been severally shown that the increase in the concentration of the plasma glucose results in the activation of the beta-cells of the islet of Langerhans of the Pancreas for the production and release of insulin. This released insulin have also been shown experimentally to affect this level of concentration of the plasma glucose. In this review however, we consider the mathematically oriented researches, most especially mathematical models, that have either shown these experimental behavioural pattern or disproved it. In the work of **Segre *et al* (1972)** on insulin kinetics in normal, diabetic and obese subjects, it was shown that insulin release in diabetic and obese subjects were not as pronounced as in the normal subjects. This means that there is a decrease in insulin response to increase in glucose concentration in the blood of these subjects. They also showed that there is a small increase in the glucose fasting level without a corresponding increase in the insulin fasting level. These results quite agree with the physiological pathology of insulin-dependent diabetes mellitus. **Porte and Pupo (1969)** showed in their work that there is a relationship between the glucose and insulin concentrations but that this relationship is non-linear. They equally stated that to give a fair prediction of the level of insulin release, one would have to know not only the glucose and insulin basal levels, carbohydrate tolerance and the size of the administered glucose, but that one is expected to know the previous history of the islets exposure to glucose. This has earlier been shown and **Orskov and Juel (1969)** showed that the insulin disappearance curve requires more than one compartment for correct interpretation. **Farquhar *et al* (1966)** showed that glucose kinetics requires more than one compartment . These information have been used when considering the mechanism of release of insulin and its action on glucose.

Grodsky *et al* (1968), Grodsky (1972) and **Sirotch *et al* (1970)** showed in their experimental and mathematical analysis that the insulin delivery rate of the beta-cells follow a proportional plus derivative type of control. Moreover, they showed that there is a time delay in insulin appearance in the blood and some oscillations in the glucose concentration with time. This oscillation can be explained experimentally by the compartmental and biphasic nature of release of insulin. **Sirotch *et al* (1970)** took notice of these facts and in their own model, had gone ahead to include the effect of the glucagon in the regulation of insulin and thus glucose level in the blood.

Kohn and Lemieux (1991) studied glycolysis in ascites tumour cells in the absence and presence of 125 mM exogenous glucose using graph theoretical modelling. They showed that the feedback regulation of the glucose level was widely distributed and in most cases due to binding of adenine nucleotide cofactors to the enzymes of the network. The addition of the glucose caused a change in the feedback regulation there by causing a relief of the inhibition of hexokinase and phosphofructokinase and thus the activation of the pyruvate kinase. This quite agrees with experimental information since addition of glucose leads to secretion of insulin and thus more entry of the glucose into the cells as the insulin binds with the receptor protein on the plasma membrane. **Brooks and Storey (1991)** further elucidated this conclusion by even suggesting that reversible binding of the phosphofructokinase to F-actin may represent cellular mechanism for controlling glycolytic flux during periods of increased metabolic demand.

For more rigorous mathematical demonstration of the mechanism of glucose and insulin control in the human system, **Subba Rao *et al* (1990)** formulated a mathematical model that even incorporated the beta-cell kinetics, glucose-insulin feedback system and the gastrointestinal absorption term for glucose. By solving these equations numerically and the subsequent analysis, they found that there is time variation of plasma glucose and insulin levels that quite agrees with the clinical observations in normal groups. However, by linear stability analysis, they also showed

that there is a change in the nature of the stability in the transition from the normal case to the insulin-dependent diabetes mellitus case. This was shown to be as a result of a decrease in the beta-cell functioning in insulin production. However, in their model, they did not consider the effect of the basal glucose level on the subsequent glucose and insulin levels. There was no interaction term that shows the non-linear nature of the glucose and insulin interaction in the human system. Also they considered the individual beta-cell rather than the aggregate insulin out-put though we know that some beta-cells may not even always produce insulin and that rate of insulin production and release is not necessarily a function of the number of beta-cells but somehow on the quantity of glucose administered and the level of exposure of these beta-cells to glucose charge

Further study on insulin kinetics using the same equations as **Subba Rao *et al* (1990)** was carried out by **Geevan *et al* (1990).** They validated the conclusions of **Subba Rao *et al* (1990)** but the analysis this time was by sensitivity analysis and the earlier conclusion are found to be clinically correct. **Hammond *et al* (1991)** studied the insulin distribution and uptake in the perfussed rat liver using mathematical models. The model allows for the determination of the vascular and sinusoidal volumes of the insulin together with the binding and the endocytic rate constants. The model also allowed for the simulation of the internal distribution and uptake of insulin pattern with any nominated input function and any set of parameters.

Quon and Campfield (1991 a) formulated mathematical models which explicitly represents the various molecular mechanisms thought of to contribute to insulin receptor regulation. With this model, they were able to reproduce the Ligard-induced down and up regulations of receptor as well as the initial spontaneous display of surface insulin receptors. Even though they have no data to validate these their claims, they believed that their model structure is sufficient to explain the insulin receptor regulation in a wide cell types and this mechanism explains the glucose and insulin interaction mechanism. In continuation of the quest for proper

understanding of the mechanism of interaction of the glucose and insulin in the control of the plasma glucose concentration. **Quon and Campfield (1991 b)** formulated another mathematical model and Computer simulation for the study of insulin sensitive glucose transporter regulation. With the model, they were able to correctly simulate the insulin sensitive, insulin concentration dependent, reversible translocation of glucose transporters as observed with increase in cell surface area . The model also can simulate pathogenic states which induce impairment of glucose transporter regulations. They concluded their work by saying that since their model can sufficiently explain glucose transporter regulation in both normal and pathological states, the model can also be of aid in the understanding of the post-receptor components of insulin resistance as seen in the insulin-dependent diabetes mellitus. **Butte (1992)** in his study showed that a change in the concentration of the insulin at the cell surface causes a change in the translocation of the transporters in the cell. This movement of the transporters helps in the maintenance of the basal level of the insulin or in the storage process of the excess glucose in the blood.

Davis (1962) modelled the glucose and insulin variation in concentration due to factors common to glucose and insulin existence in the human cells, for a normal and diabetic **(IDDM)** patient. In the model, he neglected the effect of the body cell degradation of glucose. The cells in the body as we know readily uses glucose in the provision of energy it needed for the maintenance of life once the glucose concentration is enough in the blood. Neglecting this action is an over simplification and thus this fact is included in the current study. He similarly considered the effect of the basal level of the glucose on further increase in insulin level without necessarily considering the fact that this also affects the subsequent glucose level, **Porte and Pupo (1969, 1973).** However, with these simplified assumptions, he was able to get results that compared well with experimental observations.

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In the current study, we consider an insulin-dependent diabetic patient. This patient feeds normal so that there is no continuos glucose charge of the beta-cells although the patient has high blood glucose level. The effect of the basal level of the glucose in the determination of the subsequent levels of the insulin and glucose are taken note of. Futher more, the effect of the cell metabolism of the glucose is also taken note of. Since the model is for a diabetic patient, it is expected that with insulin infusion, a normal curve as for an oral glucose tolerance test should be repeoduced. Hence in the model, insulin infusion is incorporated as this is the simplest way of correcting the disease if it is actually an insulin-dependent one. An analytical method (based on approximating XY to XY) shall be adopted, as against the numerical method, although with some approximation which has been tested with the numerical solution and found to be sufficiently good for finding the solution to the model and the subsequent analysis.

CHAPTER THREE

THE MODELS

A mathematical model describing the variations in the plasma glucose and insulin levels in an insulin -dependent diabetic patient over time is formulated here. As stated earlier, the effect of the cell metabolism as well as basal level of the glucose are to be taken care of in this formulation. Even though the insulin actions are intertwined, we shall formulate the variational equations separately with proper representation in each of the interactions between them. To show that the presence of one affects the existence of the other, we shall solve the resulting two equations simultaneously.

We shall denote the glucose level by **X** with the corresponding insulin level by **Y** ,all functions of time. Similarly, let $\mathbf{X_0}$ and $\mathbf{Y_0}$ denote the basal glucose and insulin levels respectively. By basal level here, we mean the glucose and insulin levels after an overnight fast of about 12 hours. We shall equally take it that the patient feeds normal (about three meals daily) before the initiation of the treatment so that the effect of continuos exposure of the islet to glucose charge may not arise.

GLUCOSE

As stated earlier, this is the form that the carbohydrate we eat are absorbed and metabolised by the cells of our body. Knowing that the blood plasma glucose level varies at all times, we consider the following as the principal factors that cause this:

(1) Glucose input either in the form of feeding or Oral glucose administration.

(2) In extreme high blood glucose concentration, the glucose is quickly converted to glycogen which is the storable form of the glucose in the liver and the muscles.

This conversion helps in the reduction of the blood plasma glucose concentration.

(3) Natural glucose breakdown by the cells of our body so as to get the energy needed for the maintenance of life of the individual.

(4) In long period of fasting, the liver and the muscles will release the stored glycogen and fats for conversion to glucose in order to raise the blood plasma glucose level, at least to the basal level or to sustain the brain and the nervous cells.

Having stated these factors, we now separately consider the effects of them mathematically, on the plasma glucose level after which they shall be joined together to form one general equation.

Case I

According to **Davis (1962)**, if we represent the quantity of glucose taken by **Q** and K denotethe delay parameter associated with time taken to take or eat the food, we see that the effect of this food on the plasma glucose level is described by the differential equation:

$$\frac{dX}{dt} = a_1 Z(t) = a_1 Q e^{-k(t-t_0)} \quad \text{..... (1)}$$

where a_1 is a constant associated with the quantity of food taken, the exponential term depicts the decaying form of the glucose in the blood as time progresses with t and t_o as the subsequent time and initial time respectively. This shows that the effect of the food (glucose) intake tails off after some time.

Case II

Let us recall the report of **Porte and Pupo (1969)** which demands that the effect of the level of glucose at the time in question must be taken into consideration in determining the subsequent levels of the glucose and or insulin. Suppose that the time of interest is t_o and that the level of glucose at such a time is $X_1(t_o)$ where $X_1(t_o) \geq X_o$. Let $X = X_1(t_o) + X_o$ so that

$$X_1(t_o) = X - X_o .$$

This means that $X \geq 0$ and it measures the difference between the plasma glucose at the time of interest and the basal plasma glucose level. Similarly, let $Y = Y_1(t_o) + Y_o$. Then the change in the glucose level due to the glucose and insulin interaction with one another which we assume as earlier reported to be non-linear is given as:

$$\frac{d(X_1 + X_o)}{dt} = - a_2 (X_1 + X_o)(Y_1 + Y_o) \quad \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

where a_2 is a constant which measures the carbohydrate tolerance by the cells in terms of response of receptor aggregation in the presence of insulin due to high plasma glucose level. We may further simplify this equation by putting $X_1 + X_o = X$ and $Y_1 + Y_o = Y$. Hence, we have the equation (2) as:

$$dX/dt = - a_2 XY \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

Case III

The amount of glucose being broken down to supply energy to the cells of the body depended on a lot of factors. However, we shall consider an ideal situation in which there is

no further demand for energy by the cells due to extra activities and that the energy need is just for the maintenance of life. In such a situation, the energy need is constant so that the glucose utilisation by the cells is fairly constant also. We shall state however that this energy need is not dependent so much on the level of the glucose in the blood unless in a very long period of fasting when energy needs are now being sourced from other nutrients except for brain and nerve cells. Hence, the variation in the plasma glucose contributed by this factor is described in differential form as:

$$dX/dt = -a_3 X \quad \text{for all } t \qquad \ldots\ldots\ldots\ldots (4)$$

where a_3 is the parameter that measures the rate of degradation of the glucose by these cells.

Case IV

In a normal patient, when there is long time interval between meals, the plasma glucose level tend towards the basal level. Depending on the insulin level, the glucose level may even go below X_o and thus another illness called Hypoglycaemia. However, this is not the case since this is quickly corrected by the accurate response of the liver in releasing some of the stored glycogen which are reconverted to glucose and this then raises the blood glucose level to at least the basal level and at the same time meeting up the energy need of the body cells. Hence, the contribution of this process to the over all plasma glucose variation is described by the differential equation

$$dX/dt = a_4 (X_o - X), \qquad X < X_o \qquad \ldots\ldots\ldots\ldots (5)$$

where a_4 is a constant related to the amount of the glycogen released to

be converted to glucose so as to meet up the need of the cells and also to maintain the basal level to the accepted level.

Having considered the four cases, we may now collect the equations together to get one general equation involving all these factors as:

$$dX/dt = a_1Z(t) - a_2XY - a_3X + a_4(X_0 - X)$$

$$= a_1Q\, e^{-(t - t_0)} - a_2XY - a_3X + a_4(X - X_0) \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (6)$$

INSULIN

Having discussed the biosynthesis, storage and release of insulin, we simply enumerate some of the factors that affects this insulin release where it is assumed that it has been synthesised. Even for a diabetic patient, most especially for an insulin-dependent diabetic one, there is low synthesis of the insulin and some of the factors to be mentioned here affects the release and even the production tremendously. As stated in the introduction, the insulin need to bind with the receptors before it can aggregate these receptors and therefore make passage of the glucose into the cells more easier. This action thus lead to reduction of the plasma glucose level and the binding action of the insulin also reduce the plasma insulin level. Similarly, some enzymes inactivates the insulin and the level of insulin varies according to body need. We put the factors affecting the plasma insulin level in summary form as:

(1) the blood glucose level

(2) body degradation of the insulin which shall include all forms that leads to the reduction of the available active insulin in the blood.

(3) external insulin administration since the insulin level is low and the blood glucose level is high.

As earlier stated in the introductory part, any thing that causes a change in the amount of insulin released , also affects the cell response to the glucose and thus a change in the insulin action on the plasma glucose level. Thus for an insulin-dependent diabetic patient who has a low insulin producing and release level, the rate of action of the level of insulin on the glucose level in the blood must also be low. Thus let us now formulate the mathematical relations or models of these factors to the plasma insulin level.

Case I

According to **Porte and Pupo (1969)** , the subsequent level of insulin over time in the plasma shall be truly represented by taking into consideration the basal level or the level of the glucose at the time of interest, along with other factors. Let the initial time be t_o so that $Y(t_o) \geq Y_o$ is the initial insulin concentration at such time. Hence, the plasma insulin variation due to plasma level is described by the differential equation:

$$d(Y_1 + Y_o)/dt = b_1(X_1 + X_o)$$

same as $$dY/dt = b_1X \quad \text{.....(7)}$$

where b_1 takes care of or modulates the insulin response in terms of binding with the receptor proteins and thus glucose tolerance.

Case II

As already stated, the insulin degrades by certain biochemical processes. Also stated is the non-uniformity in the level of degradation in human beings. Considering that the level of plasma

glucose affects the plasma insulin level and using b_2 as the measure of the level of degradation of the insulin, we have the equation showing the effect of this degradation on plasma insulin level as:

$$d(Y_1 + Y_o)/ dt = - b_2 (Y_1 + Y_o)$$

$$dY/dt = - b_2Y \quad \text{---------- (8).}$$

Case III

For the correction of the high plasma glucose concentration, insulin infusion becomes the only solution since the pancreas can not produce or release enough insulin that can appropriately control this level. We denote this quantity of insulin infused by $\omega(t)$. Here the equation representing the plasma insulin variation due to this insulin infusion is given as

$$d(Y_1 + Y_o) /dt = b_3\, \omega(t) \qquad \text{which is same as}$$

$$dY/dt = b_3\omega(t) \quad \text{---------- (9)}$$

where b_3 is a constant.

We may however wish to say that when a given drug is injected into the skin of a patient, not all the quantity or dose of the injected drug finally gets into the blood. Some quantity of it are held at the interstitial spaces between the cells while some are immediately used up by surrounding cells. Thus the amount of this insulin injected into the patient, (not by intravenous means), that finally gets into the blood to measure the peak must be then less than the actual dose given. Taking note of this when writing down the exact expression for the $\omega(t)$ while solving, we have the general

differential equation showing the plasma insulin variation over time due to the above mentioned factors as:

$$dY/dt = b_1 X - b_2 Y + b_3\ w(t) \qquad \text{----------} (10)$$

where we have for simplicity defined w(t) as:

$$w(t) = \begin{cases} w_o(t - t_o)/(\bar{t}-t_o), & t_o < t \leq \bar{t} \\ \dfrac{-w_o\,(t-(2\bar{t}-t_o))}{\bar{t}-t_o}, & \bar{t} \leq t < 2\bar{t}-t_o \\ o, & \text{elsewhere.} \end{cases} \qquad \text{---------- (11)}$$

Here, $\bar{t}$ stand for the half life of the drug. For this insulin, this $\bar{t}$=0.5 hour, However, in our equation, this is modified to

$$w(t) = \gamma t + \delta. \qquad \text{----------(12)}$$

Hence, the two important modelled equations to be considered and solved and to be used for the subsequent analysis are:

$$dX/dt = a_1 Q\, e^{-k(t-t_o)} - a_2 XY - a_3 X + a_4 (X_0 - X) \qquad \text{..... *}$$

$$dY/dt = b_1 X - b_2 Y + b_3 w(t) \qquad \text{----------**}$$

As earlier said, they are to be solved simultaneously by the analytical method .

CHAPTER FOUR

SOLUTION OF THE EQUATIONS FOR AN IDD PATIENT:

We wish to control the plasma glucose in the blood of an insulin dependant diabetic patient such that the term $a_4 (X_o - X)$ does not form part of the model as we require that for $t > t_o$, then $X > X_0$ Forther more, the equation is non-linear so that to apply the analyticalmethod, we need to linearise the non-linear term XY. This we shall do by approximating the value of X in the term by $\bar{X}$ where $\bar{X}$ is the value of X at any time of interest. Thus , at $t = t_o$, we have $\bar{X} = X_0$ and at any other time $t = t^*$, $\bar{X} = X^*$. With these modifications, the model equation becomes:

$$dX/dt = a_1 Qe^{k(t - t_o)} - a_2 \bar{X}Y - a_2 X \quad \text{---------- (1)}$$

$$dY/dt = b_1 X - b_2 Y + \gamma t + \delta \quad \text{----------(2)}$$

These equations shall be solved simultaneously by finding the complementary and particular solution which shall, when added up, will give the general solutions. Thus let the complementary solution to these equations be:

$$\begin{pmatrix} Xc \\ Yc \end{pmatrix} = \begin{pmatrix} \varepsilon \\ \eta \end{pmatrix} \ell^{\lambda t} \quad \text{---------- (3)}$$

From equation (1) and (2), the complementary parts of the equations are:

$$dX/dt = - a_2\bar{X}Y - a_3X \quad \text{----------(4)}$$

$$dY/dt = b_1X - b_2Y \quad \text{----------(5)}$$

from where we obtain a matrix say

$$T = \begin{pmatrix} -a_3 & -a_2 \bar{X} \\ b_1 & -b_2 \end{pmatrix} \quad \text{.....(6)}$$

The eigen - values of this matrix are got by solving for λ in the matrix :

$$\begin{pmatrix} -a_3 - \lambda & -a_2\bar{X} \\ b_1 & -b_2 - \lambda \end{pmatrix}$$

Hence, $\lambda = 0.5\,[\,-(a_3 + b_2) \pm \{(a_3 + b_2)^2 - 4(a_3b_2 + a_2b_1\bar{X})\}^{1/2}]$ ------ (7)

Secondly we find particular solutions for the equations in terms of the **Z(t)** and **w(t)** respectively. We shall denote the particular solutions by

$$\begin{pmatrix} X_z \\ Y_z \end{pmatrix} \quad and \quad \begin{pmatrix} X_w \\ Y_w \end{pmatrix}$$

Thus we have that

$$\begin{pmatrix} X_z \\ Y_z \end{pmatrix} = \begin{pmatrix} D \\ E \end{pmatrix} \ell^{-k(t-t_o)} \qquad \text{----------(8)}$$

Let us differentiate this equation (8) with respect to t and substitute into the equations

$$dX/dt = a_1 Q e^{-k(t-t_0)} - a_2 \bar{X}Y - a_3 X$$

$$dY/dt = b_1 X - b_2 Y$$

We then have

$$-kDe^{-k(t-t_0)} = a_1Qe^{-k(t-to)} - a_2\bar{X}Ee^{-k(t-to)} - a_3De^{-k(t-to)}$$

and

$$-kEe^{-k(t-t_0)} = b_1De^{-k(t-to)} - b_2Ee^{-k(t-to)}$$

These simplify into:

$$-kD = a1Q - a_2\bar{X}E - a_3 D$$

$$-kE = b_1D - b_2E$$

which gives: $(a_3 - k)\,D + (a_2 \bar{X})E = a_1 Q$

$$(b_2 - k)E - b_1 D = 0.$$

To find the values of **E** and **D** which satisfies this simultaneous equation, we have

$$\begin{pmatrix} a_3 - k & a_2 \bar{X} \\ -b_1 & b_2 - k \end{pmatrix} \begin{pmatrix} D \\ E \end{pmatrix} = \begin{pmatrix} a_1 Q \\ o \end{pmatrix}$$

Now $\begin{vmatrix} a_3 - k & a_2 \bar{X} \\ -b_1 & b_2 - k \end{vmatrix} = k^2 - (b_2 + a_3)k + a_3 b_2 + a_2 b_1 \bar{X} = Z$ ------(9)

However solving we have:

$$D = a_1 Q(b_2 - k)/Z \qquad \text{----------(10)}$$

$$E = a_1 b_1 Q/Z \qquad \text{----------(11)}$$

Thus the particular solution with respect to **Z(t)** is given as

$$\begin{pmatrix} X_z \\ Y_z \end{pmatrix} = 1/Z \begin{pmatrix} a_1 Q(b_2 - k) \\ a_1 b_1 Q \end{pmatrix} \ell^{-k(t-t_o)} \qquad \text{----------(12)}$$

For the second particular solution with respect to the term w(t), we have :

$$\begin{pmatrix} X_w \\ Y_w \end{pmatrix} = \begin{pmatrix} A \\ \beta \end{pmatrix} t + \begin{pmatrix} \boldsymbol{c} \\ F \end{pmatrix} \qquad \text{----------(13)}$$

We differentiate this solution and substitute into the equations:

$$\mathbf{dX/dt = -a_2 \bar{X} Y - a_3 X}$$

$$\mathbf{dY/dt = b_1 X - b_2 Y + b_3(\gamma t + \delta).}$$

We then have:

$$\mathbf{A = -a_2 \bar{X}\,(Bt + F) - a_3\,(At + C)}$$

$$\mathbf{B = b_1\,(At + c) - b_2\,(Bt + F) + b_3(\gamma t + \delta).}$$

On simplifying these two equations, we have

$$-(a_2\bar{X}B + a_3 A)\,t - (a_2\bar{X}F + a_3C) = A$$

$$(b_1 A - b_2 B + b_3\gamma)t + b_1C - b_2F + b_3\delta = B.$$

Solving for the values of **A,B,C** and **F**, we have

$$A = -b_3a_2\bar{X}\gamma/m$$

$$B = b_3\gamma a_3/m$$

$$C = b_3a_2\bar{X}\gamma(a_3b_2 + a_3^2)/(a_3m^2) - b_3a_2\bar{X}\delta/m$$

$$F = b_3\delta a_3/m + b_3(b_1a_2\bar{X} - a_3^2)\,\gamma/m^2$$

where $m = b_2 a_3 + a_2b_1\bar{X}$

With these values, we have the solution with respect to **w(t)** written completely as:

$$\begin{pmatrix} X_w \\ Y_w \end{pmatrix} = \frac{b_3}{m}\begin{pmatrix} -a_2\bar{X} \\ a_3 \end{pmatrix}\gamma t + \begin{pmatrix} +a_2\bar{X}\gamma(b_2a_3 + a_3^2)/(a_3m^2) - a_2\bar{X}\delta/m \\ \delta a_3/m - \gamma/m^2\left(a_3^2 - a_2b_1\bar{X}\right) \end{pmatrix} \quad \text{---(14)}$$

With these result, the general solution to equation (1) and (2) are

$$X = X_c + X_z + X_w \quad \text{----------(15)}$$

$$Y = Y_c + Y_z + Y_w \quad \text{----------(16)}$$

which when we substitute appropriately are given as:

$$X = \varepsilon e^{\lambda t} + a_1Q/Z\,(b_2\text{-}k)e^{-k(t\text{-}to)} - b_3a_2\bar{X}\gamma t/m + b_3a_2\bar{X}\gamma(b_2a_3+a_3^2)/(a_3m^2) - a_2\bar{X}\delta/m \quad \text{.....(17)}$$

and

$$Y = \eta e^{\lambda t} + a_1\,b_1Q/Z\,e^{-k(t\text{-}to)} + b_3\,a_3\,\gamma t/m + b_3\,\delta a_3/m - b_3\gamma/m^2\,(a_3^2 - a_2b_1\bar{X}) \quad \text{.....(18)}$$

solution above, we have two unknown constants, namely, ε and η of which their values need to be determined explicitly. We recall that these constants are associated with the complementary solutions so that since λ has two values, we have

$$X_c = \varepsilon_1 e^{\lambda 1 t} + \varepsilon_2 e^{\lambda 2 t} \quad \text{----------(19)}$$

$$Y_c = \eta_2 e^{\lambda 1 t} + \eta_2 e^{\lambda 2 t}$$

Deferential (19) with respect to time t, we have on substituting into the complementary equations that

$$\lambda_1 \varepsilon_1 e^{\lambda 1 t} + \lambda_2 \varepsilon_2 e^{\lambda 2 t} = -a_2 \bar{X} Y_c - a_3 X_c \quad \text{----------(a)}$$

$$\lambda_1 \eta_1 e^{\lambda 1 t} + \lambda_2 \eta_2 e^{\lambda 2 t} = b_1 X_c - b_2 Y_c \quad \text{----------(b)}$$

Using (a), we have

$$(\lambda_1 + a_3)\varepsilon_1 e^{\lambda 1 t} + (\lambda_2 + a_3)\varepsilon_2 e^{\lambda 2 t} = -a_2 \bar{X} \eta_1 e^{\lambda 1 t} - a_2 \bar{X} \eta_2 e^{\lambda 2 t}$$

$$\therefore \eta_1 = -(\lambda_1 + a_3)/(a_2 \bar{X})\varepsilon_1 \text{ and } \eta_2 = -(\lambda_2 + a_3)/(a_2 \bar{X})\varepsilon_2 \quad \text{..... c}$$

Hence, substituting for η_1 and η_2 in equations (17) and (18) , we get

$$X = \varepsilon_1 e^{\lambda 1 t} + \varepsilon_2 e^{\lambda 2 t} + a_1 Q/z\,(b_2 - k)e^{-k(t-to)} - b_3(a_2 \bar{X}/m)\gamma t$$

$$+ b_3 a_2 \bar{X} \gamma (b_2 a_3 + a_3^2)/(a_3 m^2) - b_3 a_2 \bar{X}\,\delta/m \quad \text{..... (20)}$$

$$Y = -(\lambda_1 + a_3)/(a_2 \bar{X})\varepsilon_1 e^{\lambda 1 t} - (\lambda_2 + a_3)/(a_2 \bar{X})\varepsilon_2 e^{\lambda 2 t} + a_1 b_1 Q/Z\, e^{-k(t-to)}$$

$$+ b_3 a_3 \gamma t/m + b_3 \delta a_3/m - b_3 \gamma (a_3^2 - a_2 b_1 \bar{X})/m^2 \quad \text{----------(21)}$$

Also, the explicit value of ε_1 and ε_2 are not known so that solving for them using equations (20)

and (21), we get

$$\varepsilon_1 = (\lambda_2 + a_3)/(\lambda_1 - \lambda_2)\, e^{-\lambda 1\, t^*} \{a_1 Q(b_2 - k)/Z\ e^{-k\,(t^* - to)} + b_3 a_3 \gamma t^*/m$$

$$+ b_3\, a_2 \bar{X} \gamma (b_2 a_3 + a_3^2)/(a_3 m^2) - b_3 a_2 \bar{X} \delta/m - X^*\}$$

$$+ (a_2 \bar{X} e^{-\lambda 1\, t^*})/(\lambda_1 - \lambda_2)\, \{a_1 b_1 Q/Z\, e^{-k(t^* - to)} + b_3 a_3 \gamma t^*/m + \delta a_3\, b_3/m$$

$$- b_3 \gamma (a_3^2 - a_2 b_1 \bar{X})/m^2 - Y^*\} \qquad \text{.....(22)}$$

and

$$\varepsilon_2 = (\lambda_1 + a_3)/(\lambda_2 - \lambda_1)\, e^{-\lambda 2\, t^*} \{a_1 Q(b_2 - k)/Z\, e^{-k(t^* - to)} - b_3 a_2 \bar{X} \gamma t/m$$

$$+ b_3 a_2 \bar{X} \gamma (b_2 a_3 + a_3^2)/(a_3 m^2) - b_3 a_2 \bar{X} \delta/m - X^*\}$$

$$+ a_2 \bar{X} e^{-\lambda 2\, t^*}/(\lambda_2 - \lambda_1)\, \{a_1 b_1 Q/Z\ e^{-k(t - to)} + b_3 a_3 \gamma t^*/m$$

$$+ b_3 \delta a_3/m - b_3 \gamma (a_3^2 - a_2 b_1 \bar{X})/m^2 - Y^*\} \qquad \text{.....(23)}$$

Substituting these values of ε_1 and ε_2 into equations (20) and (21) gives the complete solution to equations (1) and (2). All the constants are known or can be estimated from the detailed information that are obtainable when a problem is presented. The time t* represents the time of interest and can assume various values such as the initial time t_o if we are referring to what happens to the glucose and insulin levels at such time . The essence of the time t* other than t_o is that ε_1 and ε_2 are to be determined at times other than t_o most especially as we now have insulin infusion to determine the plasma glucose and insulin levels and this insulin has a $t_{1/2}$ value that presents different glucose responses to the levels of the insulin at such a time. The X* and Y* stands for the amount of glucose and insulin respectively in the plasma at such a time t*. The change in X* and Y* have the same importance as stated in the case of t*.

CHAPTER FIVE

RESULTS

In formulating these mathematical models used in the determination of the plasma glucose and insulin levels, many variables as stated earlier were appropriately built in and thus we had a fairly good model. Of particular importance to be mentioned among the parameters here is the pancreatic (Islet) response via insulin release when activated by the high plasma glucose concentration. In the study of **Quon and Campfield (1990 a&b),** they considered this as beta-cell kinetics. However, in our model, we feel that it should not be so but rather the net insulin release by the pancreas since not all the beta-cells release insulin. The release by the individual beta-cell is dependent on many factors such as level of activation by the glucose concentration, the healthy state of the beta-cell, age of the beta-cell , and many more. Another important factor that needsto be mentioned here is the cell response to the high plasma glucose concentration. Research has shown that cases abound where insulin level is high in the plasma and there is still high glucose level in the plasma. The cause of this high plasma glucose concentration is low cell response to high plasma glucose and insulin concentrations. The effect of cell responses to plasma glucose and insulin level has been demonstrated in our analysis in terms of transport of glucose into the cell.

The mathematical model describing the plasma glucose and insulin variation in concentration are shown by equation (1) and (2) in the form of ordinary differential equations. The solution to these equations which were solved simultaneously were given by equation (20) and (21) with equations (22) and (23) being the expressions for the constants ε_1 and ε_2. It is these solutions that are used for all the forthcoming analysis and the subsequent conclusions.

METHODS OF ANALYSIS AND ANALYSIS

For the analysis of the mathematical models using the solution to equations (1) and (2), we have to recall that for an insulin dependent-diabetic patient, the values of the parameters are not the same with a normal person's own. Except in extremely starving condition, the body cell requirement for energy provision is still the same. Hence the first step in the analysis of the model is the choice of values for the constants. The values for the constants are $a_2 = 0.02 - 0.05$, $b_1 = 0.03 - 0.25$, $a_3 = 0.02 - 0.04$, $Q = 10, 25, 50$ and 100 units, $w(t) = 6.5, 10$ and 20 units, $b_3 = 1.0$, $a_1 = 4.0$ and $k = 4.16$ with the parameters having same meaning as earlier stated. In the method of solution of these mathematical model equations, we had defined w (t) as

$$w(t) = \begin{cases} \dfrac{w_o(t - t_o)}{\bar{t} - t_o}, & t_o < t \leq \bar{t} \\ \dfrac{-w_o(t - (2\bar{t} - t_o))}{\bar{t} - t_o} & \bar{t} \leq t < 2\bar{t} - t_o \\ 0 & \textit{else where} \end{cases}$$

or further as

$$w(t) = \Upsilon t + \delta$$

It is known that not all the dose injected into the body unless by intravenous injection gets into the blood stream for usage. Certain quantity of the dose is usually held by the cell through which the fluid diffuses into the blood stream. It is assumed that absorption of the insulin injected must have almost been completed in the time t which we assumed have to be about 0.5 hours so that if the injection was given at 8.00 hours, the absorption is completed at about 8.50 hours. Similar time interval is assumed for the disappearance of the injected insulin. With this information

at the back of our mind, we find that for the 20 units injection, w(t) will be represented in terms of Υ and δ as:

$$\omega(t) = \begin{cases} 40t - 60b_1 - 320 \ , & t_o < t \le \bar{t} \\ -40t - 60b_1 + 360 \ , & \bar{t} \le t < 2\bar{t} - t_o \\ 0 & \text{elsewhere} \end{cases}$$

Hence, $60b_1$ measures the severity of the insulin dependent diabetes Mellitus. If the diabetes is severe, it is expected that not much of the dose will be held in the cells, since its concentration in the blood is very low. However if otherwise, the cell usually hold much of the dose as the glucose level equally stimulate the pancreas to release insulin and this tend to increase the plasma insulin level. Also, the severity of the diabetes affects the peripheral cell usage of the injected insulin. Hence, $60b_1$ measures the quantity of the insulin that is held at the inter and intracellular spaces. This description of the insulin-injected in the plasma is realistic enough going by the real experimental knowledge of drug kinetics in the human system and the fact that it correctly estimates ω(t) at both sides of $\bar{t}$ and at $\bar{t}$ itself. Similar model for ω(t) is developed when the dose decreases in value.

To actually carry out the analysis, we bear in mind that apart from correcting the disease, we need to see the effect of the variables in the determination of the plasma glucose and insulin concentrations. To study the effects, we first have to fix b_1 and vary a_2 after which we fix a_2 and vary b_1. Later, both b_1 and a_2 are varied. Equally, we hold every other parameter constant and vary a_3 to see its effect on the overall plasma glucose and insulin concentration. Also, a_3 is varied along with a_2, b_1 and even Q. Later, control measures of the disease is studied. Hence, certain quantity of the insulin is recommended to be injected into the patient, one at the time of breakfast and the other at the time of the dinner. It is expected that the morning dose should sustain the patient till the night dose. Also, correct quantity of food to be taken at breakfast, lunch and dinner

should be correctly estimated so that the insulin should not plunge the glucose level below the plasma basal level and thus causing another disease called Hypoglycaemia. It is expected that the night dose should be smaller than the morning dose so that the plasma glucose level should not be seriously plunged below basal level before the breakfast meal. It may have to be stated that due to the fact that the basal level of the plasma glucose is usually very high (175 - 230 mg/100cc) for a severe insulin-dependent diabetic patient, the initial dose of food and or insulin may not be same as the subsequent ones and this has to be verified if true. Similarly, the times for the meals has to be determined and reasons for the choice of these times clearly justified. The general intention in carrying out this type of corrective measure is that we want the patient to have normal glucose and insulin curves with minimal disturbances.

To show the beauty of this corrective measure, comparison is made about the palsma glucose and insulin curves for an insulin - dependent diabetic patient with and without insulin infussion. Also the normal curves with the diabetic curves for plasma glucose and insulin levels need to be shown for various degreesof diabetism. These later curves should clearly show the importance of the insulin infusion.

The final point of our analysis is the comparison of the curves resulting from this method of solution with that of the numerical solutions of the same linearised and non-linearised forms of the equations since the numerical solutions have been extensively used by many authors in carrying out their analysis and in particular since **Davis (1962)** used numerical approach in his analysis and the analysis was accepted as good, then a close agreement between our method and this numerical method should make it acceptable enough for similar analysis since the mathematical formulation of the model is theoretically good and correct.

To conclude the study, far reaching decisions are expected to be made about the doses of the insulin to be used and when. Also depending on the severity of the diabetes and then the dose

of the insulin to be infused, the required quantities of food and snacks has to be determined along with when they should be taken. The major determinants of the level of plasma glucose level has to be named and a cross check with the theoretical or experimental results have to be made to find how valid the conclusion is. If possible, further method of advancement of the model or the method of solution has to be suggested which may not have been treated in the present study.

Of importance to be noted is the method of choice of the constants. Some of them (b_3, a_3 , a_1) have been chosen arbitrarily while a_2, b_1, and b_2 have been experimentally determined to be so **(Porte and Pupo 1969), Subba -Rao et al 1990; Campbell et al, 1977).** However, it clearly has to be stated that as many as there are mathematical models describing a given biological event or system, so are the variations in some of the involved constants or parameters. The prime objective of such choices is that the model should present a realistic description of the event or system.

DISCUSSIONS

We start this discussion by explaining why we chose the values of the parameters as such. For a start, the parameter a_1 is an arbitrary constant which is tied to the quantity of the food taken and thus could be changed depending on the food quantity. However, it has to be chosen in such a way that with other parameters known, a comparatively realistic result will be obtained.

The parameter a_2 has its value obtained from experimental works. This a_2 measures the plasma glucose sensitivity to the plasma insulin level, in other words, the interaction of the plasma glucose and insulin in connection with the glucose into the body and liver cells. In a normal person, increase in the plasma insulin usually initiate greater interaction and this is in the form of greater binding rate of the insulin with the protein receptors at the plasma cell membrane and thus quicker entry of the glucose into the cell, particularly the liver cells. The chosen value for a_2 can be

supported by the studies of **Porte** and **Pupo (1969), Davis (1962), Insel et al (1975),** and even **Subba-Rao et al (1990).** The parameter a_3 has its value chosen arbitrarily although with the consideration that the rate of clearance of the plasma glucose due to the interaction between the glucose and insulin is greater than the rate of clearance by the body cells. In the same way, b_1 has been chosen after due comparison of practical works and observation of other researchers. For a normal person, b_1 was chosen as 0.5 while for an insulin-dependent diabetic patient, $\mathbf{b_1 << 0.5}$. As earlier said, this measures the sensitivity of the pancreas (islet) to glucose stimulation. In the choice of the value of b_2, consideration was made of the half life of insulin and experimentally, this has been shown to be between 2 0 and 30 minutes. With this information, b_2 was calculated to be between 2 and 3 so as to satisfies this condition although in our analysis, we decided to choose the lower limit. **Porte and Pupo (1969)** had stated this value while **Davis (1962)** had used the same value in his earlier study. The value of k has been purely chosen based on the assumed time taken for the eating of the meal and we have assumed this value to be constant irrespective of the quantity of food taken. For the choice of the basal levels, we had earlier stated that for a moderately and severely insulin-dependent diabetic patient, the plasma glucose level is about 121 mg/100cc and 231 mg/100cc respectively. Similarly, **Campbell et al (1977)** had stated that the plasma basal glucose level for a normal person is less than 95 mg/100cc and as stated earlier, is between 70 and 115 mg/100cc. Thus in our corrective approach, we assumed a condition where the patient is initially diabetic with the basal level of the glucose as high as 175 mg/100cc or/and 200 mg/100cc. This is correct for the first day and by the second day, the basal plasma glucose level comes down to 94 mg/100cc. We subsequently wish to maintain this basal level for the patient at all times.

For the results, we have that for the insulin-dependent diabetic patients, the values of the parameters are usually smaller than that for a normal person and thus given as above. Because of

these smaller values, high plasma glucose concentration ensues along with low corresponding plasma insulin concentration. To correct this anormally, insulin is injected or infused into the patient (in particular, injected). The dose of this injection has been represented by w(t).

From fig. 1, it is seen that for a normal glucose response to insulin when insulin is injected but with reduced response of the pancreas to glucose stimulation, the time taken to clear the glucose from the plasma increases with further decrease in the pancreatic response. Also, further decrease in the pancreatic response resulted to higher plasma glucose level. This then means that decrease in the pancreatic response to glucose stimulation results to low plasma insulin level so that small quantity of the insulin is available in the plasma for the binding action and hence reduced interaction between the glucose and the insulin. Fig. 7 shows the corresponding plasma insulin level to fig. 1. It is seen in this fig. 7 that when $b_1 > 0.1$, the plasma insulin curve becomes crooked. This means that at such levels of diabetism, the capacity of the pancreas to release insulin is there but that with the injection of the insulin, this capacity is inhibited until when the injected dose concentration must have reduced to a level that the remaining,quantity cannot appropriately match the corresponding remaining plasma blood glucose concentration. At such a state, there will be further demand for insulin and since the pancreas has capacity to release insulin, it will now release the stored insulin and this increases the plasma insulin level which results to another peak in insulin concentration. From figures 2,3,4, it is seen that for the various values of `$b_1$,` variation in value of `$a_2$` results in remarkable variation in the plasma blood glucose levels. This is quite expected since decrease in a_2 means less involvement of glucose in interaction due to low plasma level of the insulin. Hence at decreased value of a_2, there is high plasma glucose concentration with low amount of the glucose converted to glycogen and fats. The corresponding plasma insulin levels are shown in fig. 8, 9, 10. In general, reduction in the value of a_2 or b_1 1 with

b_1 or a_2 fixed, correspondingly results in high accumulation of the plasma glucose with more available insulin in the plasma, and longer time taken to return the plasma glucose and insulin levels to basal levels. When the binding rate of the insulin with the protein receptors at the cell membrane reduces or the rate of release of the insulin reduces, there is increase in the plasma glucose level. This increase in the plasma glucose level with increase in the plasma insulin level due to reduced insulin binding rate, increases the length of time taken to clear the glucose and even insulin in the blood plasma.

A case where a patient (IDD) is severely diabetic with b_1 value as small as 0.05 shows that the level of the plasma glucose will depend on the binding rate of the available insulin with the plasma membrane. Even with insulin injected, this cell membrane response to insulin and thus glucose entry into the cell greatly determine the plasma glucose level. However, the effect of variation in the value of 'a_2' do not markedly determine the plasma insulin concentration but may affect the length of time required to return the plasma glucose and insulin level to the basal level. These have been demonstrated in figs 5, 6, 11 and 12.

From these graphs/curves we may summarise this section by saying that the rate of interaction (cell membrane response to insulin binding action) of the glucose and the insulin as well as the pancreatic response to glucose stimulation (by releasing insulin) affects the plasma/blood glucose and insulin levels in an insulin dependent diabetic patient. The lower the value of these parameters the more severe the diabetes since these lower values always result to high concentration of plasma glucose. It is also seen that the pancreatic response to glucose stimulation is the greater cause of the insulin dependent diabetes when compared with the effect of the cell membrane response to insulin binding action (fig.26 and 27). Reduction in the rate of the binding action, even though it causes increase in the plasma glucose level, greatly cause an increase in the length of time required to clear the glucose from the blood. As can be seen in fig 5 & 6, at a fixed

b_1 the same peak value is attained but differences in the length of time required to clear this is remarkable.

Also, a case when a_3 is varied was considered. From fig 24 and 25, it is seen that reduction in the value of a_3 causes an increase in the concentration of the plasma glucose for a fixed a_2 and b_1. Fig. 25 particularly shows how variation in a_2 and a_3 affects the plasma glucose level for a fixed b_1 and food quantity. It affects both the maximum detectable plasma glucose concentration and the length of time for clearing this plasma glucose level by increasing their values. Even though it does not lead to any appreciable change in the plasma insulin level, it only leads to high plasma glucose concentration at corresponding times as compared with normal cases. This particular case is necessary to be considered because if the severity of the disease is high, less amount of the glucose enters the cell so that body cell usage of the plasma glucose is almost absent and with our analysis, it is expected that this behaviour of the plasma glucose has to be exhibited. Therefore, from our analysis, the required behavioural pattern of the plasma was established.

The next step in our analysis is the actual correction of the insulin dependent diabetes mellitus by injecting insulin into the patient. Fig. 31 shows the case of a moderately diabetic patient whose plasma basal glucose level is 175 mg/100cc. Here, $a_2 = 0.03$ with $b_1 = 0.05$ were used as the effective parameter. At 8.00 hours, 50g of glucose worth of food was taken with 20 units of insulin injected into the patient at the same time. From fig. 31, the plasma glucose level is still normal up to 13.00 hours when lunch of 50g worth of glucose meal was taken again with no further insulin injection in to the patient. However, at about 17.00 hours, the plasma glucose level starts plunging below the basal level so that a 10g glucose worth of snack was taken so that it keeps the plasma glucose level to at least the basal level until the dinner time, 18.00 hours. At this time, 100g glucose worth of meal was again taken. By this time, the insulin level in the plasma is low so that further insulin injection is necessary. However, since no more activities that demand

high energy by the cells are performed within the period 18:00 - 8:00 hours, less amount of this insulin need be injected so that the glucose will be utilised gradually. Hence, 10 units of the insulin was injected into the patient. With this level of injection and the length of period involved, another meal of 100g of glucose is recommended to be taken at 22:00 hours with no further insulin injection. This keeps the plasma glucose level above the basal level up to 05:00 hours. From this time to 08:00 hours, the plasma basal level of the glucose is maintained. In fig: 31 also, we saw a change in the quantity of the insulin injected, from 10 units to 6.5 units. From the graph and other analysis, there is no substantial change in both the plasma glucose level and the time the plasma glucose return to the basal level. Hence, we recommend that the dose of the insulin to be injected need to be at most 10 units when the starting dose is 20 units. Similarly, a case of severely diabetic patient with fasting plasma glucose as 200 mg/100cc was considered. Here we assumed $\mathbf{a_2 = 0.025}$ and $\mathbf{b_1 = 0.03}$ since the case is severe meaning further reduction in the values of both a_2 and b_1 . In this case , the patient does not need any snack to control the plasma glucose level plunging below the plasma glucose basal level before dinner. The patient was given 50g of glucose worth of food at both breakfast (8:00 hours) and . Lunch (13:00 hours) with 20 units of insulin injected at the breakfast time. The plasma glucose level was maintained above basal level up to 18:00 hours. At this time, 100g glucose worth of meal was taken with 6.5 units of insulin injected. At 22:00 hours, another 50g glucose worth of meal was taken. These two meals with the later dose of the insulin sustained the plasma glucose level above the basal level up till 08:60 hours the next morning. To at least get the plasma glucose level to the basal level on or before the next breakfast , we consider where 50g glucose worth of meal was taken at both 18:00 hours and 22:00 hours with the 6.5 units of the insulin injected. This kept the plasma glucose level above the basal level up till 06:10 hours. At least, the plasma glucose level remains at the basal level (94:00 mg/100cc) for the next two hours when the breakfast meal will be taken. This case is shown in fig:32.

From fig:31 and 32, it means that the level of severity of the disease should be clearly shown before the initial correction is made to avoid other forms of glucose-related diseases. Also, the level of severity should be taken into account when recommending the doses of the insulin to be injected at the breakfast and dinner times. Fig:30 shows a comparison in the plasma glucose level for these levels of severity. There is a wide difference in plasma glucose when equal quantity of food were given to the patient together with the same doses of the insulin. Having now brought the plasma glucose level to the normal level following this initial correction, we went ahead to determine the quantities of food and doses of the insulin that will be given to the patient and at what time this should be done, so that this normal state shall be maintained each day.

In our further analysis of the control of diabetes, we assumed that initial control has returned to normal the plasma glucose level and the severity of the disease is such that b_1=0.05 and 0.10 . Fig:15 shows the plasma glucose and insulin levels of such patients when at 08:00 hours, he was given 50g glucose worth of food with 20 units of insulin injection at this time, 50g glucose worth of food at 12:00 hours and 100g glucose worth of food at 18:00 hours with 10 units of insulin injection. To avoid the plunging of the plasma glucose level below the basal level, a snack of 25g glucose worth of food is recommended to be taken at 10:00 hours. This maintained the plasma glucose level above the basal level up to the time of launch (12:00 hours). In the same way, the 100g glucose worth of food taken at 18:00 hours with 10 units of insulin injection can not sustain the patient till the following morning when he shall take another breakfast. Therefore, the patient has to take 50g glucose worth of food at about 22:00 hours. This kept the plasma glucose level above the basal value up to 05:00 hours the following morning. Therefore, within the next three hours before the breakfast meal, the liver will be able to supply the needed glucose by converting the stored glycogen to glucose.

From fig. 15 also, we can see that quantity of food given to the two patients with different level of severity could not sustain them equally when the same doses of the insulin were injected. For the patient with the level of severity measured by $\mathbf{b_1 = 0.1}$, the plasma glucose levels were very low compared to that of $\mathbf{b_1 = 0.05}$. This is because, more insulin is available in the blood which resulted to quicker conversion of the glucose to glycogen and thus clearance from the blood. Fig:14 shows the plasma levels of the insulin for the two patients. Fig:16 shows a case when the amount of food taken at 12:00 hours was changed to 100g glucose worth . Even as at this quantity of food intake with the same amount of insulin injection, the food quantity could not still maintain the plasma glucose level of the patient with $\mathbf{b_1 = 0.10}$ above the basal level till the next meal which is dinner and at 18:00 hours. From these results, it becomes very clear that the issue of treating an insulin-dependent diabetic patient with insulin injection is not as simple as we feel. Proper examination of the patient is very necessary so that clear knowledge of the type and severity of the diabetes must be known. Therefore, to give correct treatment, laboratory examination must be conducted properly so that the physician will know the following:

(1) the major causes of the high blood glucose level - whether it is due to low pancreatic response to high plasma glucose stimulation and low cell response to insulin level (insulin-dependent causes) or it is due to non-insulin-dependent causes as earlier stated.

(2) If it is pancreatic response failure (or reduction) , to what level of severity is this. Also to what level has this affected the peripheral cell response.

(3) based on this level of severity, the correct doses of the insulin to be injected into the patient at breakfast and dinner respectively.

(4) the correct quantity of food (glucose) to be taken at the times 08:00 hours, 12:00 hours, 18:00 hours and 22:00 hours. If necessary, the quantity of snack needed and the time it should be taken.

Correct food intake is very necessary because, energy requirement of every individual is not the same. The standard requirement of glucose intake is 1g/kg body weight. This shows that 50g glucose worth of food given to a 50 kg and 80 kg persons will not present the same time of clearance in the blood for the two persons as the 80 kg person's blood will be cleared of plasma glucose quicker. From the foregoing analysis, it is evident that the severity of the disease must be known before any choice of the dose of the insulin to be injected is made. This is to avoid the plunging of the plasma glucose below fasting level and thus another glucose related disease (hypoglycaemia) resulting. However, if it is detected that the patient is simply insulin-dependent diabetic without necessarily checking for the level of severity before the 20 units of insulin (or any dose) is injected, then a thorough monitoring of the patient's plasma glucose level for the first two days of treatment is very necessary. If possible, this may even be checked for three days. This is because, the first day is expected to return the plasma glucose level to normal while the next day or two is to determine the correct subsequent quantities of the food to be given to the patient. It is also seen in this analysis that when the diabetes is insulin-dependent, that other complications result. Among these are the reductions in the peripheral cell response to glucose concentration, reduction in the clearance rate of the glucose in the plasma even when enough insulin is injected. Depending on the dose of the insulin injected, the plasma insulin level is usually higher than normal even when the plasma glucose level returns to the normal/basal level. The mechanism of glucose entry into the cells in the presence of the insulin to ensure conversion of glucose to glycogen is stopped so that rather, the liver releases the stored glycogen for conversion to glucose. This reconverted

however not affected by whatever level of insulin in the plasma and thus the situation as reported above. All these further complications resulting from the insulin-dependency of the diabetes contributes to further increase in the plasma glucose levels as shown in the graphs.

Concluding this part therefore, we say that care must be taken in the diagnosis of the case to know the exact form it takes. If the disease is not insulin-dependent and further insulin is injected into the patient, the illness won't improve since the patient has enough plasma insulin. If however the disease is insulin-dependent and other forms of treatment are being given as in the case of non-insulin-dependent diabetes, no meaningful result will also be got.

Finally, fig:21, 22 and 23 shows the comparisons of the plasma glucose and insulin levels in the patient given that the equations are solved by any of the methods; analytically and numerically for the linearised and numerically for the non-linearised equations. From fig:21 and 22, the resulting plasma glucose and insulin levels for the analytic solution and the numerically linearised solutions matches almost very perfectly. This suggests that either of the two methods can be used for the analysis without loss of any information or interpretation about the patients condition. For the numerical solution of the non-linear equations, the results also match very closely up to the maximum plasma glucose level. Difference only occurred at the clearance section which can be attributed to the clearance rate. Since our method predicts correctly the maximum plasma glucose level as predicted by the numerical method for the non-linear equations, we can confidently use our method in recommending treatment measures for an insulin-dependent diabetic cases. From the study, it is seen that the maximum time difference in the clearing of the plasma glucose when food is taken along with insulin injections is about an hour. Therefore, this time difference has to be noted when ever the timing of the meals are being considered.

Particularly, fig:24 and 25 show the effect of a_3 on the plasma glucose and insulin levels. It was shown that a decrease in the cell usage of the glucose resulted to an increase in the plasma

glucose concentration. This increase in the plasma glucose level results increase in the clearance time and lower level of plasma insulin when the glucose is cleared. As earlier stated, variation in the cell usage of the plasma glucose is a further complication of the insulin-dependent diabetes.

Fig:26 shows the plasma glucose level for a normal person compared to those of an insulin-dependent diabetic patient that had no insulin injected into him to correct the abnormality of the plasma glucose. Fig 27 shows the corresponding insulin levels. As theoretically believed, it is this low insulin level that principally causes the high plasma glucose concentration. Hence, to correct this high plasma glucose concentration as has been shown, insulin injection is unavoidable

APPENDIX I

NUMERICAL SOLUTION TO THE MODELLED DIFFERENTIAL EQUATIONS

For the numerical solutions, we considered the (approximated) linear and the non-linear equations :

The non-linear modelled system of differential equation is given as:

$$\frac{dX}{dt} = a_1 Q e^{-k(t - t0)} - a_2 XY - a_3 X \quad \ldots\ldots\ldots\ldots \quad (1)$$

and

$$\frac{dY}{dt} = b_1 X - b_2 Y + b_3 W(t) = b_1 X - b_2 Y + b_3(\gamma t + \delta)$$

$$= b_1 X - b_2 Y + \gamma t + \delta \quad \ldots\ldots\ldots\ldots \quad (2)$$

For the (approximated) linear equation of the same system, we have $XY = \bar{X}Y$ and the equations remain the same with the same programme .

Method

Let $f_1 (t, X, Y) = a_1 Q e^{-k(t - t0)} - a_2 XY - a_3 X$ $\ldots\ldots\ldots\ldots$ (3)

$f_2 (t, X, Y) = b_1 X - b_2 Y + (\gamma t + \delta) b_3$ $\ldots\ldots\ldots\ldots$ (4)

In equation (4), we have the values for δ and γ as before.
Using the Runge - Kuta method (of order 4) of numerical solution to differential equations, we have the following definitions :

$$\frac{dX}{dt} = f_1 (t, X, Y) = a_1 Q e^{-k(t - t_0)} - a_2 XY - a_3 X \quad \ldots\ldots\ldots\ldots \quad (5)$$

$$\frac{dY}{dt} = f_2 (t, X, Y) = b_1 X - b_2 Y + \gamma t + \delta \quad \ldots\ldots\ldots\ldots \quad (6)$$

where X and Y are all functions of t.

To determine the values of X and Y at any point, we then have that

$$X_{n+1} = X_n + \frac{h}{6} [K_{1n} + 2K_{2n} + 2K_{3n} + K_{4n}] \quad \ldots\ldots\ldots\ldots \quad (7)$$

$$Y_{n+1} = Y_n + \frac{h}{6} [l_{1n} + 2l_{2n} + 2l_{3n} + l_{4n}] \quad \ldots\ldots\ldots\ldots \quad (8)$$

where $K_{1n} = f_1(t_n, X_n, Y_n)$

$$K_{2n} = f_1(t_n + \frac{h}{2}, X_n + \frac{k_1}{2}, Y_n + \frac{L_1}{2})$$

$$K_{3n} = f_1(t_n + \frac{h}{2}, X_n + \frac{k_2}{2}, Y_n + \frac{L_2}{2})$$

$$K_{4n} = f_1(t_n + h, X_n + k_3, Y_n + L_3$$

$$L_{1n} = f_2(t_n, X_n, Y_n)$$

$$L_{2n} = f_2(t_n + \frac{h}{2}, X_n + \frac{L_1}{2}, Y_n + \frac{L_1}{2})$$

$$L_{3n} = f_2(t_n + \frac{h}{2}, X_n + \frac{K_2}{2}, Y_n + \frac{L_2}{2})$$

$$L_{4n} = f_2(t_n + h, X_n + K_3, Y_n + L_3)$$

When $t_n = t_0$ ie $n = 0$, we have $X_0 = 94.00$ and $Y_0 = 0.00$.

ANALYSIS

For the analysis and the discussion that followed, we have the value for the constants as follows. $a_1 = 4$, $a_2 = 0.02$ -0.05, $a_3 = 0.02$ - 0.04, $b_1 = 0.05$ and 0.10, $b_2 = 2.0$, and b_3, δ and λ o be determined from the given expressions in the thesis, Q = 10, 25,50 and 100 units. For the corrective processes, we have Q = 25, 50 and 100 units, with $\omega(t)$ = 6.0, 10 and 20 units which has to be defined in terms of γ and δ.

The Fortran Programme used for the generation of the values used in the graphs is given as:

```
External f1 , f2
Open (11, file = "Mbah.Data")
h  = ?
t  = 8.00
X  = 94.00
Y  = 0.00
N  = ?
Nstep = 0
Write (11, 104)  Nstep, T, X, Y
N  = N-1
Do 10 Nstep  =  1, N
K1  = h*f1 (T, X, Y)
l1  = h * f2 (T, X, Y)

T1  = T + 0.5 * h
```

```
X1 = X + 0.5 * K1
Y1 = Y + 0.5 * l1
K2 = h * f1 (T1, X1, Y1)
l2 = h * f2 (T1, X1, Y1)
X2 = X + 0.5 * K2
Y2 = Y + 0.5 * l2
K3 = h * f1 (T1, X2, Y2)
l3 = h * f2 (T1, X2, Y2)
X3 = X + K3
Y3 = Y + l3
K4 = h * f1 (T, X3, Y3)
l4 = h * f2 (T, X3, Y3)

        X = X + 1.0/6.0 * (K1 + 2 * K2 + 2 * K3 + K4)
        Y = Y + 1.0/6.0 * (L1 + 2 * L2 + 2 * L3 + L4)
        T = T + h
10      Write (10, 104) Nstep, T, X, Y
        Close (11)
100     Format (3  F10.5, I4)
104     Format (IX, I4, 3F10.3)
        Stop
        End.

        Function f1(t, X, Y)
        f1 = a1Q exp [-K(t - 8.00)] - a2 XY  - a3 X
        Return
        End.

        Function f2 (t, X, Y)
        f2 = b1 X - b2Y +γt + δ
        Return
        End.
```

The values of δ and γ are shown as shown in the main work for the effective interval of value of existence of the feeding period. This can be modified in various forms. It can be used for both the approximated and the non-linear modelled equations. In the approximated equations, we have to linearise the non-linear term XY to $\bar{X}Y$ as already stated where $\bar{X} = X(t_0) = X_0$.

APPENDIX 1I

Here is presented the FORTRAN program used for the determination of the glucose and insulin levels in the blood when all the values of the constants are known and the equation solved analytically.

```
Open (30, file = "OGE.DAT")
H = ?
a2 = ?
a3 = ?
b1 = ?
b2 = ?
Q = ?
X1 = ?
Y0 = ?
δ = ?
γ = ?
T = ?
K = ?
X0 = ?
N = ?
T0 = 8.00
Nstep = 0

Write (11, 200) Nstep, T, X, Y
N = N - 1
Do 30 Nstep = I, N
w = a2 * b2 + b1 * a2 * X1
Z = K ** 2 - (b2 + a3) * K + a3 * b2 + b1 * a2 * X1
G1 = 0.5 * [-(b2 + a3) - ((b2 + a3) ** 2 - 4 * (a3 * b2 + b1 * a2 * X1)) ** 0.5
G2 = 0.5 * [-(b2 + a3) + ((b2 + a3) ** 2 - 4 X w) ** 0.5]
D = (a2 * x1 * δ * (b2 *a3 + a3 **2)/(a3 * w ** 2) - (a2 * X1 * γ)/w
S = a1 * Q * (b2 - K)/Z * exp (-K * (T0 - 8.0)) - a2 * X1 *δ * T0/w - X1
S1 = γ * a3/w - δ/w ** 2 (a3 ** 2 - b1 * a2 * X1)
S2 = (a1 * b1 * Q)/Z * exp (-K * (T0 - 8.00)) + a3 * δ * T0/w - y0
V1 = (G2 + a3)/(G1 - G2) * exp (-G1 * T)
V2 = (G1 + a3)/(G2 - G1) * exp (-G2 * T)
V3 = (a2 * X1)/(G1 - G2) * exp (-G1 * 8.00)
V4 = (a2 * X1)/(G2 - G1) * exp (-G2 * 8.00)
E1 = V1 (D + S) + V3 (S1 + S2)
E2 = V2 (D + S) + V4 (S1 + S2)
```

$C_1 = E_1 * \exp(a_1 * T) + E_2 * \exp(G_2 * T)$
$C_2 = ((a_1 * Q * (b_2 - K)) * \exp(-K * (T - T_0))/Z - (a_2 * X_1 * \delta * T))/w$
$C_3 = -((G_1 + a_3) * E_1 * \exp(G_1 * T))/a_2 * X_1)$
$C_4 = -((G_2 + a_3) * E_2 * \exp(G_2 * T))/(a_2 * x_1)$
$C_5 = (a_1 * Q * b_1 * \exp(-K * (T - T_0)))/Z + (a_3 * \delta * T)/w$
$X = C_1 + C_2 + D$
$Y = C_3 + C_4 + C_5 + S_1$
$T = T + H$

```
30      Write (11, 200) Nstep, T, X, Y
200     Format (2x, I3, 3F10.3)
        Stop
        End.
```

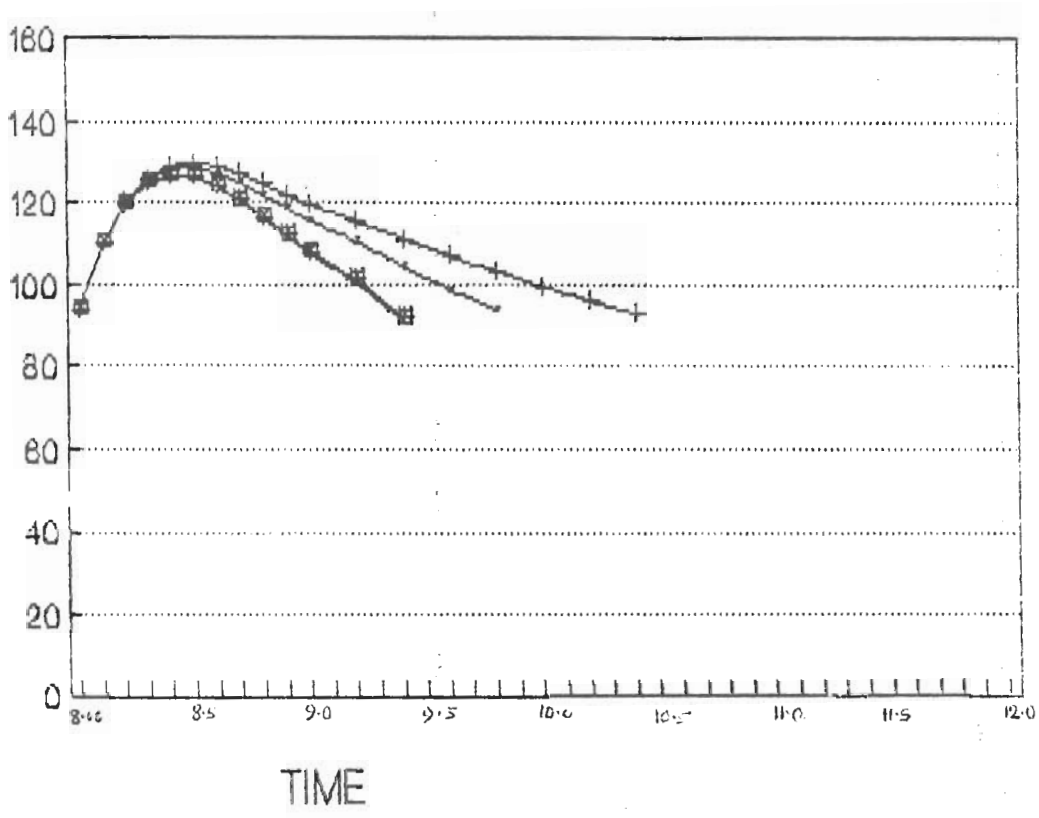


Fig. 1 GLUCOSE LEVELS FOR b_1 VARIED

GLUCOSE/INSULIN VARIATIONS IN THE BLOOD

EFFECT OF VARIATION OF b_1 WHEN $a_2 = 0.06$

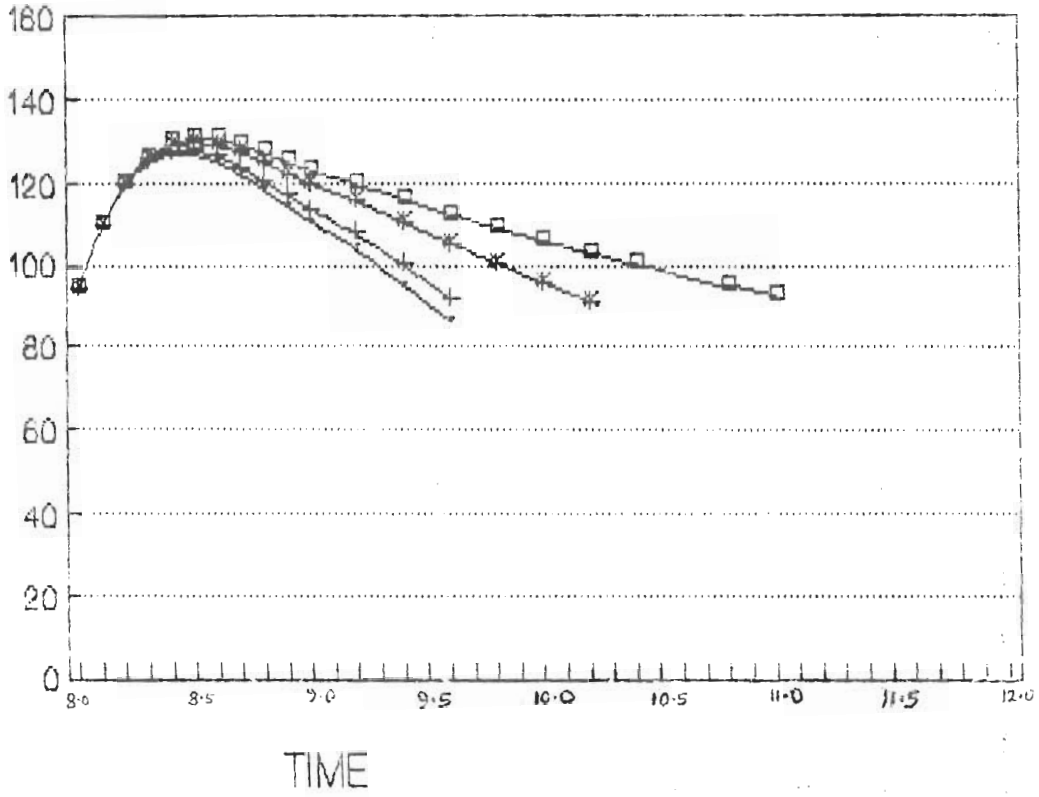


Fig. 2 GLUCOSE LEVELS FOR b_1 VARIED

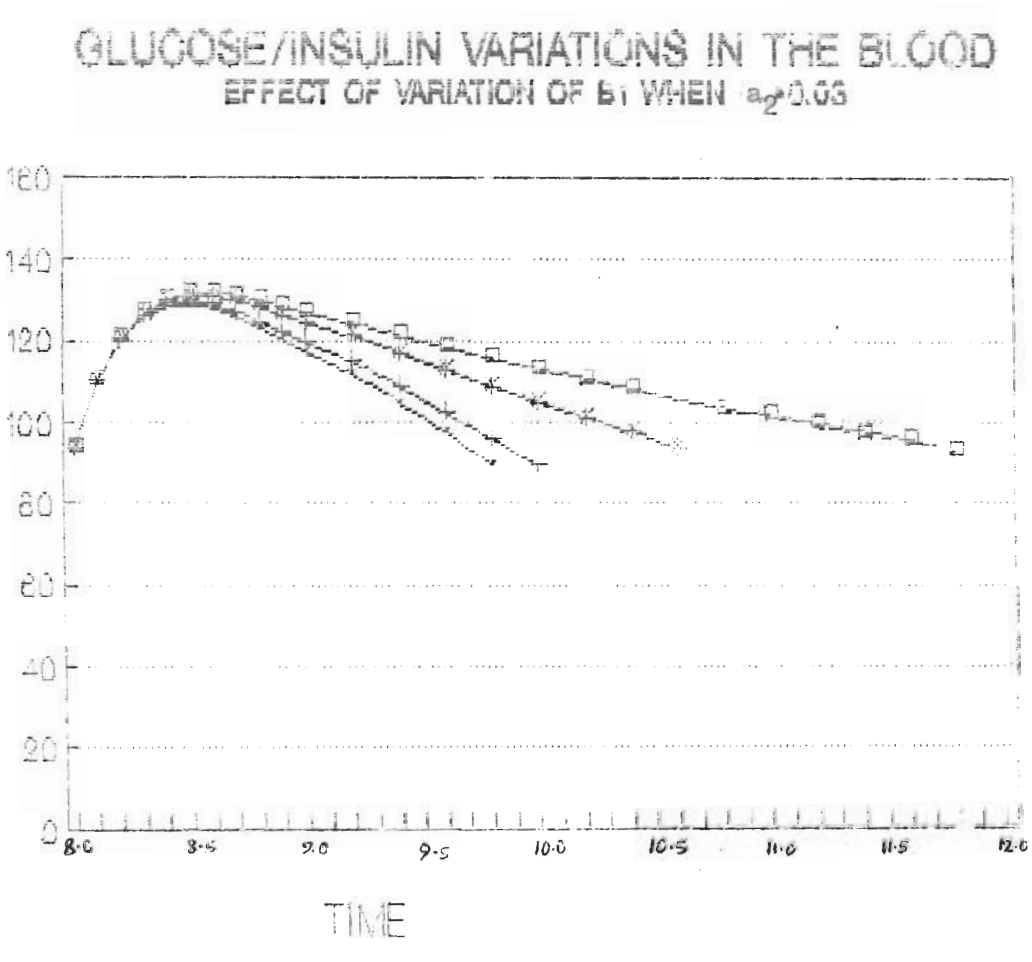


Fig. 3 GLUCOSE LEVELS FOR THE b_1

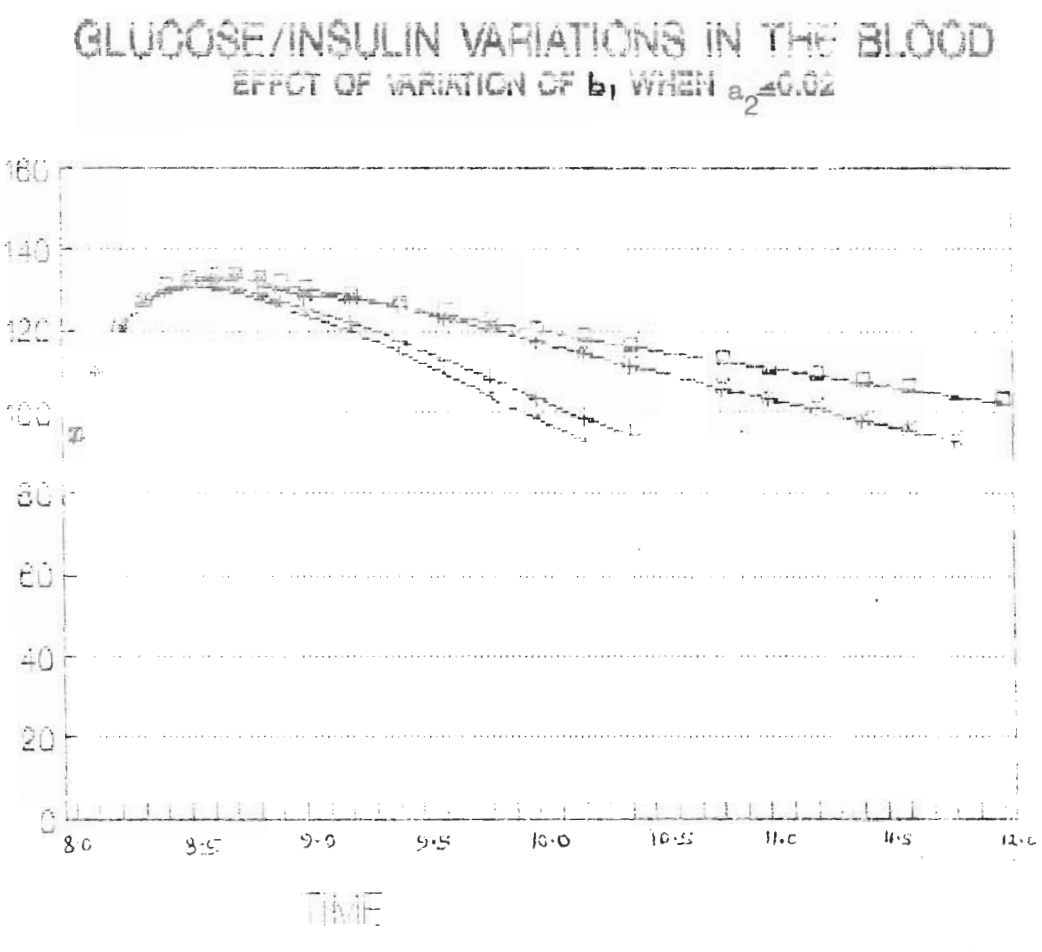


Fig.4 GLUCOSE LEVELS FOR THE b_1 VARIED

GLUCOSE/INSULIN VARIATIONS IN THE BLOOD
EFFECT OF VARIATION OF a_2 WHEN b_1=0.1

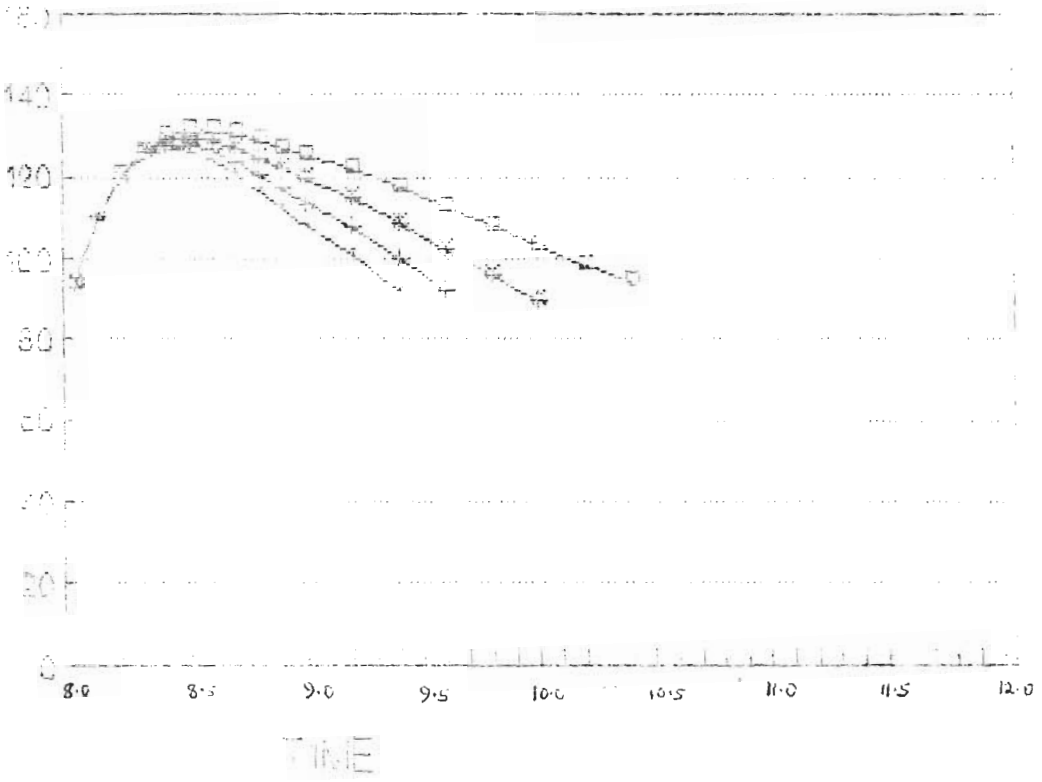


Fig. 5 a_2=0.05 a_2=0.04 a_2=0.03 a_2=0.02

GLUCOSE LEVELS FOR THE b_1 VARIED

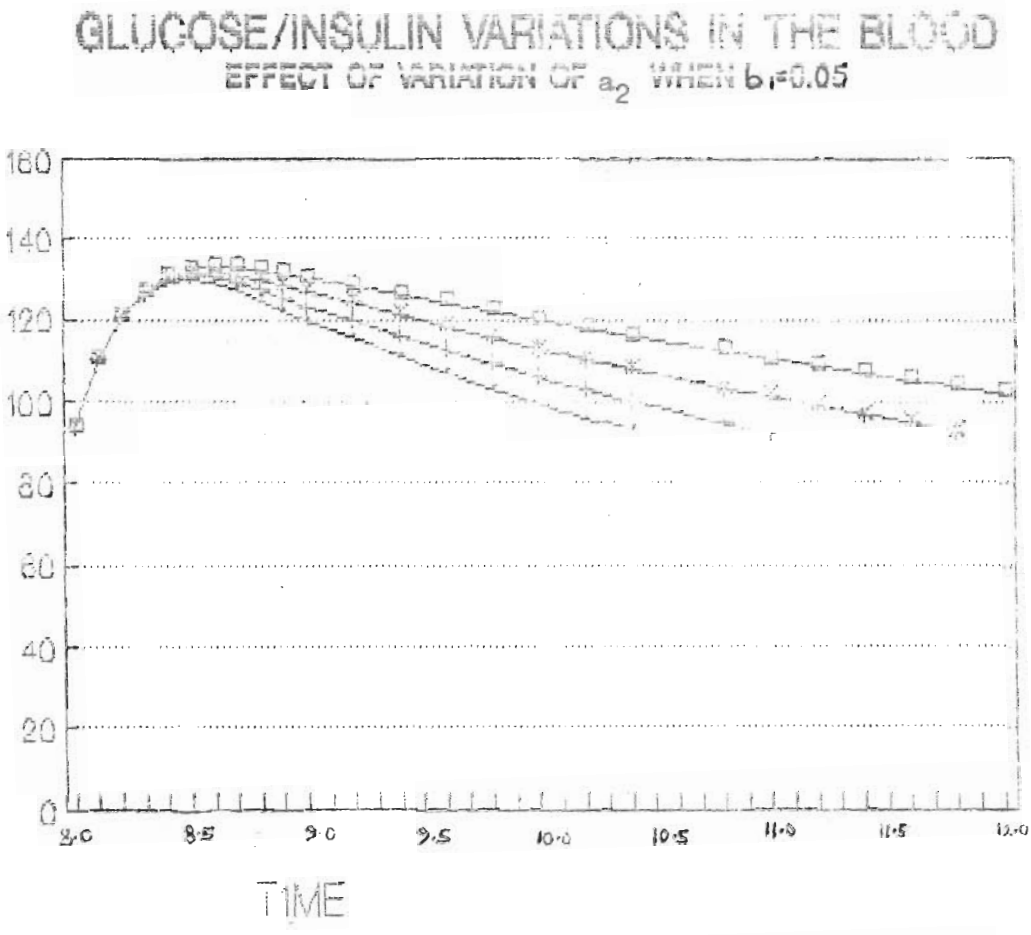


Fig. 6

GLUCOSE LEVELS FOR b_1 GIVEN

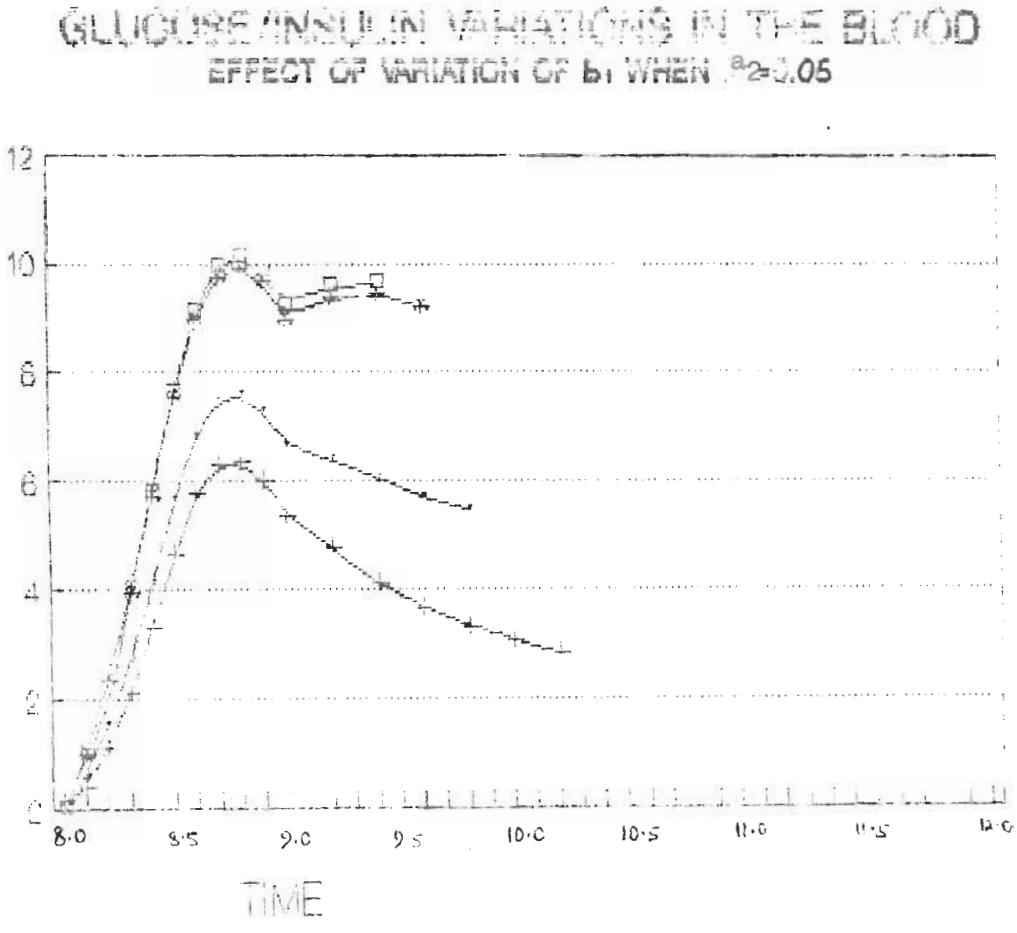


Fig. 7 — b_1=0.10 — b_1=0.05 — b_1=0.20 — b_1=0.205

INSULIN LEVELS FOR THE b_1 VARIED

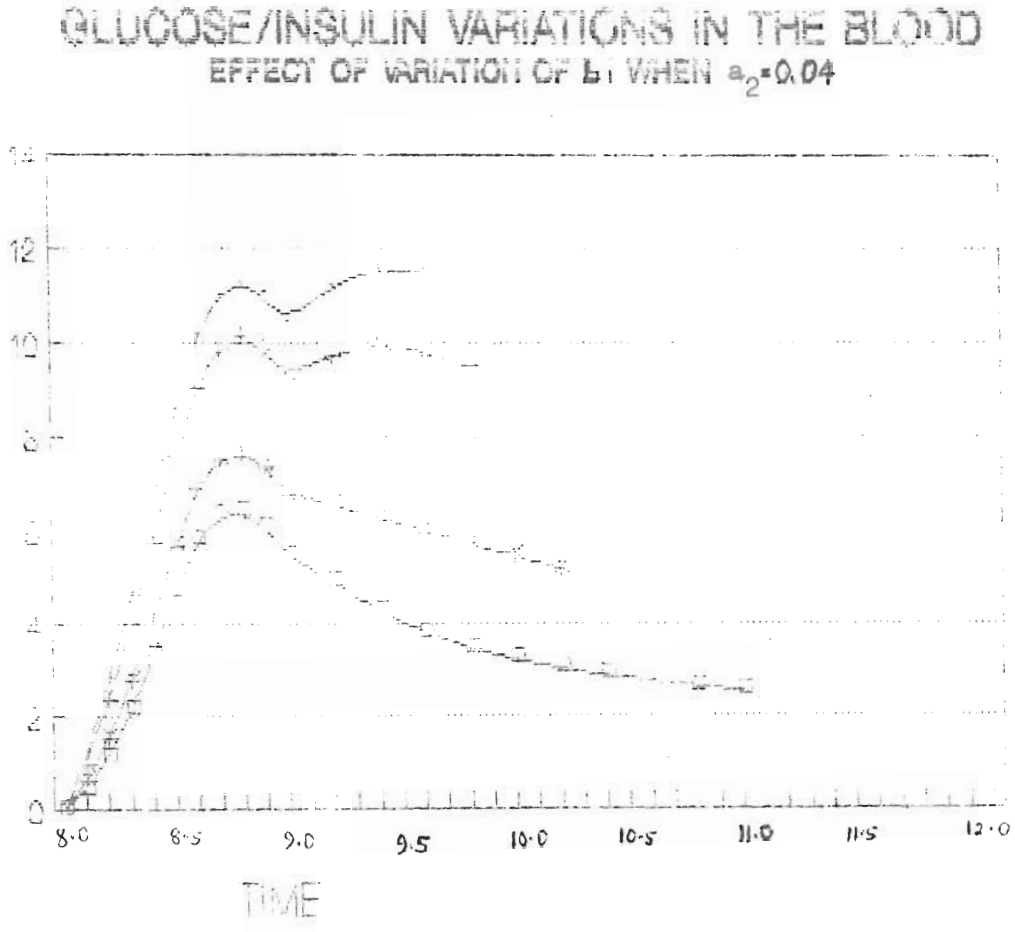


Fig. 8 —— b_1=0.25 ··· b_1=0.20 ✳ b_1=0.10 ⊟ b_1=0.05

INSULIN LEVELS FOR THE b_1 VARIED

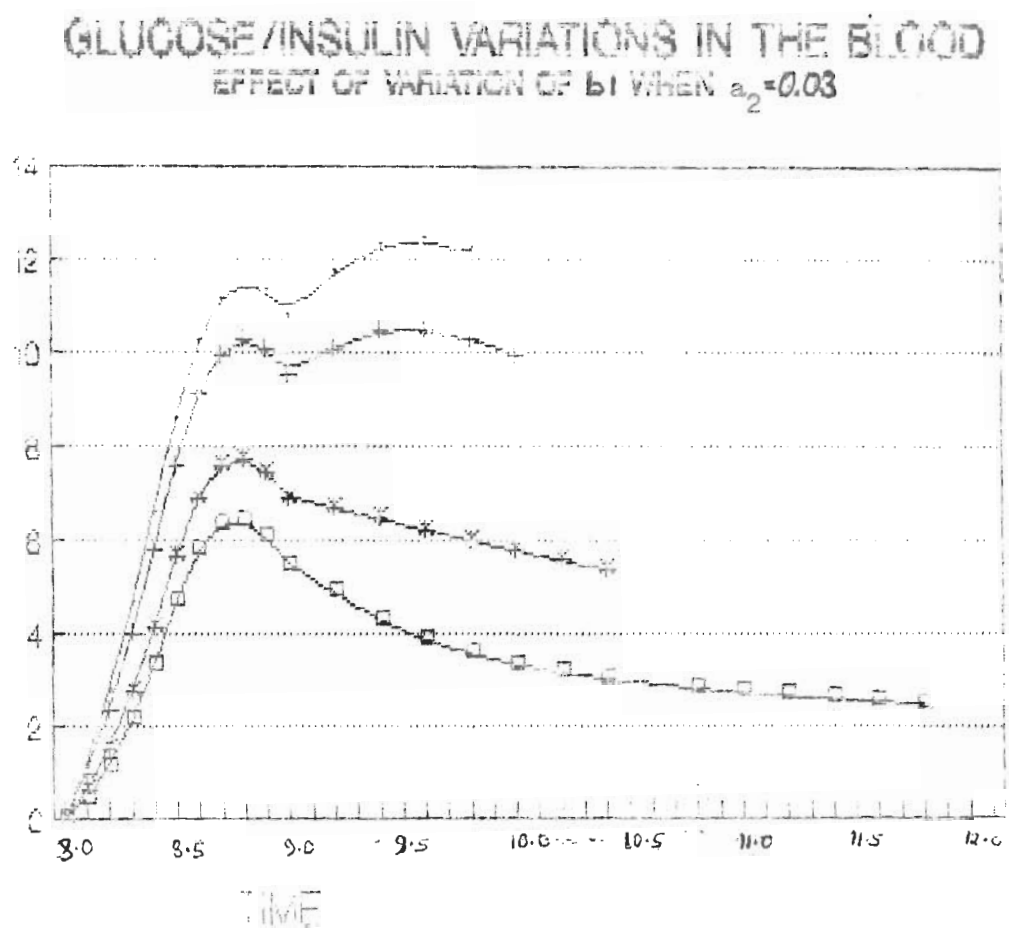


Fig. 9 b_1=0.25 b_1=0.20 b_1=0.10 b_1=0.05

INSULIN LEVELS FOR THE b_1 VARIED

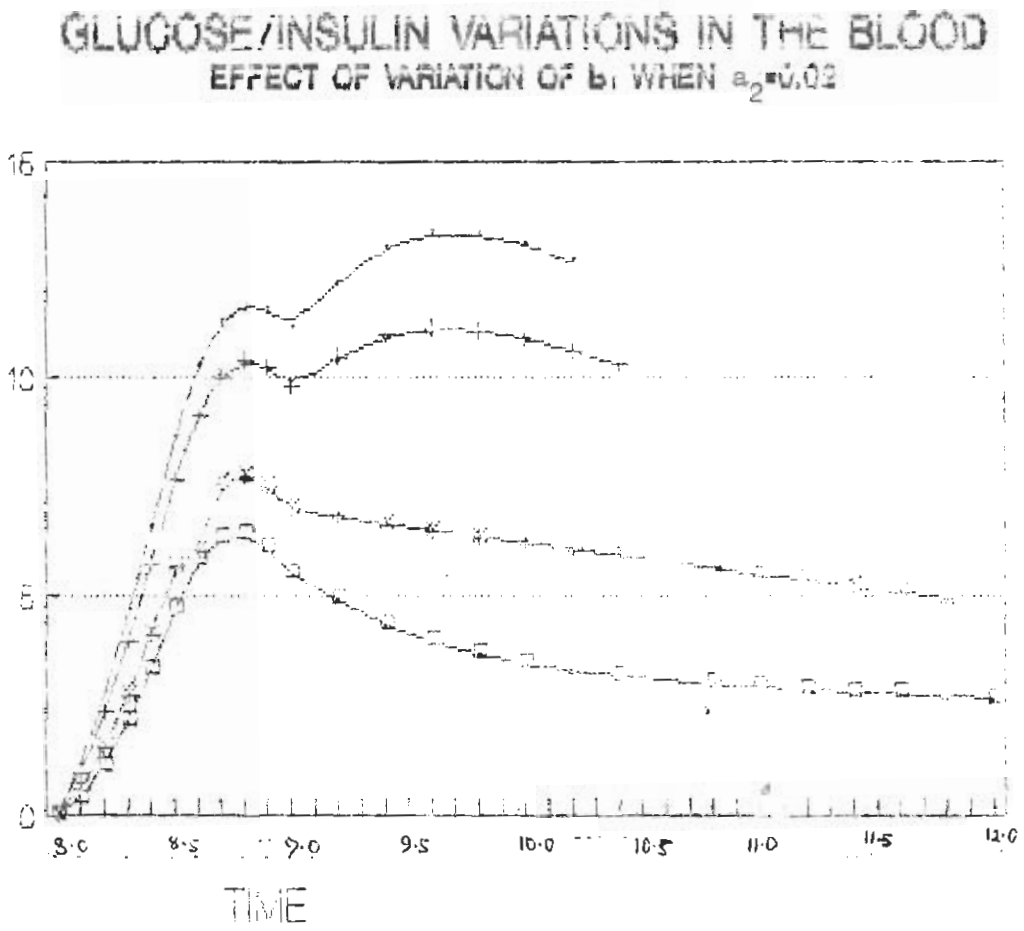


Fig. 10 —— b_1=0.25 —·— b_1=0.20 —·— b_1=0.10 - - b_1=0.05

INSULIN LEVELS FOR THE b_1 VARIED

GLUCOSE/INSULIN VARIATIONS IN THE BLOOD
EFFECT OF VARIATION OF a_2 WHEN b_1=0.05

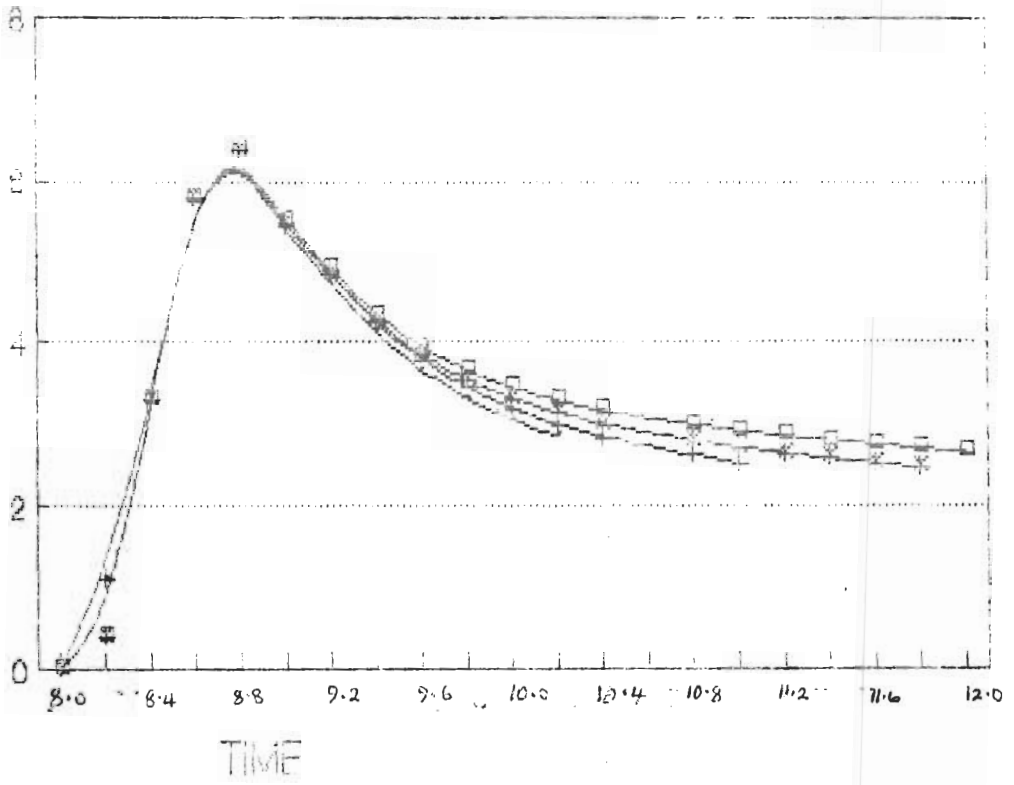


Fig. 11 a_2=0.05 a_2=0.04 a_2=0.03 a_2=0.02

INSULIN LEVELS FOR THE a_2 VARIED

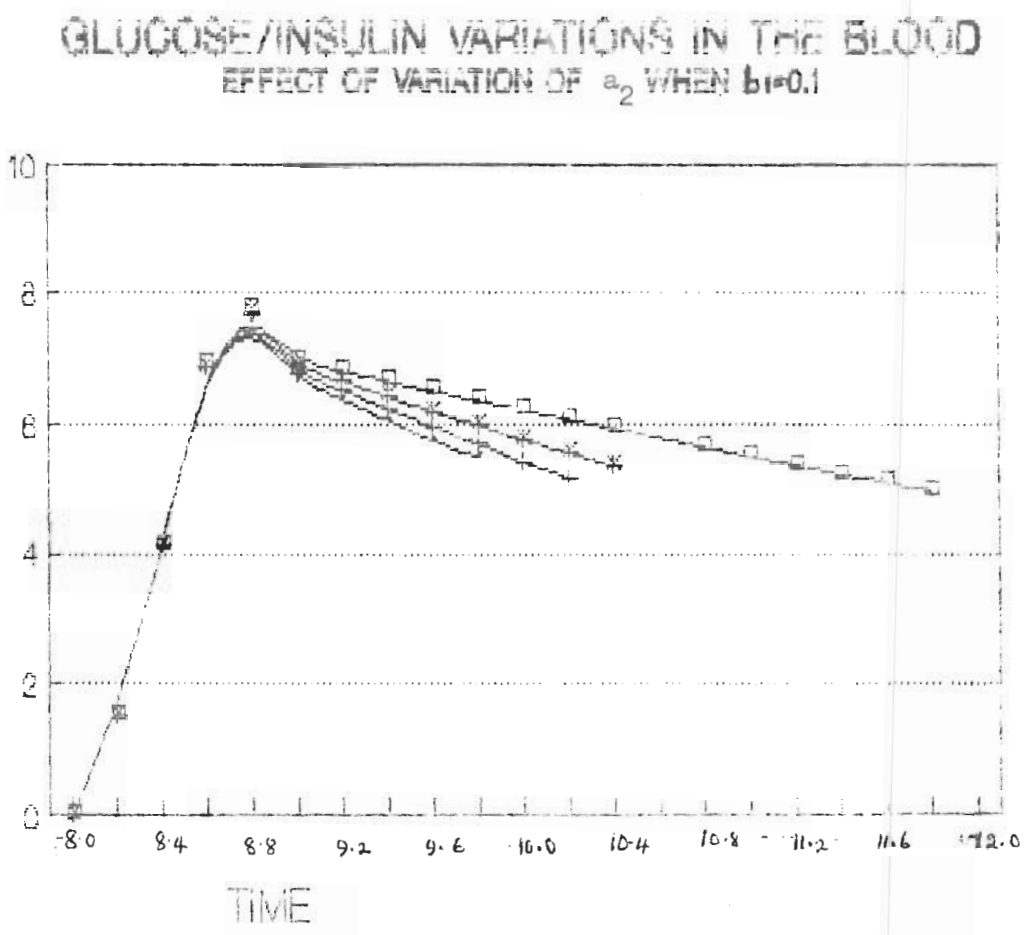


Fig. 12 —•— a_2=0.05 —+— a_2=0.04 —*— a_2=0.03 —□— a_2=0.02

INSULIN LEVELS FOR THE a_2 VARIED

GLUCOSE/INSULIN VARIATIONS IN THE BLOOD
FEEDING AT DIFFERENT TIMES

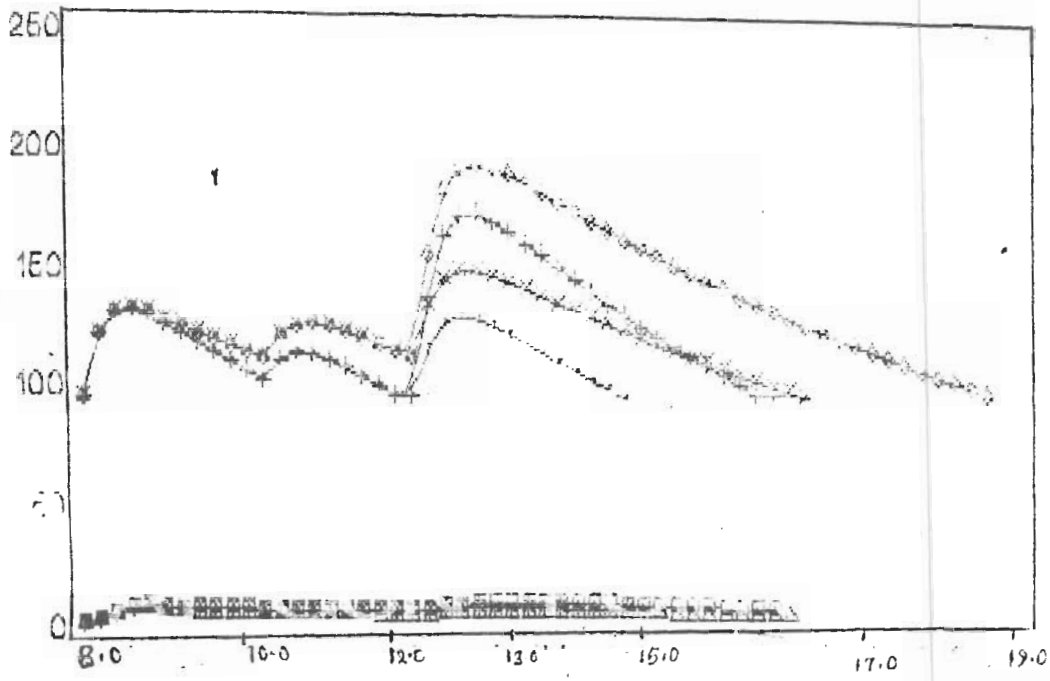


Fig. 13

b_1=0.1&Q=50 b_1=0.1&Q=100 b_1=0.1&Q=50 b_1=0.1&Q=100
b_1=0.05&Q=50 b_1=0.05&Q=100 b_1=0.05&Q=50 b_1=0.05&Q=100

GLUCOSE AND INSULIN LEVELS AT SUCH TIMES

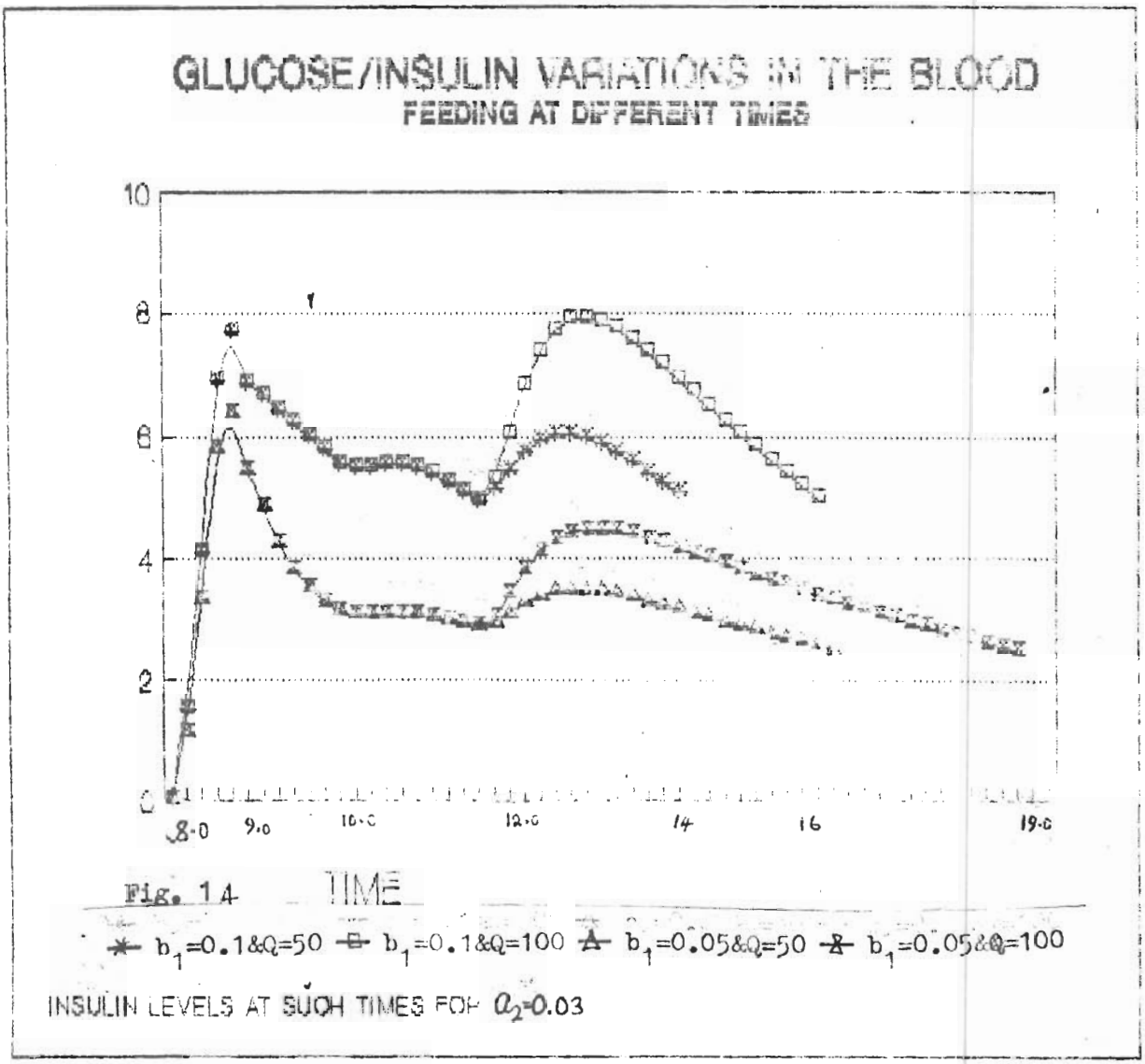

GLUCOSE/INSULIN VARIATIONS IN THE BLOOD
FEEDING AT DIFFERENT TIMES
10
8
6
4
2
0
8·0
9·0
10·0
12·0
14
16
19·0
TIME
b1=0.1&Q=50
b1=0.1&Q=100
b1=0.05&Q=50
b1=0.05&Q=100
INSULIN LEVELS AT SUCH TIMES FOR a2=0.03

Fig. 14

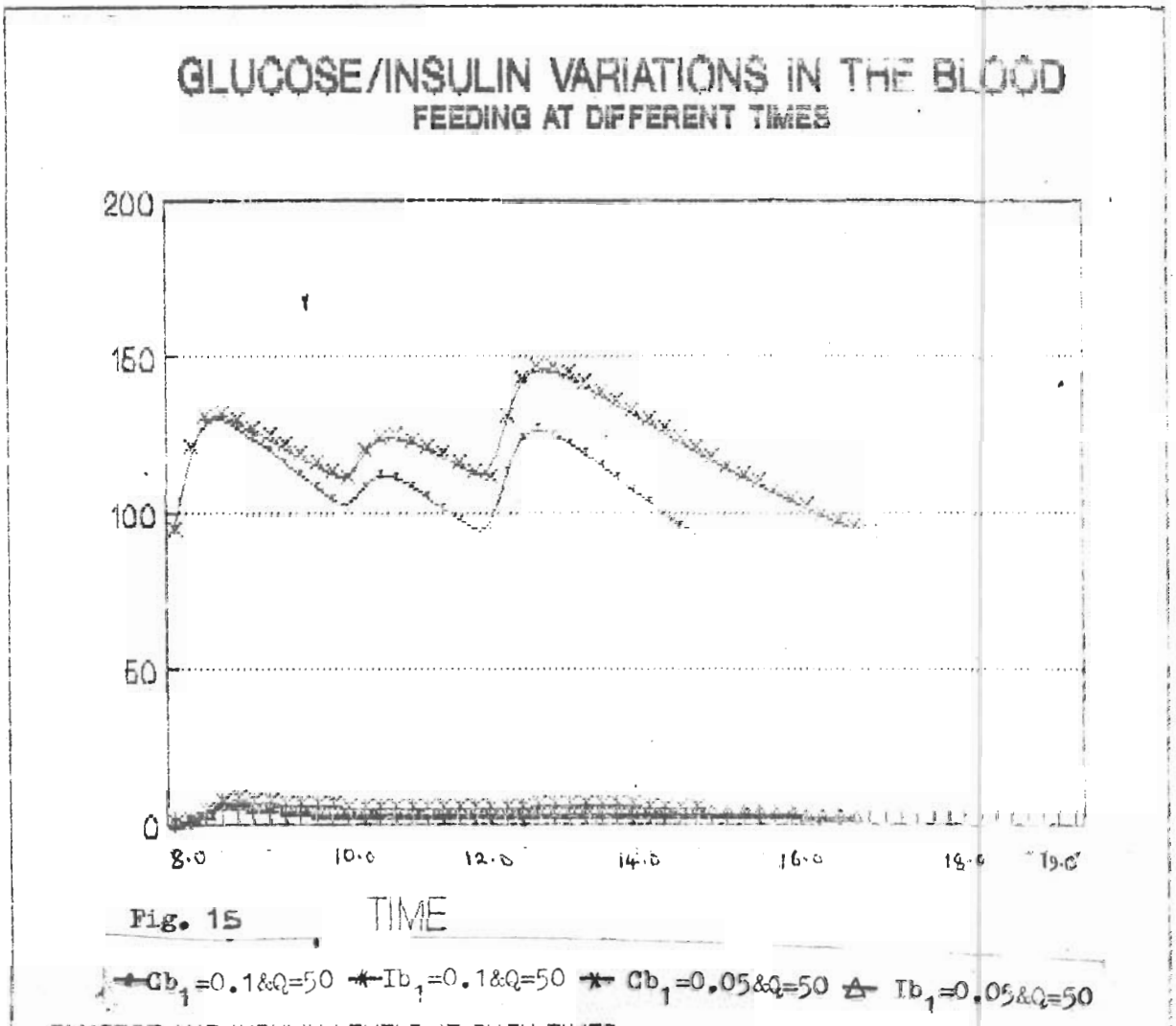

GLUCOSE/INSULIN VARIATIONS IN THE BLOOD
FEEDING AT DIFFERENT TIMES
200
150
100
50
0
8.0
10.0
12.0
14.0
16.0
18.0
20.0
TIME
Cb1=0.1&Q=50
Ib1=0.1&Q=50
Cb1=0.05&Q=50
Ib1=0.05&Q=50
GLUCOSE AND INSULIN LEVELS AT SUCH TIMES

Fig. 15

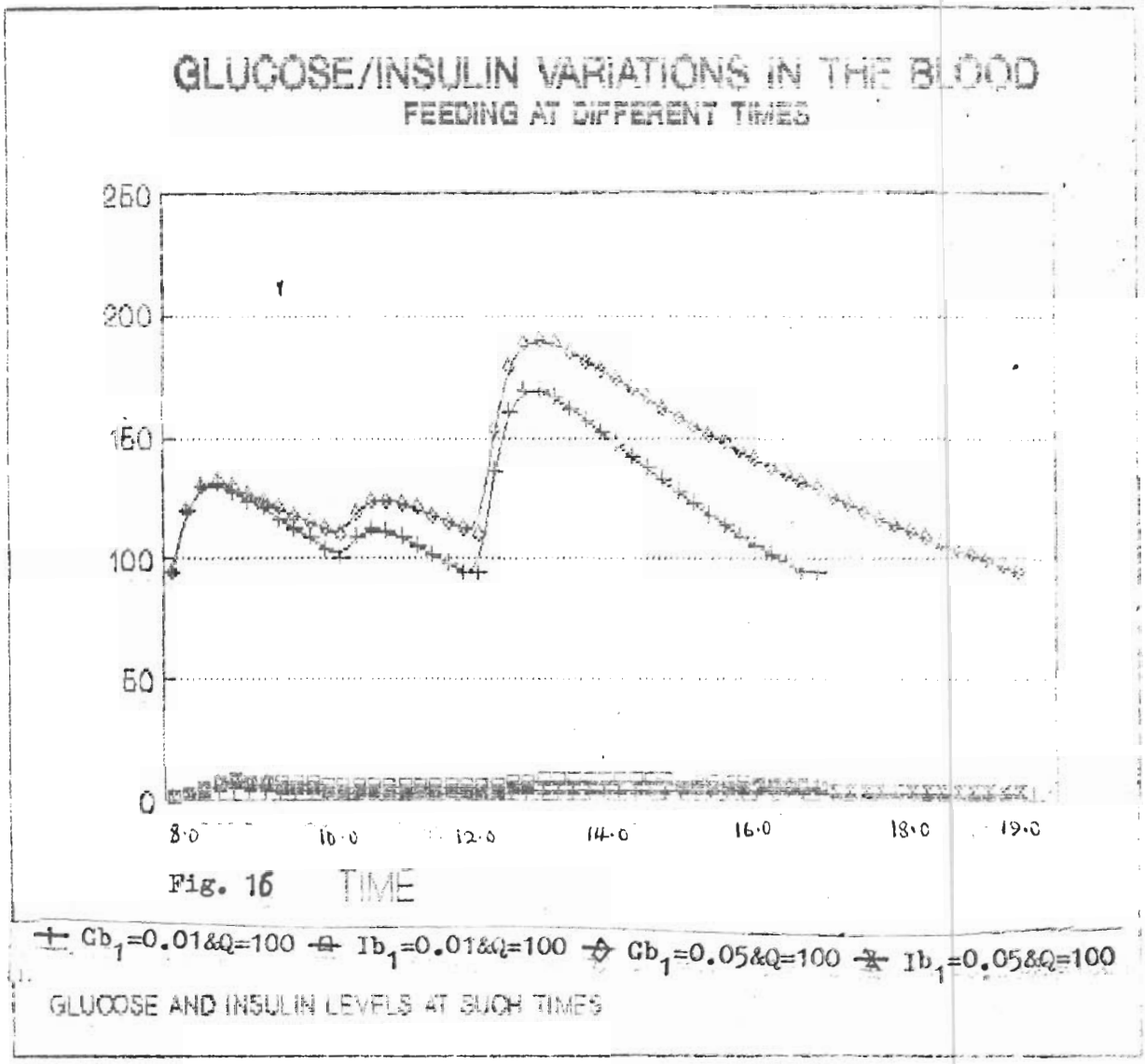

GLUCOSE/INSULIN VARIATIONS IN THE BLOOD
FEEDING AT DIFFERENT TIMES
250
200
150
100
50
0
8·0
10·0
12·0
14·0
16·0
18·0
19·0
TIME
Gb1=0.01&Q=100
Ib1=0.01&Q=100
Gb1=0.05&Q=100
Ib1=0.05&Q=100
GLUCOSE AND INSULIN LEVELS AT SUCH TIMES

Fig. 16

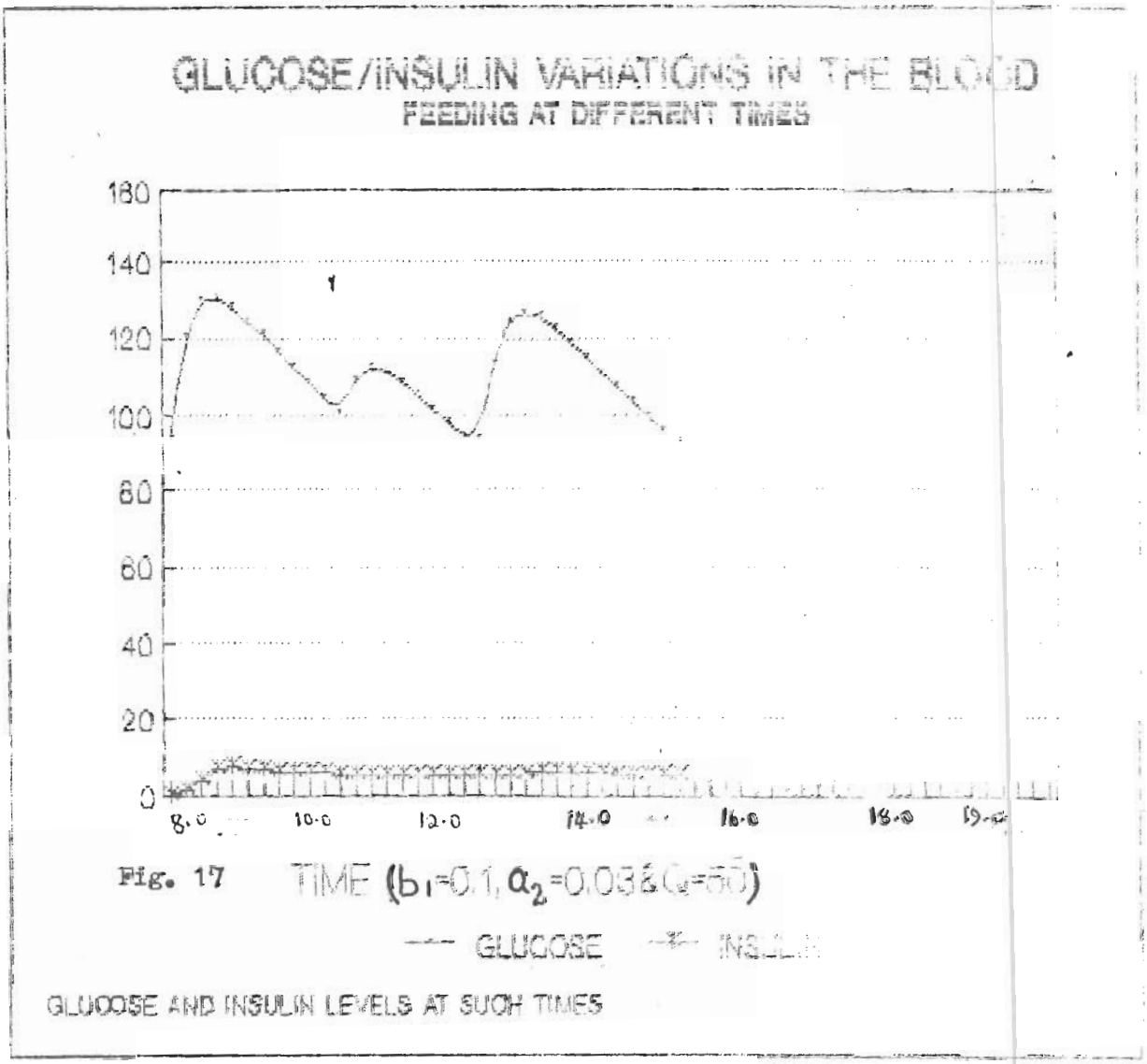

GLUCOSE/INSULIN VARIATIONS IN THE BLOOD
FEEDING AT DIFFERENT TIMES
180
140
120
100
80
60
40
20
0
8.0
10.0
12.0
14.0
16.0
18.0
TIME (b_1=0.1, α_2=0.03 & C_0=60)
GLUCOSE
INSULIN
GLUCOSE AND INSULIN LEVELS AT SUCH TIMES

Fig. 17

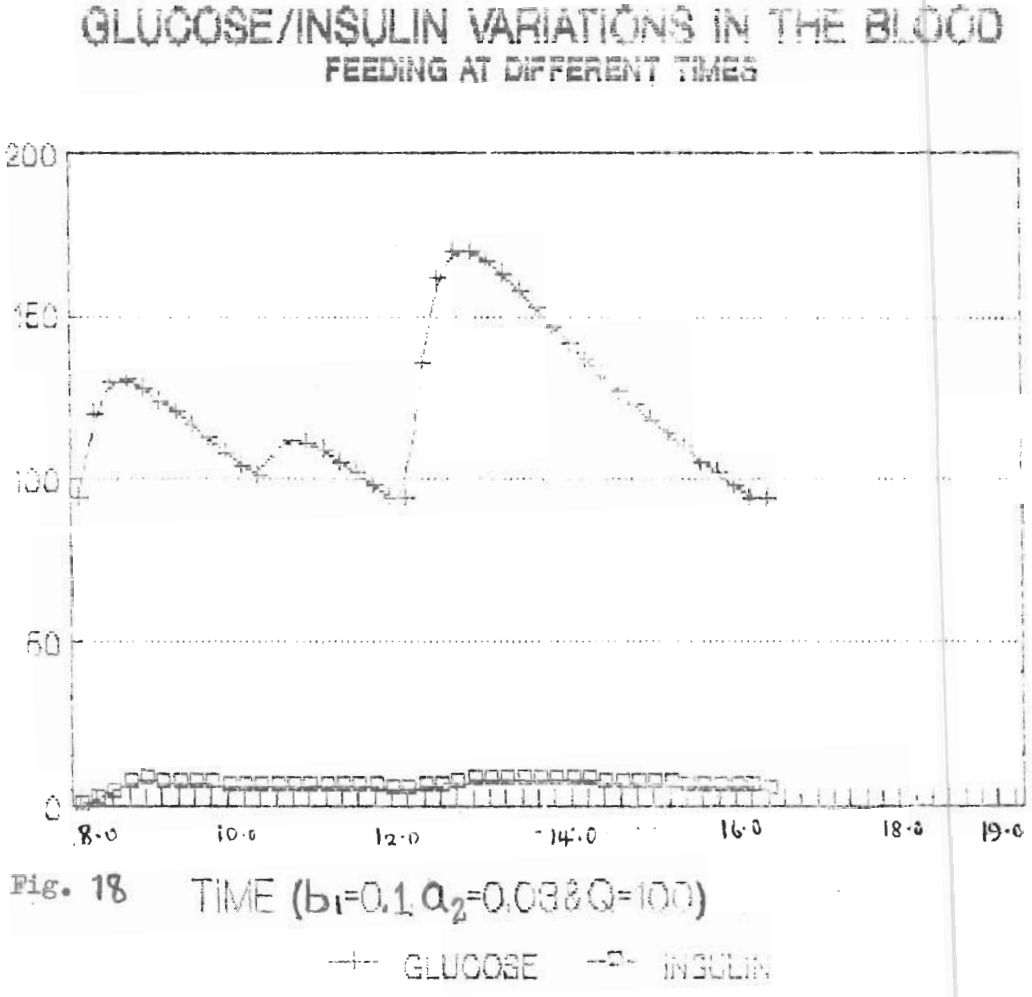


Fig. 18

GLUCOSE AND INSULIN LEVELS AT SUCH TIMES

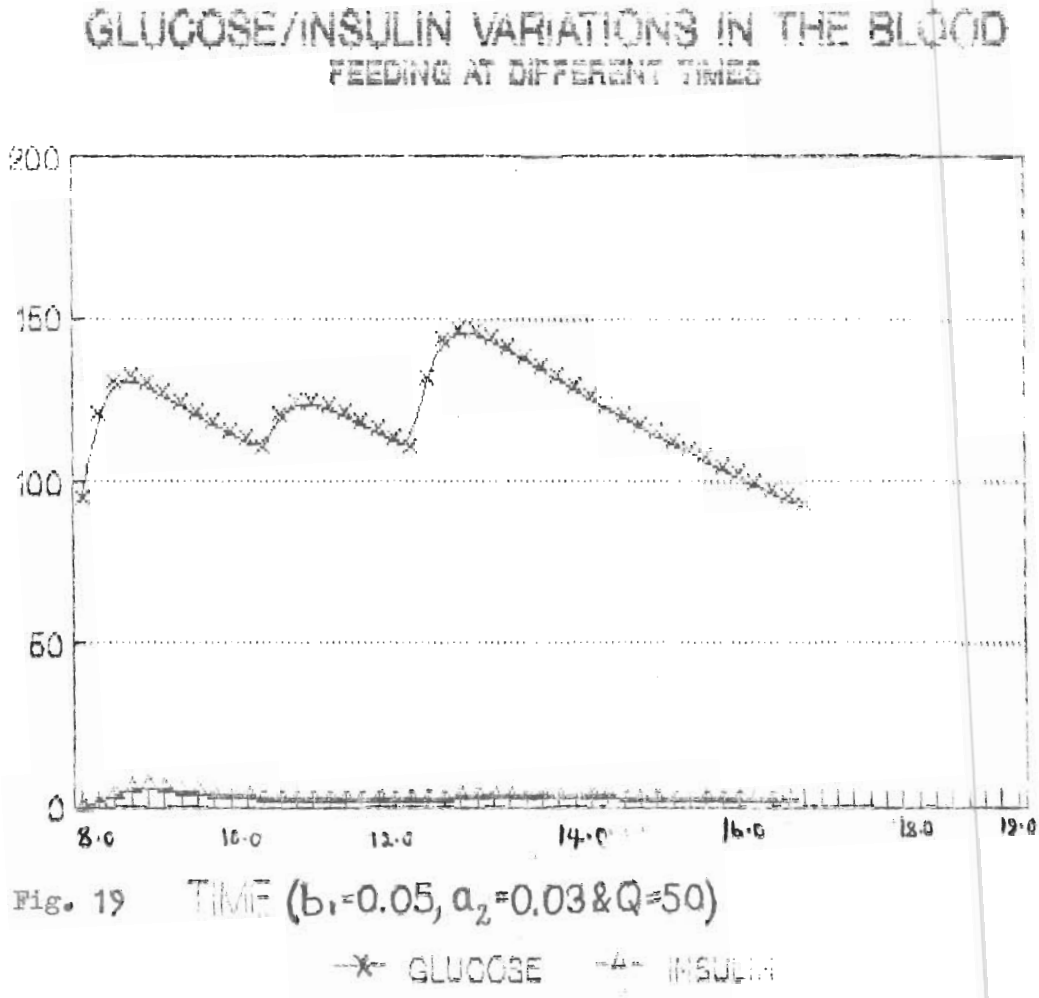


Fig. 19

GLUCOSE AND INSULIN LEVELS AT SUCH TIMES

GLUCOSE/INSULIN INTERACTIONS
FEEDING AT DIFFERENT TIMES

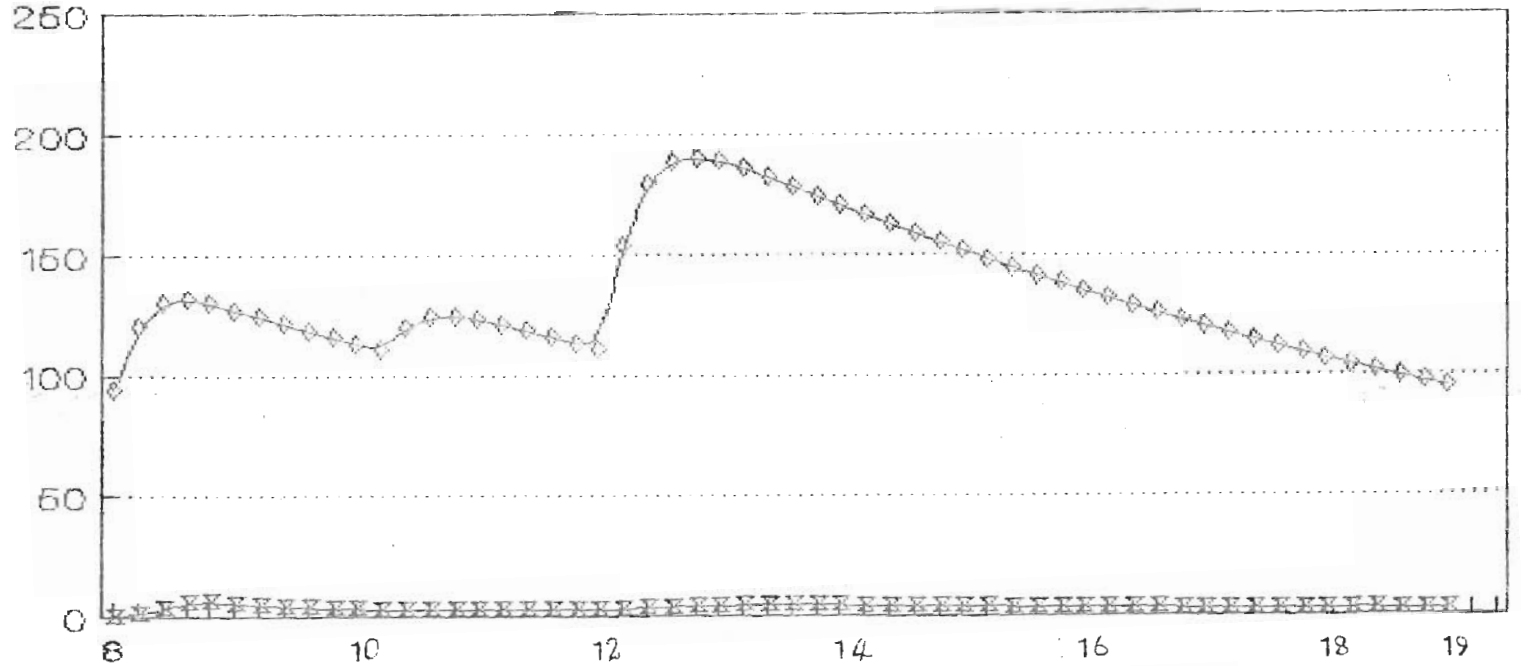


Fig. 20

GLUCOSE AND INSULIN LEVELS AT SUCH TIMES

GLUCOSE/INSULIN VARIATION IN THE BLOOD
A CASE STUDY OF A DIABETIC PATIENT

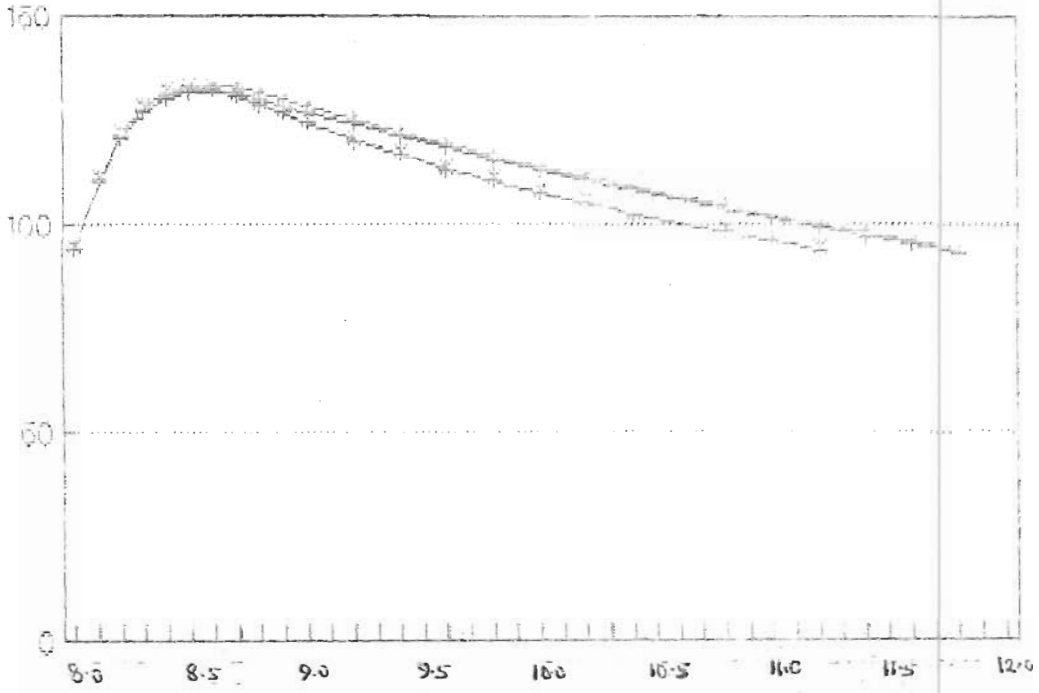


Fig. 21

COMPARISON OF METHODS OF SOLUTION OF THE MODELLED EQUATIONS

GLUCOSE/INSULIN VARIATIONS IN THE BLOOD
A CASE STUDY OF A DIABETIC PATIENT

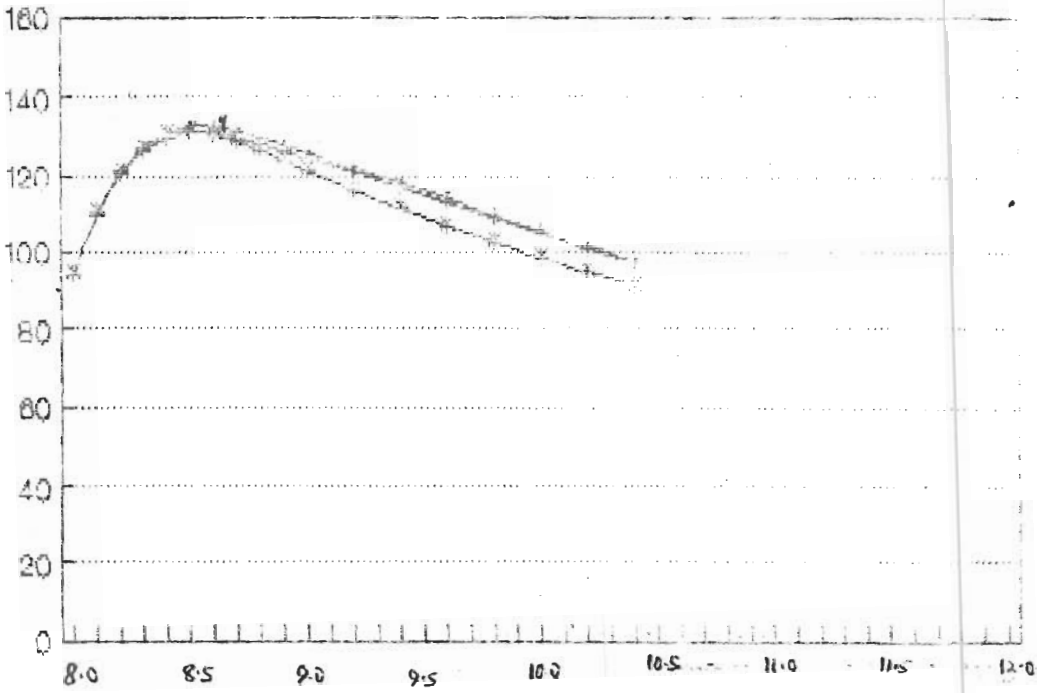


Fig. 21 TIMF (a_2=0.03 & b_1=0.1)

ANALYTICAL METHOD — APPROX. IN XY (NUM) — NON-LINEAR IN XY (Num)

COMPARISON OF METHODS OF SOLUTION OF THE MODELLED EQUATIONS.

GLUCOSE/INSULIN VARIATIONS IN THE BLOOD
A CASE STUDY OF A DIABETIC PATIENT

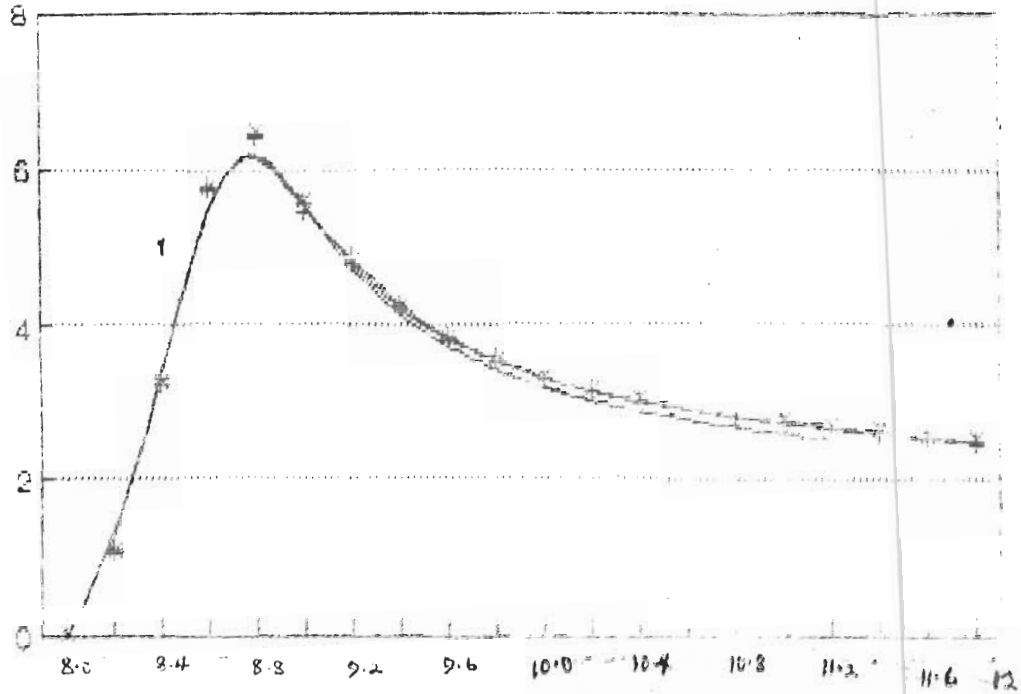


Fig. 23 TIME (=0.03, b1=0.05 & C=50)

NON-LINEAR IN X' (NUM) ANALYTICAL METHOD Y (NUM)

COMPARISON OF INSULIN LEVELS USING THE THREE METHODS

GLUCOSE/INSULIN VARIATIONS IN THE BLOOD

EFFECT OF VARIATION OF a_3 ON THE GLUCOSE/INSULIN LEVELS.

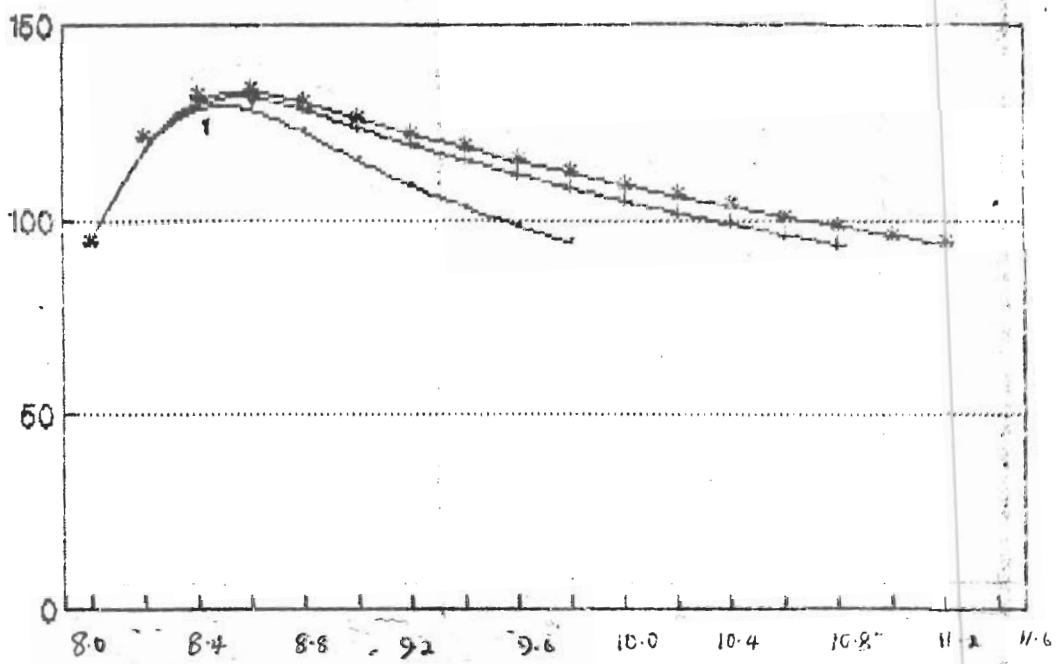


Fig. 24

SOLVING NUMERICALLY THE LINEARISED FORM OF THE MODELLED EQUATIONS.

GLUCOSE/INSULIN VARIATIONS IN THE BLOOD

EFFECT OF VARIATION OF a_2 ON THE GLUCOSE/INSULIN LEVELS.

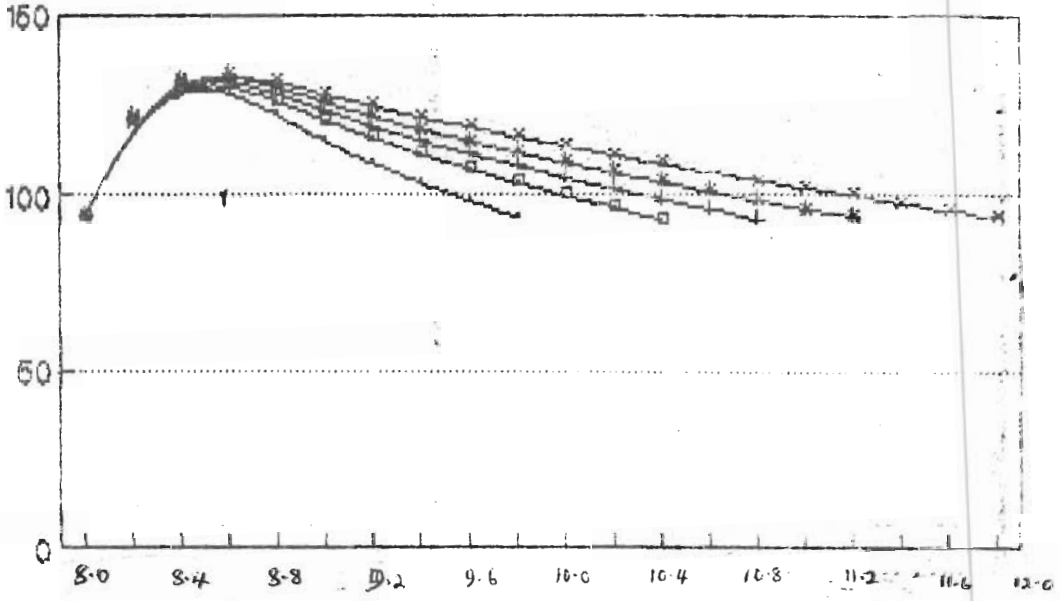


Fig. 25 TIME (b_1=0.05 & Q=50)

a_2=0.05 & a_3=0.04 a_2=0.03 & a_3=0.04 a_2=0.03 & a_3=0.03

a_2=0.05 & a_3=0.03 a_2=0.03 & a_3=0.02

SOLVING NUMERICALLY THE LINEARISED FORM OF THE MODELLED EQUATIONS.

WITHOUT INSULIN INFUSION

Glucose/Insulin interactions

Normal and Diabetic cases.

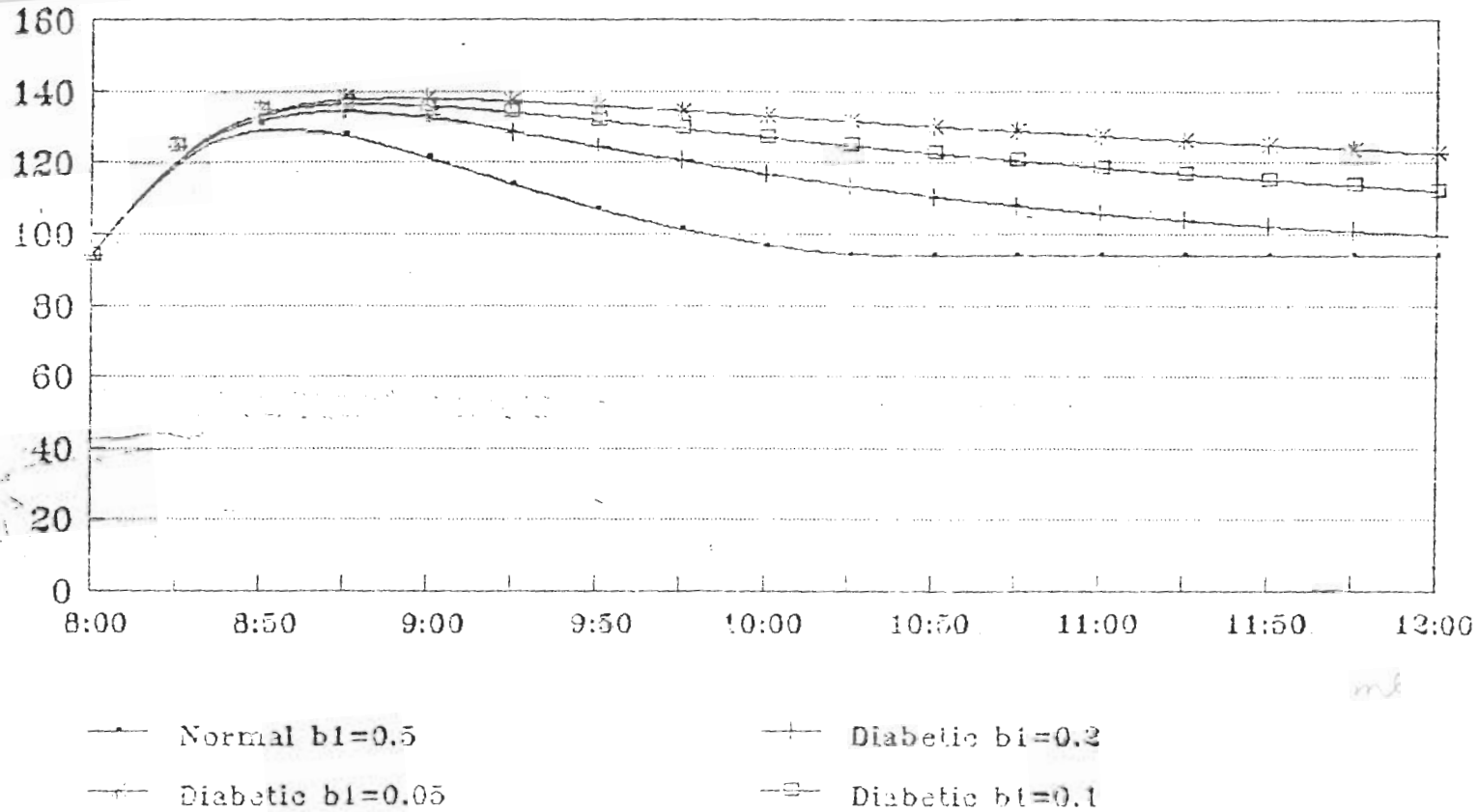


Fig. 26

Comparison of the results.

Glucose/Insulin interactions.
Normal and Diabetic cases.

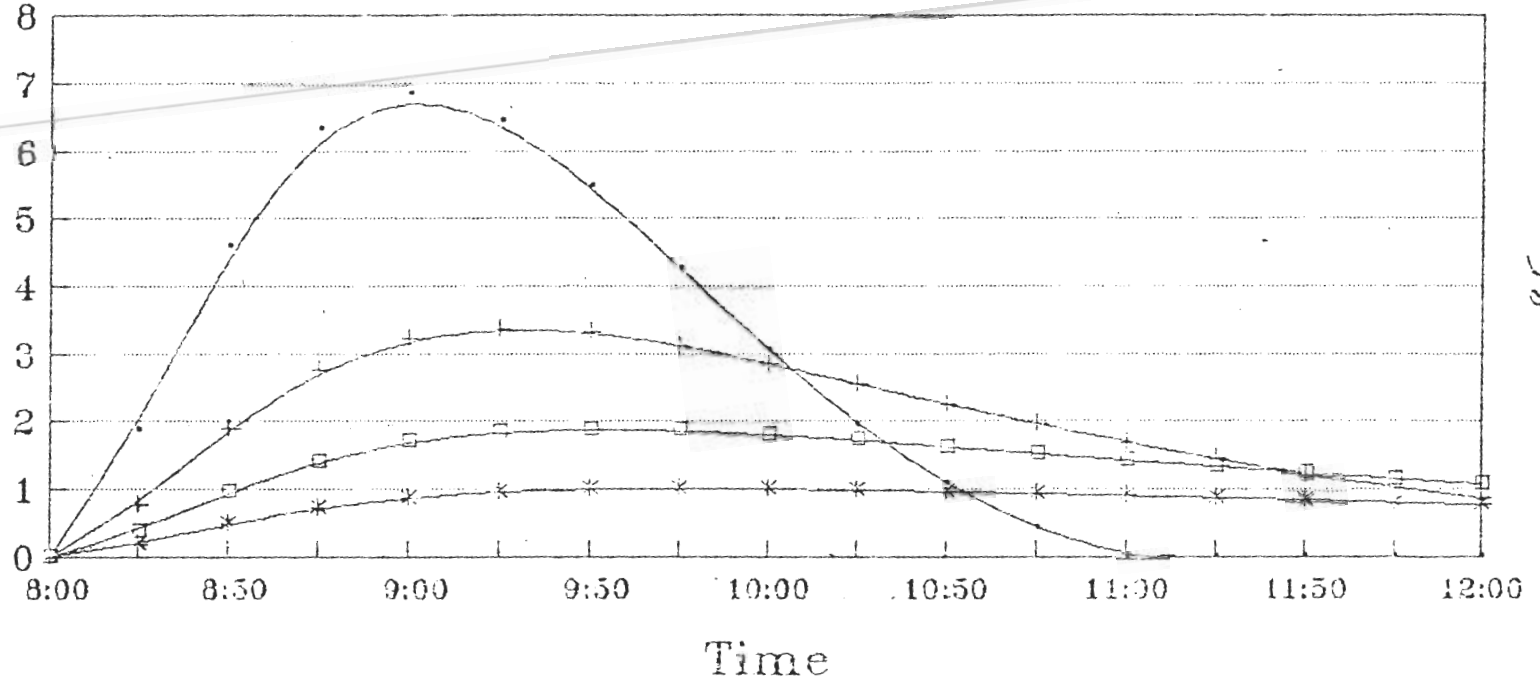


Fig. 27

Insulin levels without further infusion.

GLUCOSE/INSULIN INTERACTIONS IN MAN
EFFECT OF VARIATION OF a_3 ON THE GLUCOSE/INSULIN LEVELS.

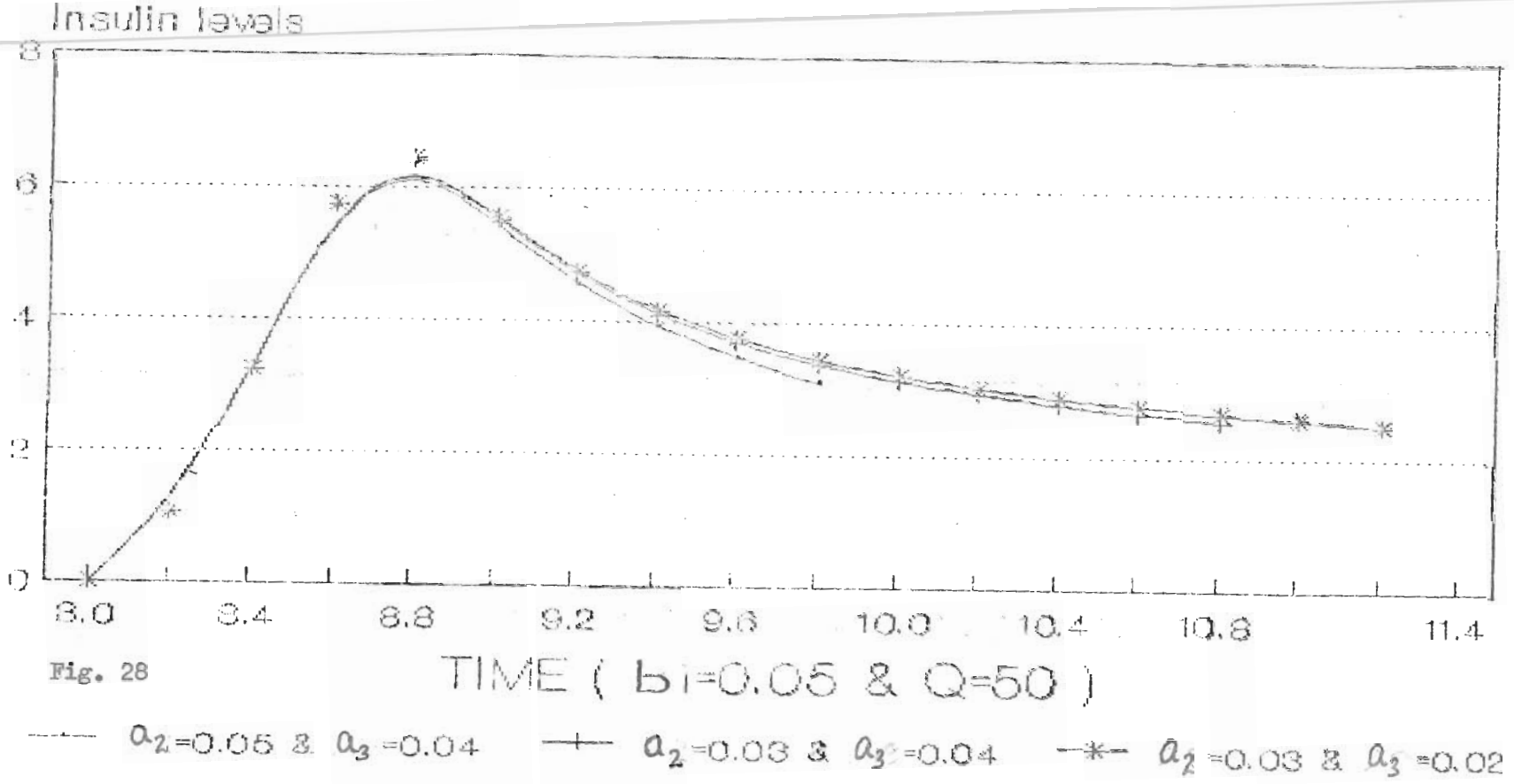


Fig. 28

...LVING NUMERICALLY THE LINEARISED FORM
... THE EQUATION.

GLUCOSE/INSULIN INTERACTIONS IN MAN
EFFECT OF VARIATION OF a_3 ON THE GLUCOSE/INSULIN LEVELS.

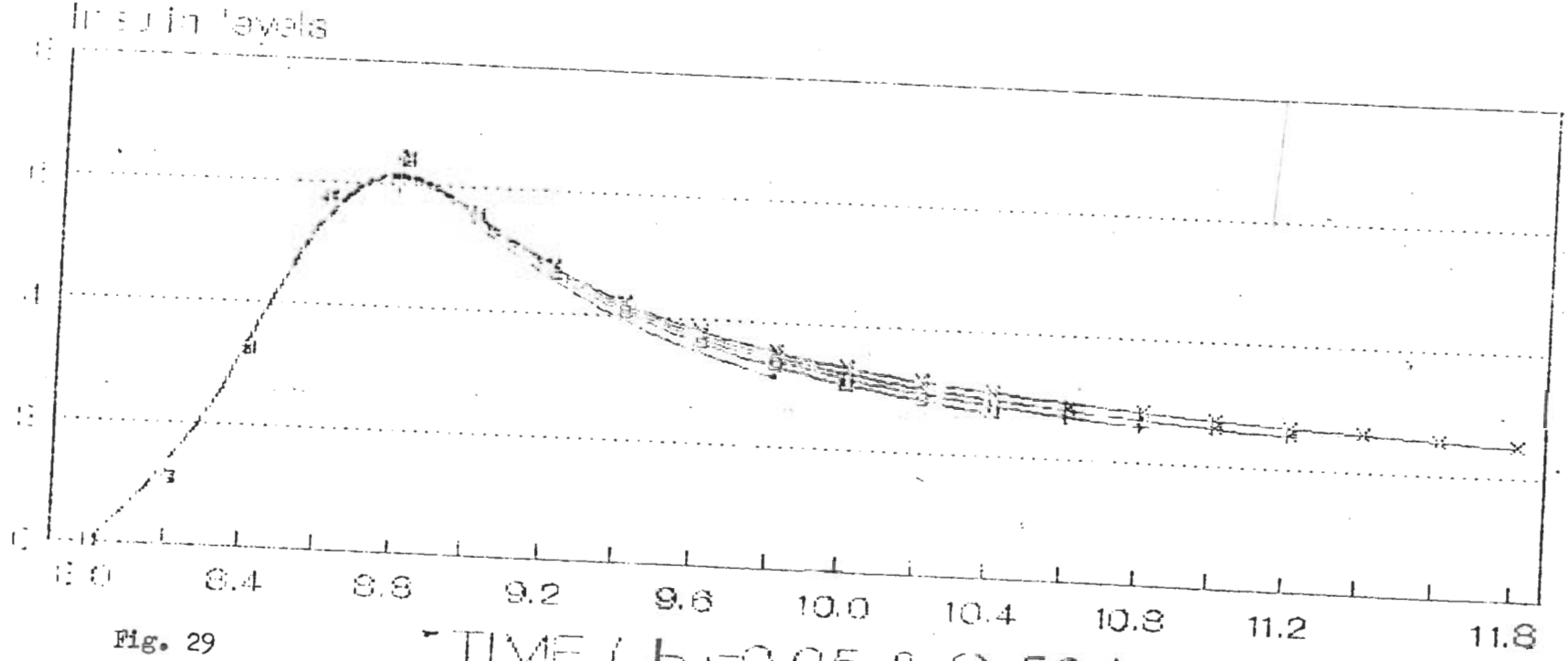
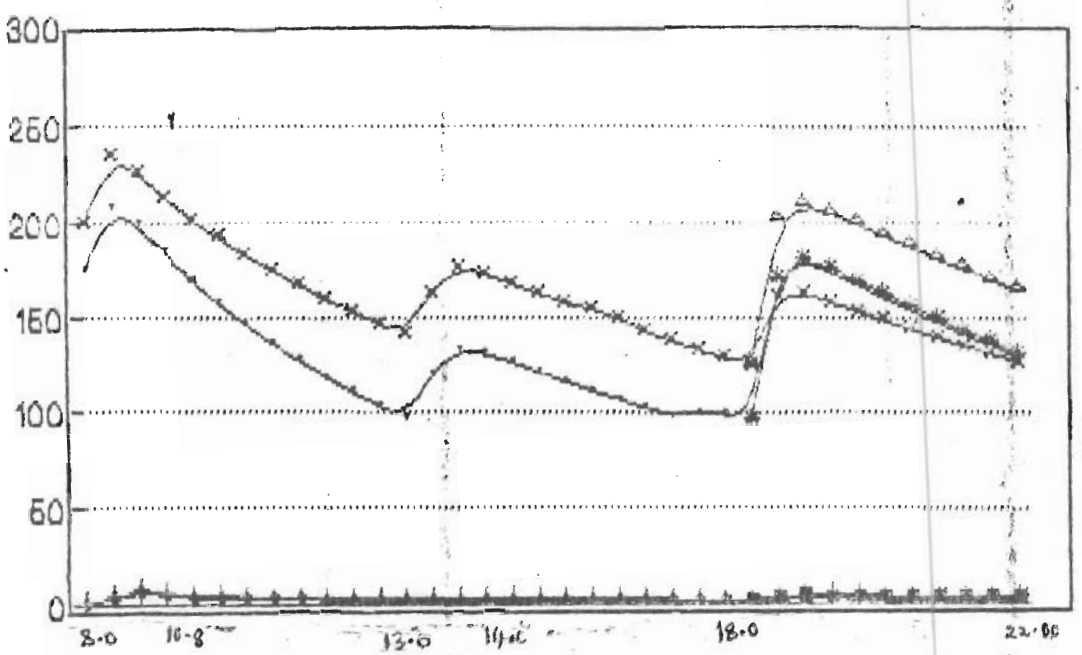


Fig. 29

NUMERICALLY THE LINEARISED FORM
EQUATION.

GLUCOSE/INSULIN VARIATIONS IN THE BLOOD
INITIAL TREATMENT WITH INSULIN INFUSION



TIME (HOURS)

Fig. 30

CQ=100&W=10 IQ=100&W=10 CQ=100&W=6.5 IQ=100&W=6.5

CQ=50&W=6.5 IQ=50&W=6.5 CQ =100&W=6.5 IQ=100&W=6.5

GLUCOSE AND INSULIN LEVELS FOR THE VARIED INSULIN DOSE.

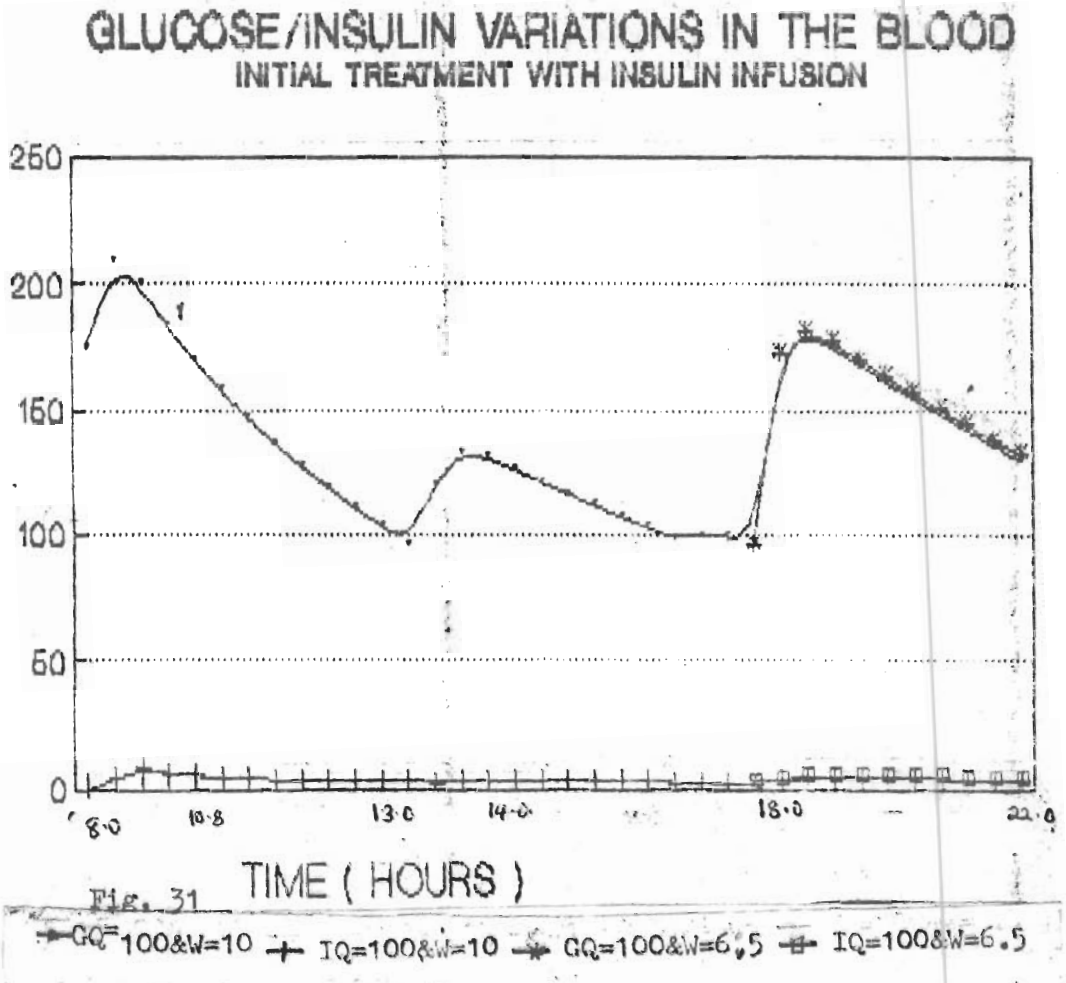


Fig. 31

GLUCOSE AND INSULIN LEVELS FOR THE VARIED INSULIN DOSE.

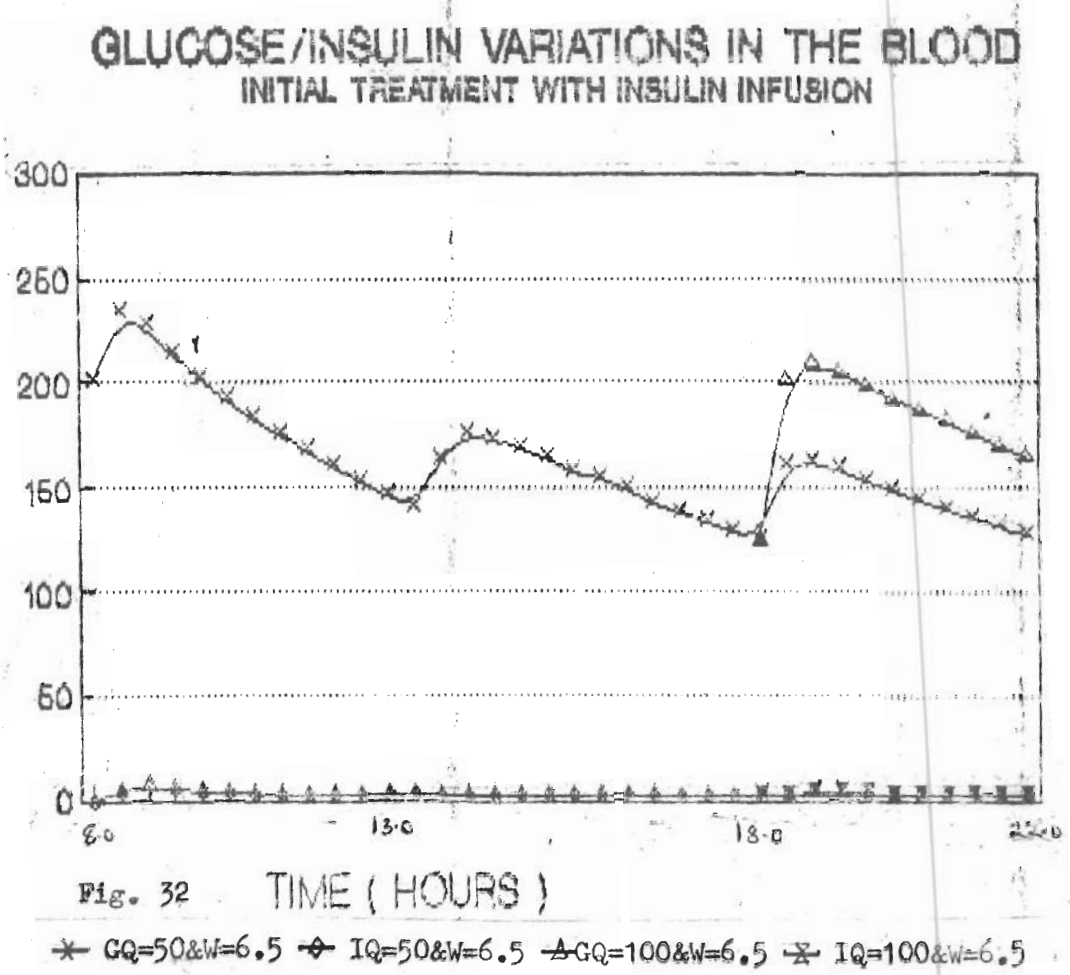


Fig. 32

GLUCOSE AND INSULIN LEVELS FORR THE
VARIED GLUCOSE AND INSULIN DOSE

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