THE GUT: A NOVEL PARTICIPANT IN GLUCOSE HOMEOSTASIS?

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UNIVERSITY OF IBADAN

THE GUT: A NOVEL PARTICIPANT IN GLUCOSE HOMEOSTASIS?

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By

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The Vice-Chancellor, Deputy Vice-Chancellor (Administration), Deputy Vice-Chancellor (Academic), The Registrar and other Principal Officers, Provost of the College of Medicine, Dean of the Faculty of Basic Medical Sciences, Deans of other Faculties and Postgraduate School, Dean of Students, Distinguished Ladies and Gentlemen.

Preamble

I give God the glory for this opportunity to stand before this audience in this hallowed chamber today to present an inaugural lecture on behalf of Faculty of Basic Medical Sciences. It is indeed a privilege to be asked to give this lecture some ten years after the University has pronounced me a Professor of Physiology. I am told that by tradition, inaugural lectures are to be given in the first five years of achieving the feat of becoming a professor. However, it is not unusual in recent times to see professors in the twilight of their career give such lectures almost simultaneously with their valedictory lectures! I thank the Dean of my Faculty for giving me this opportunity.

Today's inaugural lecture is the fourth from the Department of Physiology. The previous three lectures were delivered by my teachers and former Heads of Department. The first lecture from the department was delivered in 1984 by Professor R.A. Elegbe, whose lecture was titled: "Physiology: Genesis and Revelation of Medicine". He was followed by Professor D.D.O. Oyebola in 1987 on the topic, "Hospitals or Healers?: The Dilemma of Nigerian Patients", and Professor Adeyombo Bolarinwa in 2002 on "Leaving Certainty for Uncertainty: From the Stomach to the Womb".

Today's lecture is titled: The Gut: A Novel Participant in Glucose Homeostasis? I intend to discuss in this lecture, first, current knowledge on glucose homeostasis and its importance to the mammalian body. Secondly, I will discuss the emerging knowledge on the contribution of the gut to the regulation of blood glucose and highlight my contribution and those of other colleagues in providing evidence to support the role of the gut in glucose regulation. In doing this, I intend to

highlight the fact that it is only recently, as a result of studies carried out in our carbohydrate metabolism laboratory in the Department of Physiology in this University that it became known that the gut is an active paricipant in the regulation of blood glucose. Lastly, I will explain the likely physiological significance of this newly found function of the gut in the glucose homeostatic process.

The Gastro-Intestinal Tract (GIT)

The gut is scientifically known as the gastrointestinal tract. The anatomy of the GIT in mammals is well documented (Miller et al. 1961). Basically, it consists of the conduit that starts in the oral cavity and terminates in the anus. It is made of the oral cavity, the oesophagus, stomach, small intestine and large intestine. The small intestine consists of two parts: the relatively fixed and short proximal portion or duodenum, and the relatively moveable long distal portion, the ileum. The large intestine starts at the junction of the lieum and with the caecum and ends at the ano-rectal junction (fig. 1).

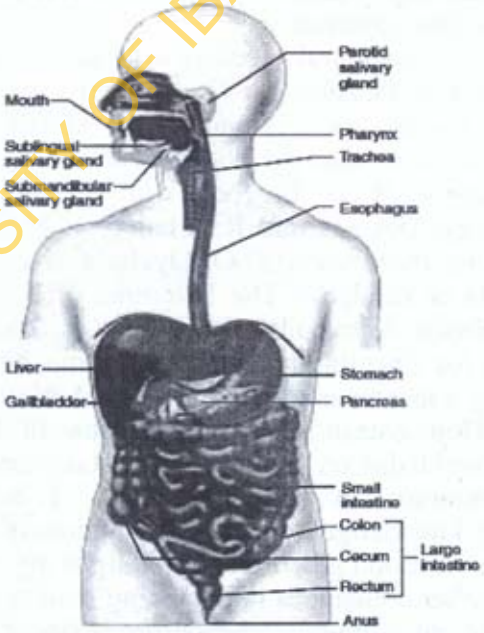

Fig. 1: The gastrointestinal tract (Adapted from Vander et al. 2001).

The gastrointestinal tract is the portal through which ingested food, vitamins, minerals and fluids enter the body. Proteins, fats and complex carbohydrates are broken down (digested) into absorbable units as they pass along the gastrointestinal tract. The products of digestion cross the intestinal mucosa and enter the lymph or blood through which they are transported to body tissues for immediate use as metabolic fuel or for storage. The principal dietary carbohydrates are polysaccharides, disaccharides and monosaccharides. While the monosaccharides are absorbed without further breakdown, the disaccharides are rapidly hydrolysed into hexoses such as fructose, galactose and glucose which are then absorbed in the intestine. The fructose and galactose are later converted into glucose (Crane 1968). Consequently, monosaccharides and disaccharides cause a prompt increase in plasma glucose concentration, whereas, carbohydrate presented in the form of polysaccharides after 12 - 18 hours of fasting, enters the blood stream more slowly and causes less dramatic increase in plasma glucose (Levine and Haft 1970). Therefore, in view of its carbohydrate digestive and absorptive functions, the role of the intestine in post-feeding rise in blood glucose is not in doubt.

Plasma Glucose: From Origin to Fates

Arterial plasma glucose values throughout a 24-h period average approximately 90 mg/dl, with a maximal concentration usually not exceeding 165 mg/dl such as after ingestion of carbohydrate meal (Rizza et al. 1980), and remaining above 55 mg/dl even after exercise (Wahren et al. 1978) or a moderate fast (30 - 60h) (Consoli et al. 1987). This relative stability of blood glucose contrasts with the situation for other substrates such as glycerol, lactate, free fatty acids, and ketone bodies whose fluctuations are much wider (table 1) (Gerich 1993).

This narrow range defining normal blood glucose level (normoglycaemia) is maintained through an intricate regulatory and counterregulatory neuro-hormonal system: a

decrease in plasma glucose as little as 20 mg/dl (from 90 to 70 mg/dl) will suppress the release of insulin and will decrease glucose uptake in certain areas in the brain (e.g. hypothalamus where glucose sensors are located); this will activate the sympathetic nervous system and trigger the release of counterregulatory hormones (glucagon, catecholamines, cortisol and growth hormones) (Gerich 1988). All these changes will increase glucose release into plasma and decrease its removal so as to restore normal blood glucose level. On the other hand, a 10 mg/dl increment in plasma glucose will stimulate insulin release and suppress glucagon secretion to prevent further increments and restore normal plasma glucose level.

Table 1: Circulating Substrates and Regulatory Hormones after Overnight, Moderate and Prolonged Fasting

	Overnight fast (12-16h)	Moderate fast (30-60h)	Prolonged fast (>1 week)
Substrates (mmol/l)			
Glucose	5.0	4.0	3.0
Free fatty acids	0.5	1.0	1.5
Glycerol	0.05	0.1	0.2
3-Hydroxybutyrate	0.02	0.5	1.0
Lactate	0.8	0.8	0.7
Glutamine	0.6	0.5	0.4
Alanine	0.3	0.2	0.2
Hormones			
Insulin (pmol/l)	60	40	20
Glucagon (ng/l)	100	150	150
Cortisol (mmol/l)	0.3	0.5	0.9
Growth hormone ng/l)	<2	4	8
Triiodothyronine (nmol/l)	1.8	1.6	0.9
Epinephrine	0.2	0.4	0.6

Source: Gerich 1993.

The normal blood glucose level is maintained by a balance between glucose entering the blood stream and that leaving it. Glucose entering the circulation includes glucose absorbed from the intestine from ingested carbohydrate, glucose released from stored glycogen (glycogenolysis) and glucose newly synthesised from non-carbohydrate sources (gluconeogenesis) (fig. 2). In humans, glucose removed from plasma may have different fates in different tissues and under different conditions (postabsorptive vs postprandial), but the pathways for its disposal are relatively limited. It may be immediately stored as glycogen or may undergo glycolysis, which can be non-oxidative producing pyruvate (that can be reduced to lactate or transaminated to form alanine), or oxidative through conversion to acetyl CoA that is further oxidized through the tricarboxylic acid cycle to form carbon dioxide and water. Non-oxidative glycolysis carbons undergo gluconeogenesis and the newly formed glucose is either stored as glycogen or released into plasma (fig. 3).

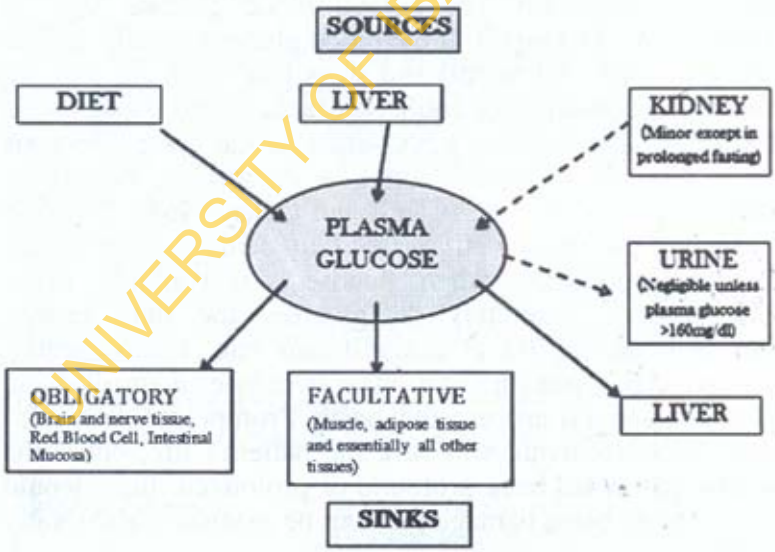

Fig. 2: Sources and sinks of plasma glucose (From Best and Taylor's *Physiological Basis of Medical Practice*. Ed. J.M. West, pp 793).

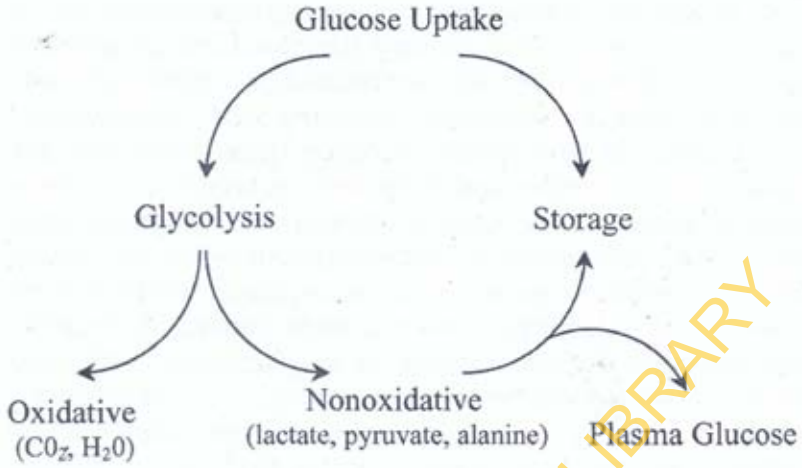

Fig. 3: Route of postprandial glucose disposal (From Woerle et al. 2003).

Importance of Glucose Homeostasis

Maintenance of blood glucose levels within fairly narrow limits (glucose homeostasis) is of vital importance in the mammalian organism. The normal blood glucose level in humans is 70 - 110 mg/dl. If the blood glucose rapidly falls to a low level (40 - 50 mg/dl) and stays low, even for 5 or 10 minutes, the consequence could be dramatic and drastic. This is because under ordinary circumstances, the central nervous system depends absolutely upon a continuing minute-to-minute supply of glucose (Cahill and Owen 1968). Whereas most tissues can readily utilise free fatty acids or other blood-transported substances when glucose is unavailable, nerve tissue depends absolutely on glucose, the only energy substrate it can utilise at a significant rate. Consequently, sustained hypoglycaemia (e.g. after overdose of insulin) can lead to coma and if uncorrected, death. Prompt intervention to correct hypoglycaemia will save the patient's life, but if the hypoglycaemia has been profound or prolonged, there would be irreversible brain damage that can be extensive and totally disabling.

Abnormal elevations of blood glucose levels (hyperglycaemia) do not pose any analogous acute threat, yet prolonged hyperglycaemia is also ultimately life-threatening.

If blood glucose levels above 300 or 400 mg/dl are sustained for days, the patient will lose a large amount of glucose in the urine (glucosuria). This will entail an obligatory loss of water and electrolyte, leading to progressive dehydration, decrease in blood volume (hypoglycaemia), hypotension, shock and coma. Prolonged hyperglycaemia also, then, can ultimately lead to death.

These dramatic consequences of extreme acute departures from the norm illustrate the importance of glucose homeostasis. It should be stressed, however, that even relatively small departures from the norm may be deleterious if sustained chronically. For example, a growing body of evidence indicates that even modest hyperglycaemia over a period of years may account for the dysfunction of the nervous system, blood vessels, kidneys and other tissues associated with end organ effects of diabetes mellitus (Butler and Rizza 1989).

Regulation of Blood Glucose Levels and Glucose Homeostasis

The relative constancy of blood glucose level in the normal animal under varied conditions of feeding and fasting indicates the existence of adequate regulating mechanisms. On the other hand, the hyperglycaemia and the great dependence of the blood glucose level of the diabetic organism on the kind and amount of ingested food indicates a profound disturbance in the regulating mechanisms. Blood glucose concentration is dependent upon the balance of glucose entering and leaving the blood circulation (fig. 2).

Sources of the Blood Glucose Pool

There are only three sources of blood glucose (table 2).

(A) Dietary Sources

Very few foods contain significant amounts of free glucose. Significant quantities of glucose are presented in form of disaccharides, especially sucrose, and in the form of polysaccharides (mainly, starch in plant foods and some

glycogen in animal foods). Disaccharides are rapidly hydrolysed; the fructose and galactose moieties are rapidly absorbed and converted to glucose. Consequently, monosaccharides and disaccharides cause a prompt increase in blood glucose concentration whereas glucose presented in the form of polysaccharides enters the blood stream more slowly and causes less of a spike in blood glucose concentration.

(B) Glucose from Liver through Glycogenolysis

Three to four hours after carbohydrate ingestion, the liver reverts from net glucose uptake and glycogen storage to net glucose release (Butler and Rizza 1989). Hepatic glucose release continues to increase over the next several hours until it equals glucose utilization, resulting in a stable blood glucose concentration. After an overnight fast, glucose production is almost exclusively by glycogenolysis in the liver (Wahren et al. 1971).

(C) Glucose from Liver through Gluconeogenesis

Amino acids derived from dietary proteins (with the exception of lucine) can all contribute to *de novo* glucose formation. For example, alanine, after transamination to yield pyruvate, can be converted quantitatively to glucose under the right conditions (Cahill 1970).

In prolonged fasting or in diabetic ketoacidosis, acetone, generated by decarboxylation of acetoacetate, has the potential to contribute carbons to glucose formation, but this is a minor pathway. Thus, the triglycerides in diet are a rather insignificant source of carbon atoms for gluconeogenesis, since only the carbon atoms in the glycerol moiety can contribute (Jeanrenand 1968). The glycerol released from the triglycerides can be readily converted to glucose in the liver. Thus about 10% of the carbon atoms in a triglyceride constitute a source of glucose formation (Hirsch and Goldrick 1964; Galton 1968). While fatty acids do not contribute carbon atoms for gluconeogenesis, they nevertheless strongly stimulate gluconeogenesis from other precursors (Galton 1968).

Table 2: Sources of Plasma Glucose

1.	Dietary sources	Polysaccharide - starch Dissaccharides - Sucrose - Maltose - Lactose
2.	Liver	Glycogenolysis - Glycogen ⟹ Glucose
3.	Liver	Gluconeogenesis - Amino acids - Glycerol - Free Fatty Acids ⟹ Glucose

Sinks for Blood Glucose

All body tissues can and do utilise blood glucose. Some are obligatory users i.e. they cannot use alternative substrates when glucose is unavailable. The nervous system in man for instance, requires about 125 - 150 gm of glucose daily under most conditions. However, in prolonged starvation (5 - 6 weeks), the brain undergoes an interesting metabolic switch that allows it to utilise ketone bodies in place of over 50% of its usual glucose requirement (Owen et al. 1967). During such starvation, fatty acids are continually mobilised from the huge stores of adipose tissue triglycerides, and a portion of them is continually converted to ketone bodies in the liver. This adaptation in metabolism of the brain ensures that it can survive with less drastic depletion of muscle protein to provide substrates for new gluconeogenesis (Cahill 1970).

A few other tissues utilise glucose almost exclusively. These include red blood cells, the intestinal mucosa and the renal medulla (Kealey 1983; Kreisberg 1972). Their use of glucose is largely or exclusively via anaerobic glycolysis. Most of the body tissues, however, are facultative users of glucose. When free fatty acid levels are high and glucose levels are low, as in fasting state, these tissues can and do switch to free fatty acid as their primary metabolic fuel (Levin and Haft 1970).

The Liver as a Glucostat

The liver (fig. 4) is both a source and a sink for blood glucose. In fact, both uptake and release of glucose are going on at all times in the liver. The net balance is under multiple controls such as hormonal and neural signals, that determine whether at any given time it represents a source (net input into the blood stream) or a sink (net uptake from the blood stream). In the absence of the supervening hormonal or neural signals, the liver shows a net output of glucose when the blood glucose level is low and a net uptake of glucose when the blood glucose level is high (Hers 1976). Because of this dual role in the regulation of blood glucose, the liver is therefore referred to as a "glucostat".

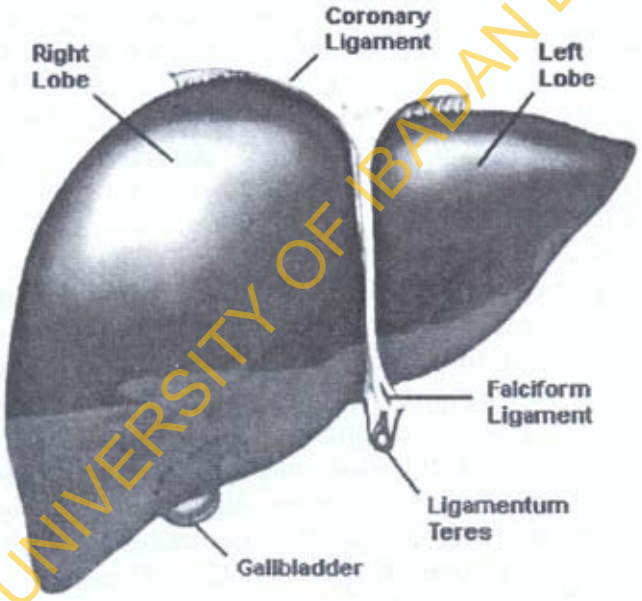

Fig. 4: The liver (©2008 WebMD, LLC).

The increase in blood glucose and the hormone insulin concentrations associated with ingestion of a mixed meal, results in stimulation of glycogen synthase and inhibition of

glycogen phosphorylase (Hems and Whitton 1980). This reciprocal change in enzyme activity, together with an inhibition of glucose-6-phosphatase activity, causes a decrease in hepatic glucose release and a net increase in hepatic glycogen (Newgard et al. 1984). The observation in animals of an inverse relationship between glucose release (or uptake) and portal venous glucose concentration when insulin concentration remains constant has led to the suggestion that portal venous glucose concentrations regulate hepatic glucose release, whereas insulin determines the sensitivity of the liver to glucose (Bergman and Buccolo 1974).

Apart from the liver, there are many other organs which play important roles in glucose homeostasis. A few of the key organs will be briefly mentioned in this presentation.

Roles of Extra-Hepatic Tissues in Glucose Homeostasis

(A) The Kidney (fig. 5)

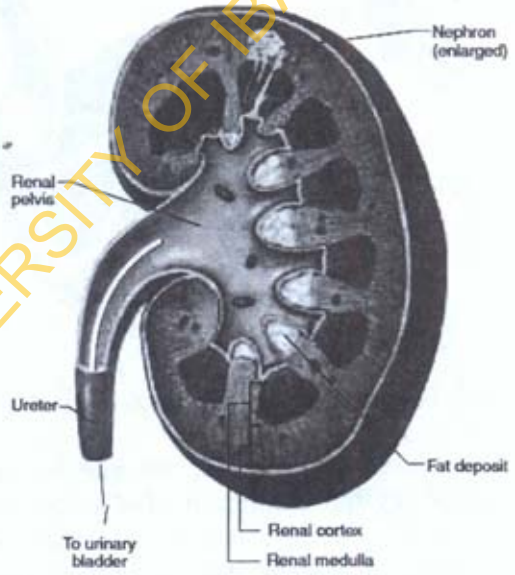

Fig. 5: The kidney (From Vander et al. 2001).

It has been known for many years that the kidney is an auxiliary glucose-producing organ. Under normal conditions, the kidneys are a site of glucose utilisation rather than glucose production according to catheterisation studies in dogs. However, renal gluconeogenesis becomes important during prolonged starvation (Johnson and Madison 1968; Owen et al. 1969). In obese humans starved for 35 to 40 days, the kidneys contributed 45% of the glucose released into the blood (Owen et al. 1969).

(B) Skeletal Muscle (fig. 6)

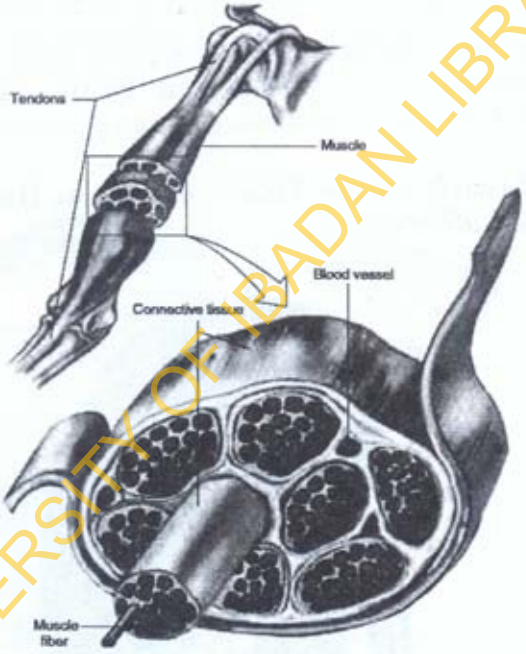

Fig. 6: Skeletal muscle (From Vander et al. 2001).

In the post absorptive state, at rest, the skeletal muscle takes in and consumes negligible amount of glucose (Andres et al. 1956; Mahler et al. 1968). After a carbohydrate meal, the arterial blood glucose and its insulin content both rise. The effect is to permit entry of glucose into skeletal muscle

(Levine and Haft 1970). If the insulin level of the plasma had not risen, glucose entry would still be increased owing to the increase in the substrate level (Soskin and Levine 1937), although insulin is probably the more important factor in augmenting glucose uptake (Wick and Drury 1951). The presence of additional insulin not only serves to increase transport rates, but also shifts the glucose that has entered preferentially into the path of glycogen synthesis. This is due to an activation of the synthetase step (Larner et al. 1968).

Although skeletal muscle has the greatest total glycogen store, it is unable to release significant amounts of glucose since it lacks glucose-6-phosphatase (Lackner et al. 1984). The product of glycogen breakdown in the skeletal muscle is therefore lactic acid which is released into circulation and subsequently taken up by the liver and reconverted to glucose via gluconeogenesis. This process is referred to as the Cori cycle (Cori 1931). The Cori cycle may account for 10 to 40 per cent of hepatic glucose output (Kreisberg et al. 1970). The maintenance of normal glycogen content in skeletal muscle is important for heavy muscular work, although fatty acids could supply at least 60% of the metabolic fuel (Issekut and Paul 1968).

(C) Adipose Tissue (fig. 7)

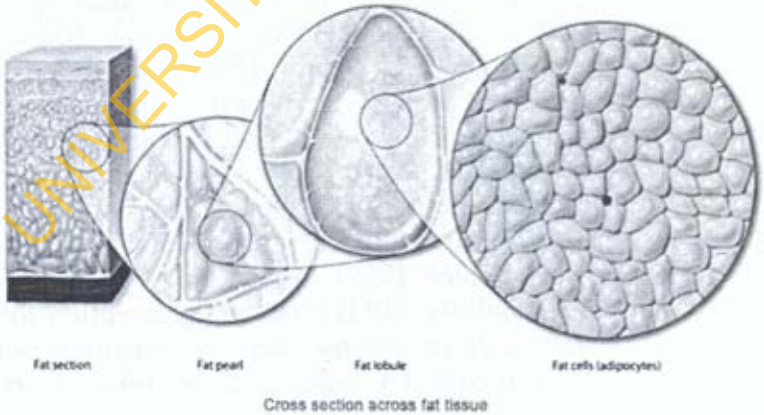

Fig. 5: Adipose tissue.

The fat cell is involved in glucose homeostasis in two ways. Firstly, during fasting and in diabetes mellitus, lipolysis (breakdown of fat) is activated (Jeanrenand 1968). Secondly, when a particular adipose tissue segment in the body builds fat from glucose directly. This serves to lower blood glucose levels and to sequester temporarily or permanently a glucose load. The adipose cell has a transport system that is also sensitive to insulin.

The Role of Gut in Glucose Homeostasis

Under normal condition, the gastrointestinal tract is not known to be quantitatively involved in glucose homeostasis. Apart from its well known glucose absorption role, the role of gastrointestinal tract in glucose metabolism and its homeostasis in the post-absorptive period is not clear. Most of the early data available on the metabolism of the intestine in situ were based on measurement of oxygen consumption and carbon dioxide production (Alteveer et al. 1973). Several other workers have investigated the problem of intestinal metabolism of glucose with the use of in vitro preparations. Hohenleitner and Senior (1969) perfused isolated canine intestinal segment with various liquids including radio-labelled glucose to estimate the extent of carbohydrate metabolism under various conditions. In this study, the actively contracting preparations removed perfusate's glucose at a high rate; and since high lactate production was associated with considerable glucose removal from the perfusate, Hohenleitner and Senior (1969) suggested that most of the lactate was probably derived from the metabolism of the perfused glucose. However, the occassional outpouring of lactate far beyond that which could be accounted for from glucose utilised from the perfusate alone suggests that tissue glycogen may also be utilised under some conditions (Hohenleitner and Senior 1969). About thirty years earlier, Dicken and Weil-Malhrbe (1941) had called attention to the high rate of aerobic glycolysis by intestinal mucosa in vitro, an observation subsequently confirmed by other workers

(Anderson 1974; Leese and Bronk 1975; Hanson and Parson 1976). Thus, glucose was generally regarded as the major source of energy of the gastrointestinal tract and was usually the only substrate added in experiments involving incubation of the intestine in vitro.

However, Grayson and Kinnear (1962), using heat production as the main indicator of metabolic activity had shown that the intestine is a site of high metabolic activity. They computed that the gastrointestinal tract contributes about 30% of the body's heat production by processes which are independent of digestion, absorption or bacterial activity. Subsequent work by Durotoye and Grayson (1971) showed that oxidative processes alone could not account for this high level of heat production. When glucose uptake was measured and converted into energy equivalent, they found that the net glucose uptake was far in excess of what could be accounted for on the basis of oxidative metabolism alone. When catechlamines were administered (Durotoye and Grayson 1971), it was reported that the increases observed in glucose uptake and oxygen consumption were not compatible in quantity. A decade later, Grayson and Oyebola (1983) measured glucose uptake and oxygen consumption in the upper jejunum of dogs. They showed that the intestine has a capacity for a huge glucose uptake which was far more than could be accounted for on the basis of oxidation. When the animal was challenged with adrenaline or noradrenaline, glucose uptake and oxygen consumption by the intestine rose; but the increase in glucose uptake was far more than the increase in oxygen consumption. Also, the increase in glucose uptake and oxygen consumption did not occur at corresponding times (fig. 8).

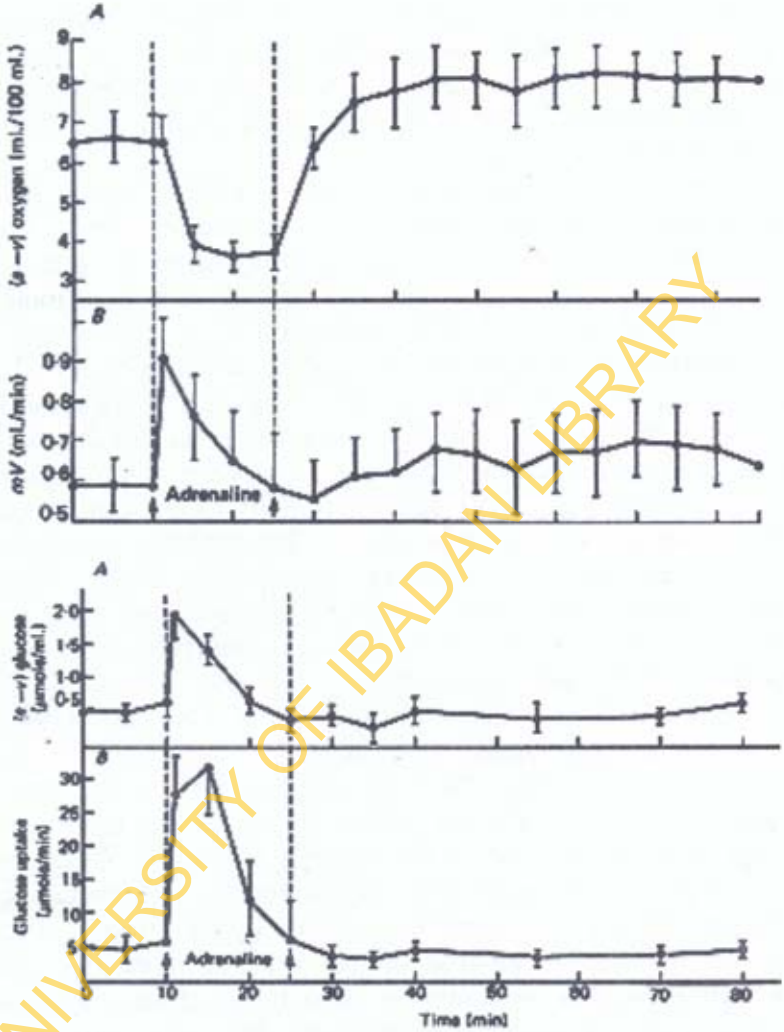

Fig. 8: Effects of adrenaline on intestinal glucose uptake, (A-V) glucose, jejunal blood flow and oxygen consumption (From Grayson and Oyebola 1983).

While a huge increase occured in glucose uptake during adrenaline infusion, oxygen consumption actually decreased. Again, Grayson and Oyebola (1985) showed that when nicotine was administered, it caused several folds increase in

glucose uptake and oxygen consumption by the canine small intestine. They therefore, concluded that since the results from the nicotine study are essentially similar to those of adrenaline; effects of nicotine on blood glucose are secondary to its action on the adrenal gland whereby catecholamines are released. Similar findings were reported in the canine terminal ileum (Oyebola and Durosaiye 1988).

Current evidence suggests that the huge amount of glucose taken up by the gastrointestinal tract is largely not utilized for oxidative metabolism and that glucose is not the main substrate of intestinal metabolism. Windmueller and Spaeth (1978) showed that isolated, vascularly perfused preparations of rat intestine took up from the circulation nearly as much glutamine as glucose, and glutamine accounted for more than 30% of the carbon dioxide produced. Indeed, the authors showed that the substrates preferred for oxidative metabolism in the intestine are glutamine and ketone bodies and glucose contributes only about 7%.

These results and those of earlier workers suggest that the gastrointestinal tract is more involved in glucose homeostasis than in glucose metabolism. The exact nature of this involvement is however not clear. A number of questions therefore remain unanswered. Firstly, since it was observed that the gastrointstinal tract will take large quantities of glucose during hyperglycaemia induced by adrenaline or nicotine (Grayson and Durotoye 1971; Grayson and Oyebola 1983, 1985), will the gut take up large quantities of glucose if hyperglycaemia is induced by other means or is this response specific to catecholamine-induced hyperglycemia only? How will the gastrointestinal tract respond to infusion of other sugars such as fructose and galactose instead of glucose? What will the response of the gastrointestinal tract be with respect to glucose handling when blood glucose level is reduced below normal resting value? What are the mechanisms of the increased glucose uptake by the intestine? Since the gastrointestinal tract is a very extensive organ, a dearth of information exists on whether glucose handling is

confined to any particular part of the gut or occurs along the whole length of the gastrointestinal tract. Lastly, are the above observations species specific or do they occur in other animals?

Since most of our studies are on dogs, we also decided to use another animal model, the rabbit, to ascertain that the gut handling of glucose in post-absorptive state is not animal or species specific. We therefore designed a series of experiments to provide possible answers to the questions posed above, that is, to investigate gastrointestinal glucose handling during hyperglycemia induced by injection of glucagon or adrenaline, infusion of glucose, fructose or galactose and during insulin-induced hypoglycaemia. We also attempted to elucidate the mechanisms of the observed responses.

GIT Response to Hyperglycaemia

(A) Effects of Adrenaline

In a series of experiments in our laboratory and using dogs as our animal model, (Alada and Oyebola 1996) we challenged the animal by injecting adrenaline or glucagon to produce different levels of hyperglycaemia. In low dose, adrenaline increased the arterial glucose level from a basal value of 104.50 ± 12.32 mg/dl to a peak value of 168.75 ± 14.48 mg/dl 10 min post injection. Venous glucose level also increased from a basal value of 102.89 ± 10.22 mg/dl to 161.25 ± 14.08 mg/dl 10 min post injection. These increases were significant. The (A – V) glucose also increased significantly reaching its peak value 10 min post injection. With the high dose, adrenaline caused a greater increase in the arterial and venous glucose levels and the (A – V) glucose (see table 3).

Table 3: Effects of Intravenous Injection of Low (1 µg/kg) and High (5 µg/kg) Doses of Adrenaline on Arterial Glucose Level, Venous Glucose Level and Arterio-venous (A - V) Glucose difference in the Dog (n = 5)

		0 min	5 min	10 min	15 min	20 min	25 min	30 min	45 min	60 min	75 min	90 min
Arterial glucose level (mg/dl)	Low dose	104.50 ±12.32	104.25 ±12.23	110.75 ±13.70	163.50 ±14.08	168.75 ±14.48	159.25 ±13.01	150.75 ±12.35	144.50 ±9.16	131.00 ±9.73	117.75 ±0.64	113.75 ±10.28
	High dose	107.50 ±11.16	106.50 ±15.11	113.00 ±14.33	**179.25 ±12.78	**182.25 ±10.99	**173.00 ±12.08	155.25 ±15.27	138.50 ±8.92	127.25 ±13.20	127.25 ±13.20	115.50 ±8.22
Venous glucose level (mg/dl)	Low dose	102.90 ±10.22	102.67 ±11.13	110.00 ±10.81	156.75 ±15.64	161.25 ±14.08	156.78 ±11.76	148.46 ±13.02	143.44 ±11.45	129.91 ±10.21	129.91 ±10.21	111.63 ±11.35
	High dose	105.24 ±10.91	104.59 ±9.83	112.00 ±8.35	**169.75 ±10.63	**173.50 ±10.18	*167.75 ±13.71	152.64 ±9.11	136.41 ±8.90	126.23 ±9.65	126.23 ±9.65	112.33 ±8.14
(A-V) Glucose difference (mg/dl)	Low dose	1.61 ±0.49	1.58 ±0.80	0.75 ±0.82	6.75 ±0.85	7.50 ±0.85	2.50 ±1.91	2.29 ±0.24	1.06 ±0.67	1.09 ±0.41	1.09 ±0.41	2.12 ±0.51
	High dose	1.76 ±0.72	1.91 ±0.78	1.00 ±0.83	**9.50 ±1.12	*8.75 ±.083	**5.25 ±1.04	2.61 ±0.36	*2.09 ±0.27	1.02 ±0.24	1.02 ±0.24	3.17 ±0.78

(* < P 0.05. ** < P 0.01)

The effect of adrenaline on the intestinal glucose uptake was that both low and high doses of adrenaline increased glucose uptake which reached maximum value 5 min post-injection with the low dose. The low dose caused about 600% increase in glucose uptake while the high dose produced 700% increase. The later is significantly different from the former (fig. 9). The increases in glucose uptake also corresponded in timing with the increases in arterial and venous glucose levels. The increase in jejunal glucose uptake is most probably a metabolic response by this segment of the bowel to the high levels of blood glucose. This response is similar to that reported for the upper jejunum (Grayson and Oyebola 1983), terminal ileum (Oyebola and Durosaiye 1988) and large bowel (Alada et al. 2001). These results therefore confirm earlier findings that the gut will increase its glucose uptake when blood glucose is increased by adrenaline.

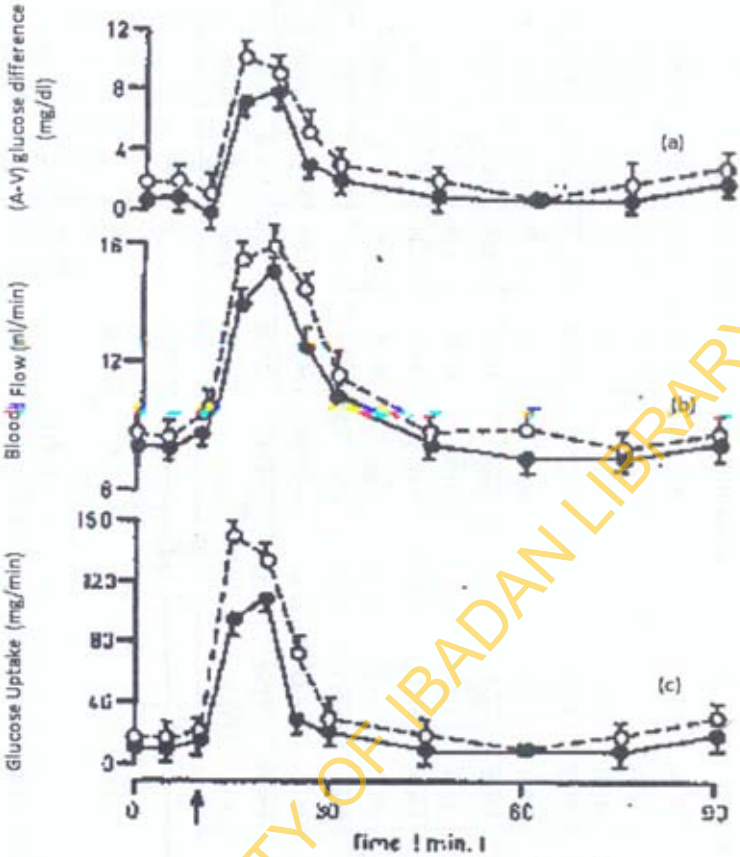

Fig. 9: Effects of intravenous injection of low dose (●--●) and high dose (○--○) of adrenaline on (A-V) glucose difference (a), Blood flow (b) and intestinal glucose uptake (c), in the dogs. Arrow shows point of injection.

(B) Effect of Glucagon

Glucagon also caused an immediate rise in both arterial and venous glucose levels (table 4). The increase in blood glucose level reached a maximum 15 min post-injection. The (A – V) glucose also increased in response to glucagon. Glucose levels and (A – V) glucose response were significantly higher at the high dose than at the low dose of glucagon.

Table 4: Effect of Intravenous Injection of Low (3 ng/kg) and High (8 ng/kg) Doses of Glucagon on Arterial and Venous Glucose Levels and Arterio-venous (A - V) Glucose difference in the Dog (n = 5)

		0 min	5 min	10 min	15 min	20 min	25 min	30 min	45 min	60 min	75 min	90 min
Arterial glucose level (mg/dl)	Low dose	102.50 ±10.15	101.85 ±12.13	106.17 ±11.78	125.20 ±16.20	140.20 ±13.12	146.60 ±12.11	142.40 ±10.01	135.60 ±11.35	129.50 ±17.31	120.30 ±9.38	113.00 ±10.01
	High dose	*107.69 ±9.16	**107.69 ±9.16	**111.37 ±11.25	127.40 ±10.32	**148.40 ±12.37	**157.60 ±12.05	**152.70 ±12.77	*142.60 ±10.18	132.10 ±15.22	124.10 ±10.32	117.10 ±10.12
Venous glucose level (mg/dl)	Low dose	100.40 ±12.27	100.20 ±12.81	103.80 ±9.17	118.20 ±11.31	130.60 ±12.72	130.40 ±15.17	136.20 ±13.05	132.20 ±11.51	128.00 ±12.09	118.00 ±12.41	112.20 ±12.26
	High dose	105.80 ±13.04	*106.00 ±12.47	*109.60 ±10.11	119.40 ±10.13	*137.80 ±10.83	*142.40 ±11.13	**143.20 ±13.67	136.40 ±12.85	129.20 ±10.21	121.00 ±10.18	116.60 ±10.03
(A-V) Glucose difference (mg/dl)	Low dose	1.65 ±0.24	1.65 ±0.24	2.37 ±0.23	7.00 ±0.18	9.60 ±0.36	10.60 ±0.32	6.20 ±0.29	3.40 ±0.16	1.50 ±0.23	2.30 ±0.18	0.80 ±0.28
	High dose	1.89 ±0.15	1.61 ±0.18	**1.77 ±0.15	***8.00 ±0.12	**13.60 ±0.27	**15.20 ±0.11	***9.50 ±0.17	***7.20 ±0.33	***2.90 ±2.90	***3.10 ±0.15	0.50 ±0.12

The effect of glucagon on intestinal glucose uptake was that glucagon caused a significant increase in glucose uptake which reached a peak value 15 min post-injection (fig. 10).

Glucagon at a dose of 3ng/kg produced about 700% increase in glucose uptake, and 900% increase in glucose uptake occurred when the high dose (8ng/kg) was given. This study also showed that glucagon increased bowel glucose uptake.

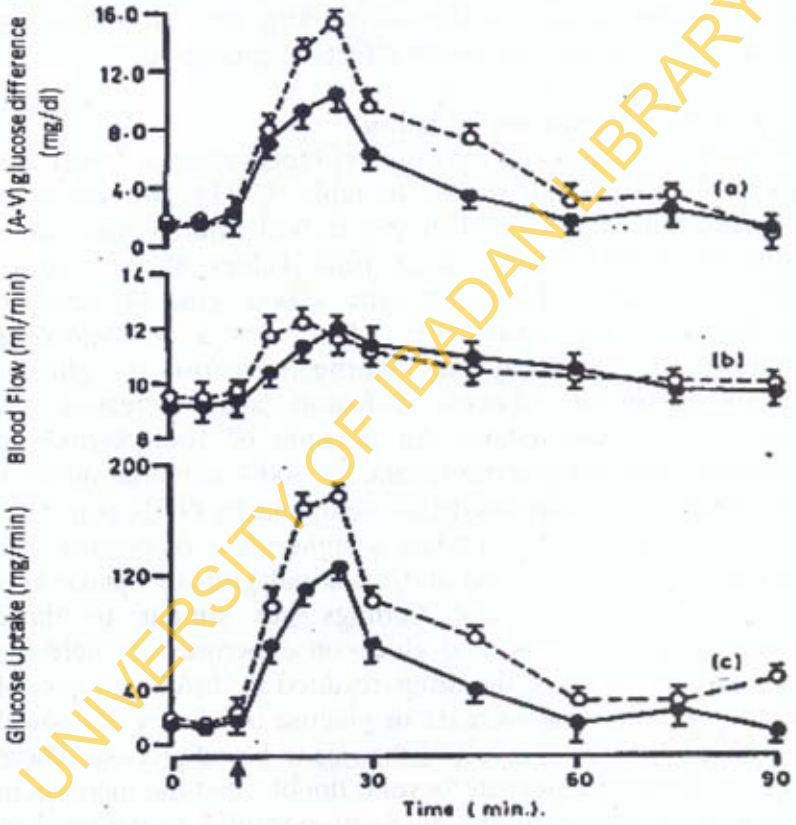

Fig. 10: Effect of intravenous injection of low dose (●--●) and high dose (○--○) of glucagon on (A-V) glucose difference (a), Blood flow (b) and intestinal glucose uptake (c), in the dogs. Arrow shows point of injection.

A similar finding was observed in an earlier study (Grayson and Durotoye, unpublished observations). The increase of about 700% in (A – V) glucose at the peak of response to glucagon injection showed that glucagon caused a significant increase in glucose extraction. The increases in (A – V) glucose and glucose uptake occurred simultaneously. It is interesting to note that higher blood glucose levels induced by a higher dose of glucagon caused a higher increase in glucose extraction and bowel glucose uptake. These observations suggest a dose-dependent relationship in the glycaemic and glucose uptake effects of glucagon.

(C) Effects of Glucose Infusion

The effects of glucose infusion on blood glucose levels and (A –V) glucose are shown in table 5. The two doses of glucose caused an immediate rise in both arterial and venous glucose levels reaching their peak values at the end of infusion period. Thereafter, the blood glucose returned gradually to the basal level. There was a corresponding increase in (A – V) glucose during the period the glucose levels increased. Glucose infusion also increased the intestinal glucose uptake. An infusion of 10mg/kg/min of glucose increased glucose uptake by 560% while an infusion of 20 mg/kg/min increased glucose uptake by 600% (fig. 11).

It is to be noted that when a higher dose of glucose was infused, (A – V) glucose and intestinal glucose uptake also increased further. These findings are similar to those observed in adrenaline and glucagon experiments where the two doses of each of the drugs resulted in different levels of hyperglycaemia and increase in glucose uptake by the bowel was higher at higher levels of the rise in blood glucose. These results, therefore, indicate beyond doubt , that the increase in the glucose uptake by the gut is proportional to the level of increase in blood glucose and that the gut will increase its glucose uptake irrespective of the cause of the hyper-glycaemia.

Table 5: Effect of Intravenous Infusion of Low Dose (10 mg/kg/min) and High Dose (20 mg/kg/min) of Glucose on Arterial and Venous Glucose Levels in the Dog (n = 5)

		0 min	5 min	10 min	15 min	20 min	25 min	30 min	45 min	60 min	75 min	90 min
Arterial Glucose Level (mg/dl)	Low Dose	102.97 ±10.01	103.14 ±10.21	104.80 ±6.16	163.40 ±5.39	181.80 ±6.35	181.20 ±7.28	171.60 ±8.68	160.30 ±6.18	146.50 ±5.18	130.38 ±6.01	118.40 ±9.21
	High Dose	107.00 ±9.29	106.50 ±10.11	114.42 ±8.17	169.00 ±5.17	188.50 ±5.03	***234.00 ±4.85	173.25 ±7.28	157.27 ±4.12	142.28 ±10.10	130.54 ±4.16	121.00 ±5.80
Venous Glucose Level (mg/dl)	Low Dose	101.40 ±8.07	101.60 ±8.15	102.80 ±9.85	156.80 ±7.32	171.80 ±8.15	172.00 ±9.79	168.20 ±6.35	158.20 ±6.84	144.10 ±6.10	128.80 ±8.61	116.80 ±5.30
	High Dose	105.25 ±8.17	106.75 ±8.88	112.50 ±6.76	160.75 ±6.04	176.75 ±8.01	***227.00 ±10.81	171.15 ±7.12	156.25 ±5.23	140.75 ±6.75	129.50 ±7.19	120.00 ±6.01

(*** - $P < 0.001$)

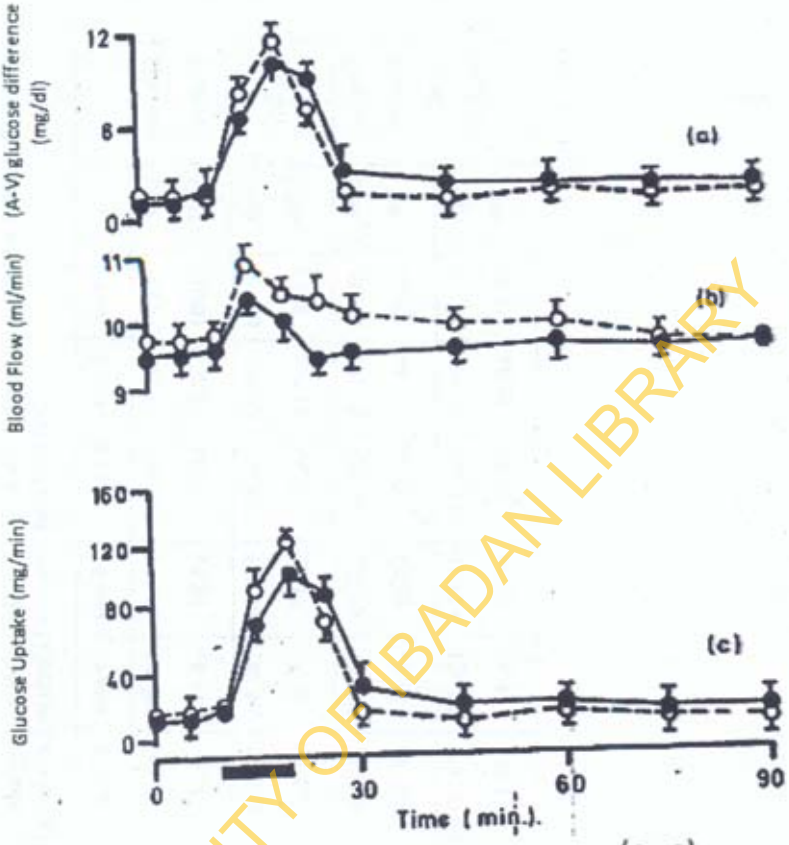

Fig. 11: Effects of intravenous infusion of low dose (●--●) and high dose (○--○) of glucose on (A-V) glucose difference (a), Blood flow (b) and intestinal glucose uptake (c), in the dogs. Solid horizontal bar indicates infusion period.

(D) Effect of Diabetes Mellitus

Since the gut of normal animals has been shown in previous studies from our laboratory to play a modulatory role in glucose homeostasis, a logical question that arises is: What is the role of the gut in glucose handling in diabetes mellitus? For instance, does our earlier conclusion that the gut of normal dogs will increase their glucose uptake during

hyperglycaemia irrespective of its cause apply to hyperglycaemia of diabetes mellitus?

The need to provide answers to the above questions led us to undertake another study using alloxan-induced diabetic dogs (Alada et al. 2005). The fasting arterial blood glucose level in the diabetic dog was 247.75 ± 4.75 mg/dl (table 6). Fasting venous glucose was correspondingly elevated while resting blood flow (10.35 ± 0.08 ml/min) was essentially the same as that of a normal dog. Diabetes mellitus resulted in huge increases in glucose extraction and glucose uptake. Glucose extraction in the diabetic dog was almost eight times that of normal dogs. Also, the resting glucose uptake of 178.40 ± 6.93 mg/min in the diabetic dog was almost eight-fold compared to the glucose uptake in normal dogs. A comparison of the effect of normal saline on glucose uptake in normal and diabetic dogs showed that glucose uptake in diabetic dogs was between 672 to 1003% higher than in normal dogs from the basal levels to peak of uptake and these differences were highly significant at the 1% level (tables 6 and 7).

This study is the first report as far as we are aware, of glucose uptake in the gut of a diabetic animal *in the fasting (post-absorptive) state.* There are of course hundreds of studies of gut glucose uptake in both normal and diabetic animals and man following ingestion of different meals (Capaldo et al. 1999). An interesting finding in this study is that the hyperglycaemia of diabetes mellitus resulted in an enormous increase in glucose uptake by the canine intestine. This result is similar to our earlier findings in normal dogs where glucose uptake by the gut was increased following hyperglycemia induced by adrenaline (Grayson and Oyebola 1983), glucose infusion, adrenaline injection and glucagon injection respectively (Alada and Oyebola 1996), nicotine (Grayson and Oyebola 1985) and cow's urine concoction (Oyebola 1982). The result of the study provides further support for our earlier conclusion that the gut of a normal or a diabetic dog will increase its glucose uptake in response to hyperglycaemia, irrespective of the cause of hyperglycaemia (Alada and Oyebola 1996).

Table 6: Effect of Normal Saline on Arterial and Venous Glucose, (A-V), Glucose, Jejunal Blood flow and Intestinal Glucose uptake in Diabetic Dogs (n =4)

	0 min	5 min	10 min	15 min	30 min	45 min	60 min	75 min	90 min
Arterial glucose(mg/dl)	247.75 ±4.42	247.50 ±3.65	248.50 ±4.48	248.75 ±3.65	246.75 ±5.33	249.25 ±5.75	248.50 ±5.25	248.25 ±4.48	245.25 ±4.90
Venous glucose(mg/dl)	230.50 ±3.85	230.75 ±3.34	230.75 ±3.58	229.75 ±4.26	229.75 ±4.32	232.50 ±4.42	231.50 ±4.82	232.25 ±4.22	232.50 ±2.25
(A-V) glucose(mg/dl)	17.25 ±0.74	16.75 ±0.74	17.25 ±0.89	17.25 ±0.42	17.00 ±1.28	16.75 ±0.96	17.00 ±1.46	16.50 ±0.25	16.25 ±0.74
Blood flow (ml/min)	10.35 ±0.08	10.40 ±0.07	10.30 ±0.09	10.40 ±0.10	10.35 ±0.10	10.30 ±0.11	10.35 ±0.04	10.40 ±0.12	10.40 ±0.12
Glucose uptake(mg/min)	178.40 ±6.93	174.25 ±8.05	177.60 ±9.11	179.30 ±4.15	176.00 ±13.64	172.10 ±8.10	175.90 ±15.03	171.55 ±2.50	168.70 ±6.88

Table 7: Effect of Normal Saline on Arterial and Venous Glucose, (A-V) Glucose, Jejunal Blood flow and Intestinal Glucose uptake in Normal Dogs (n = 4)

	0 min	5 min	10 min	15 min	30 min	45 min	60 min	75 min	90 min
Arterial glucose (mg/dl)	109.00 ±1.76	109.25 ±1.71	107.25 ±1.82	108.25 ±2.36	109.25 ±2.30	109.00 ±2.09	108.50 ±1.08	109.00 ±2.37	109.25 ±1.82
Venous glucose (mg/dl)	106.75 ±1.85	107.50 ±2.02	105.75 ±2.13	106.50 ±2.19	107.00 ±2.00	107.00 ±2.00	106.50 ±1.60	107.50 ±2.56	107.00 ±2.09
(A-V) glucose (mg/dl)	2.25 ±0.22	1.75 ±0.42	2.00 ±0.35	1.75 ±0.42	2.25 ±0.22	2.00 ±0.20	2.25 ±0.22	1.50 ±0.25	2.00 ±0.35
Blood flow (ml/min)	10.27 ±0.09	10.20 ±0.07	10.20 ±0.07	10.20 ±0.10	10.25 ±0.11	10.35 ±0.04	10.25 ±0.08	10.35 ±0.04	10.20 ±0.16
Glucose uptake (mg/min)	23.10 ±2.34	17.75 ±4.09	20.35 ±3.57	17.80 ±4.13	23.05 ±2.19	20.70 ±2.09	23.05 ±2.19	15.55 ±2.63	20.30 ±3.48

It has been reported by earlier workers that in hyperglycaemia of diabetes mellitus, glucose uptake in the liver and muscle is impaired (Butler and Rizza 1989). In this study, the reverse occurred in the gut, that is to say, glucose uptake in the gut is tremendously increased in untreated diabetes mellitus. We did not measure liver and muscle glucose uptake in this study, but if the findings of Butler and Rizza (1989) about a decrease in glucose uptake in the liver and muscle in diabetes mellitus apply to our animals, this suggests but does not prove, that a reciprocal relationship exists between the liver and the intestine in their response to diabetic hyperglycaemia with respect to glucose uptake. Whether such reciprocity actually exists can only be proven by simultaneous measurements in the same animal of hepatic and gut glucose uptakes in the post-absorptive state. The possibility deserves further investigation. However, the enormous quantity of glucose taken up by the gut in diabetic hyperglycaemia suggests that the post-absorptive gut in the diabetic state may well be involved in reducing the degree of diabetic hyperglycaemia by mopping up a lot of glucose from the circulation. Since there was no increase in blood flow, the huge glucose uptake observed in the diabetic state is due mainly to increased glucose extraction.

An interesting observation in this study is the huge difference in the arterial glucose levels in the normal and diabetic dogs. While arterial glucose level in normal dogs was 109.00 ± 1.76 mg/dl, a value that is similar to values reported for normal dogs in our earlier study (Alada and Oyebola 1996), the resting arterial glucose level in the diabetic dogs was 247.75 ± 4.42 mg/dl (table 6). At no time was resting arterial glucose less than 235.25 mg/dl in any of the diabetic dogs (table 8). It should be noted that these fasting glucose levels in the diabetic dogs are far higher than the peak of hyperglycaemic response to adrenaline, glucagon and glucose injections. This difference is most probably due to the fact that the pancreases were intact in the later group of animals

and were able to produce insulin to counter the effects of the hyperglycaemic agents injected.

Since this and previous studies have established that the canine intestine will increase its glucose uptake in response to hyperglycaemia irrespective of its cause, it is tempting to expect that the amount of glucose taken up should be proportional to the degree of hyperglycaemia. The possibility of such a relationship was examined. The results presented in table 9 however showed that it is unlikely that such a direct relationship exists at least in insulin-treated dogs. The percentage changes in glucose uptake were far in excess of the corresponding percentage changes in arterial blood glucose. These suggest that insulin (and other unknown factor(s)) influence glucose uptake apart from glycaemic level.

Some earlier workers (Levine and Haft 1970, Butler and Rizza 1989) had reported that in both insulin sensitive and insulin insensitive tissues, the blood glucose concentration is a key factor determining the rate of glucose uptake. The transport mechanism of glucose across the cell membrane is saturable only at extremely high glucose concentration (Park et al. 1968). Indeed, under conditions of complete absence of insulin (e.g. in some diabetics) when blood glucose level rises to very high values, the absolute rate of glucose uptake has been reported to be as high as it is in normal subject (Felig 1980). The above results therefore lead to the conclusion that the gastrointestinal glucose uptake is largely in response to blood level of glucose.

Table 8: Arterial Glucose (mg/dl) after 2.5, 5.0, 7.5 and 10.0 iu/kg of Insulin in Diabetic Dogs

	0 min	5 min	10 min	15 min	30 min	45 min	60 min	75 min	90 min
2.5 iu/kg	245.75 ±4.08	246.00 ±2.82	218.75 ±5.06**	221.25 ±4.64**	230.75 ±4.44*	233.75 ±2.70	239.75 ±3.56	240.25 ±1.29	243.00 ±3.62
5.0 iu/kg	243.00 ±3.76	242.00 ±4.06	196.50 ±3.05**	187.25 ±1.63**	212.25 ±1.67**	222.25 ±1.67**	231.00 ±2.67*	234.00 ±3.01	234.75 ±3.30
7.5 iu/kg	235.25 ±4.25	236.25 ±3.27	172.50 ±3.27**	141.50 ±4.71***	151.50 ±6.63**	170.00 ±5.18**	180.50 ±2.28**	188.00 ±2.55**	192.25 ±4.94**
10.0 iu/kg	235.50 ±4.85	235.75 ±5.26	174.25 ±2.06**	146.75 ±34.86***	154.25 ±2.53**	178.50 ±3.63**	183.75 ±4.22	190.25 ±5.58**	191.75 ±5.80**

(*p<0.05, **p<0.01, ***p<0.001)

Table 9: Percentage (%) change in Arterial Glucose and Glucose uptake in Insulin Treated Dog*

Insulin	% Change	0 min	5 min	10 min	15 min	30 min	45 min	60 min	75 min	90 min
5.0 iu/kg	Arterial glucose	243.00 mg/dl	0.0	19.0	22.9	12.6	8.3	4.9	3.7	3.3
	Glucose uptake	182.10 mg/min	4.3	31.7	33.5	25.0	20.7	12.4	10.0	7.3
7.5 iu/kg	Arterial glucose	235.25 mg/dl	0.0	26.7	39.8	35.6	26.4	23.2	20.0	18.2
	Glucose uptake	169.85 mg/min	3.4	45.8	65.5	60.1	46.9	38.1	25.8	24.2
10iu/kg	Arterial glucose	235.50 mg/dl	0.0	26.0	37.7	30.2	24.2	21.9	19.2	18.6
	Glucose uptake	166.40 mg/min	0.0	45.5	85.6	57.8	42.7	35.0	23.9	19.5

*All values from 5 min to 90 min are in percent (%) (N=4)

GIT Response to Hypoglycaemia

In order to provide answers to the question of what the response will be with respect to glucose handling when blood glucose level is reduced below normal resting values, we investigated the role of gastrointestinal tract in glucose handling following insulin-induced hypoglycemia.

(A) Effect of Insulin in Normal Dogs

The effect of insulin on blood glucose levels and glucose uptake is shown in table 10 and figure 12.

Following injection of insulin, both the arterial and venous glucose levels were reduced below resting values. However, 5 – 20 min post-injection of insulin, the level of glucose in the venous blood from the upper jejunual segment was higher than the arterial glucose in the blood flowing into the segment. In other words, within this period, the gastro-intestinal tract released glucose into the blood stream. This is most probably a metabolic response of the gastrointestinal tract to the arterial hypoglycaemia. Indeed, the intestinal glucose released at the peak of the response was about 400% higher than the resting glucose uptake before insulin injection. This observation is consistent with the suggestion made by Grayson and Oyebola (1985) who noted that in the general context of glucose homeostasis, glucose uptake can occasionally be negative, presumably to correct hypo-glycaemia. This study therefore presented evidence that when the blood glucose is reduced to a hypoglycaemic level using insulin, the gastrointestinal tract actually pushes out glucose to correct the hypoglycaemia. The most striking feature of this finding is that even a slight reduction in arterial glucose level that did not reach significant hypoglycaemic level produced a huge negative glucose uptake which lasts for a considerable period of time.

Table 10: Effects of Intravenous Injection of Low Dose (5 i.u/kg) and High Dose (8 i.u./kg) Insulin on Arterial and Venous Glucose Levels, and Arterio-venous (A-V) Glucose difference in the Dog (n=5)

		0 min	5 min	10 min	15 min	20 min	25 min	30. min	45 min	60 min	75 min	90 min
Arterial glucose level (mg/dl)	Low dose	107.45 ±3.82	108.00 ±4.39	106.31 ±2.62	104.81 ±1.57	105.95 ±6.25	107.56 ±3.16	107.70 ±4.63	107.70 ±4.15	106.75 ±2.57	106.56 ±4.81	105.61 ±1.03
	High dose	119.20 ±2.91***	119.10 ±3.86**	120.30 ±4.15***	92.15 ±3.09**	53.10 ±5.72***	54.23 ±5.34***	75.40 ±2.32***	99.10 ±2.32**	109.32 ±5.16***	123.10 ±2.19***	120.00 ±2.21***
Venous glucose level (mg/dl)	Low dose	105.69 ±2.75	106.21 ±4.66	104.90 ±3.30	105.43 ±5.69	108.49 ±2.64	110.76 ±4.02	110.55 ±5.28	108.78 ±6.01	106.72 ±4.68	106.01 ±1.88	105.60 ±1.68
	High dose	116.00 ±1.87**	116.20 ±1.92**	115.10 ±3.58***	87.21 ±4.10***	60.25 ±3.09***	57.00 ±5.78***	80.00 ±6.63***	95.24 ±4.81***	106.17 ±4.02	117.25 ±13.13***	115.74 ±3.22***
(A-V) Glucose difference (mg/dl)	Low dose	1.76 ±0.81	1.79 ±0.31	1.41 ±0.28	-0.53± 0.46	02.54 ±0.31	3.20 ±0.31	-3.22 ±0.22	-1.08 ±0.63	0.03 ±0.52	0.55± 0.50	0.01± 0.23
	High dose	1.89 ±10.53	1.94 ±0.45	2.16 ±0.51*	1.06 ±0.56	7.15 ±0.62***	-2.77 ±0.60	-4.60 ±0.40	3.86 ±0.51**	3.15 ±0.52***	4.85± 0.44***	4.27± 0.34***

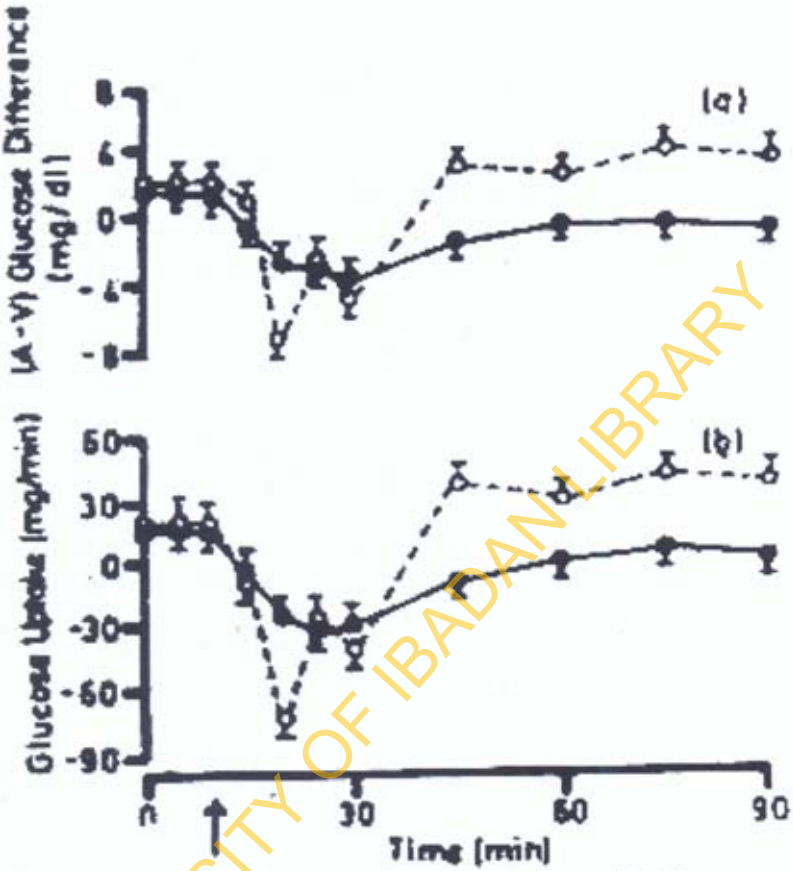

Fig. 12: Effects of intravenous injection of low dose (●--●) and high dose (○--○) of insulin on (A-V) glucose difference (a), and intestinal glucose uptake (b), in the dogs (Arrow shows point of injection).

(B) Effect of Insulin in Diabetic Dog

The results of insulin administration in doses of 2.5, 5.0, 7.5 and 10.0 iu/kg are shown in tables 8, 11, 12 and 13. Insulin caused a reduction in gut glucose uptake in a dose-dependent manner in the diabetic dogs. Since insulin had no effect on blood flow at all the doses studied, the decrease in glucose uptake was due mainly to reduction in glucose extraction. However, at no instance was a negative glucose uptake

observed as recorded in normal dogs given insulin in this study and in our earlier study (Alada and Oyebola 1996). The reason for this is not clear. The diabetic state may be responsible for the difference in some yet to be identified ways. The glycaemic level may be involved in this. For instance, a close look at arterial glucose levels in all animals given insulin (table 8) shows that at no instance did arterial glucose fall below 141 mg/dl in any of the animals. This value is still well above the resting arterial blood glucose level of 109.00 ± 1.76 mg/dl in normal dogs.

Our findings have been corroborated by Mithieux et al. (2004) who used molecular techniques to identify abundance of glucose-6-phosphatase in the intestine of rat and man. Glucose-6-phosphatase is a very crucial enzyme in the control of glucose homeostasis. It catalyses the last biochemical reaction of gluconeogenesis and glycogenolysis, i.e. hydrolysis of glucose-6-phosphate to glucose and phosphate ion. It is therefore unique in that it confers on any tissue in which it is expressed the capacity to release glucose into the blood stream. The liver and the kidney possess this capacity and are known to have high expression of glucose-6-phosphatase (Ashmore and Weber 1959; Nordlie et al. 1999; Adrogue 1992; Mithieux 1997).

Table 11: Effect of 5.0 iu/kg Insulin on Arterial and Venous Blood Glucose, (A-V) Glucose, Jejunal Blood flow and Intestinal Glucose uptake in Diabetic Dogs

	0 min	5 min	10 min	15 min	30 min	45 min	60 min	75 min	90 min
Arterial glucose (mg/dl)	243.00 ±3.76	242.00 ±4.06	196.50 ±3.05**	187.25 ±1.63**	212.25 ±1.67**	222.25 ±2.56**	231.00 ±2.67*	234.00 ±3.01	234.75 ±3.30
Venous glucose (mg/dl)	225.50 ±3.05	225.25 ±3.73	185.00 ±2.53**	176.25 ±1.60**	199.25 ±1.67**	207.75 ±2.43**	215.75 ±2.41*	218.25 ±2.60	218.75 ±3.00
(A-V) glucose (mg/dl)	17.50 ±0.56	16.75 ±0.42	11.50 ±0.56**	11.00 ±0.35**	13.00 ±0.35**	14.50 ±0.25**	15.25 ±0.42**	15.75 ±0.56*	16.00 ±0.35
Blood flow (ml/min)	10.40 ±0.09	10.45 ±0.07	10.80 ±0.07	11.00 ±0.12	10.50 ±0.05	10.50 ±0.04	10.45 ±0.06	10.45 ±0.05	10.45 ±0.04
Glucose uptake (mg/min)	182.10 ±6.77	174.25 ±4.92	124.30 ±6.54***	121.15 ±5.06***	136.55 ±4.20**	144.43 ±5.47**	159.45 ±5.13*	163.88 ±6.22	168.85 ±4.25

(*- $P < 0.005$; **- $P < 0.001$: N = 4)

Table 12: Effect of 7.5 i.u/kg Insulin on Arterial and Venous Blood Glucose, (A-V) Glucose, Jejunal Blood flow and Intestinal Glucose uptake in Diabetic Dogs

	0 min	5 min	10 min	15 min	30 min	45 min	60 min	75 min	90 min
Arterial glucose (mg/dl)	235.25 ±4.25	236.25 ±3.27	172.50 ±3.27**	141.50 4.71***	151.50 ±6.63***	170.00 ±2.28**	180.50 ±2.28**	188.00 ±2.55**	192.25 ±4.94**
Venous glucose (mg/dl)	219.00 ±3.48	220.50 ±3.33	164.00 ±2.72**	136.25 ±4.52***	145.25 ±6.11**	161.50 ±4.62**	170.50 ±1.58**	176.00 ±2.03**	180.00 ±3.86**
(A-V) glucose (mg/dl)	16.25 ±0.22	15.75 ±0.65	8.50 ±0.56**	5.25 ±0.22***	6.25 ±0.55***	8.50 0.43**	10.00 ±0.61**	12.00 ±0.61*	12.25 ±0.82*
Blood flow (ml/min)	10.40 ±0.06	10.50 ±0.07	11.10 ±0.11	11.15 ±0.08	10.80 ±0.10	10.60 ±0.06	10.50 ±0.05	10.50 ±0.06	10.50 ±0.06
Glucose uptake (mg/min)	169.85 ±3.04	164.00 ±7.76	91.95 ±5.06***	58.60 ±2.84***	67.66 ±6.36***	90.20 ±5.14***	105.05 ±6.69*	126.02 ±6.64*	128.73 ±9.04*

(*- P < 0.05; **- P < 0.01; ***- P < 0.001; N = 4)

GIT Response to Other Sugars

The next question was: How will the bowel respond with respect to glucose uptake if the animal was infused with other sugars instead of glucose? We therefore investigated the effects of infusion of fructose and galactose on intestinal glucose uptake using similar dog experimental set up as in previous studies (Alada and Oyebola 1996). The results of the study are shown in tables 14 and 15 and figures 13 and 14.

Different doses of fructose or galactose produced different levels of increase in blood glucose. There were also increases in intestinal glucose uptake in response to infusion of different doses of fructose or galactose. In fact, at the highest doses, infusion of fructose and galactose increased the gut glucose uptake by as much as 600% and 250% respectively. The increases in glucose uptake by the gut appeared to be a metabolic response to the fructose or galactose-induced increases in blood glucose levels. Although the intestinal glucose uptake response to fructose or galactose is lower than the response to glucose, it is difficult to escape the conclusion that the bowel also increased its glucose uptake in response to fructose or galactose-induced hyperglycaemia.

Table 13: Effects of Different Doses of Insulin on Intestinal Glucose uptake in Diabetic Dogs

Dose of insulin	0 min	5 min	10 min	15 min	30 min	45 min	60 min	75 min	90 min
2.5 iu/kg (mg/min)	173.35 ±4.17	174.30 ±8.28	165.15 ±5.33	172.28 ±2.80	174.25 ±2.75	175.75 ±4.95	175.28 ±0.62	178.76 ±2.45	179.40 ±6.78
5.0 iu/kg (mg/min)	182.10 ±6.77	174.25 ±4.92	124.30 ±6.54***	121.15 ±5.06***	136.55 ±4.20**	144.43 ±5.47**	159.45 ±5.13*	163.88 ±6.22	168.85 ±4.25
7.5 iu/kg (mg/min)	169.85 ±3.04	164.00 ±7.76	91.95 ±5.06***	58.60 ±2.84***	67.66 ±6.36***	90.20 ±5.14***	105.05 ±6.69**	126.02 ±6.64*	128.73 ±9.04*
10.0 iu/kg (mg/min)	166.40 ±4.78	168.00 ±6.65	90.75 ±4.94***	69.00 ±4.68***	70.20 ±6.94***	95.40 ±4.97**	108.14 ±5.92**	126.60 ±6.64*	133.88 ±13.10*

(*- $P < 0.005$; **- $P < 0.01$; ***- $P < 0.001$; $N = 4$)

Table 14: Effects of Fructose infusion on Arterial Blood Glucose Levels and (A-V) Glucose in Dogs
Values are expressed as mean ± SEM, (N=5)

	Dose	0 min	5 min	10 min	15 min	20 min	25 min	30 min	45 min	60 min	75 min	90 min
Arterial Glucose (mg/dl)	0.15 mg/kg/min	99.2 ±1.87	98.0 ±1.87	98.0 ±1.70	97.2 ±1.93	95.8 ±1.16	95.2 ±1.82	94.6 ±1.33	96.6 ±2.66	91.8 ±1.02	89.2 ±2.63	80.0 ±2.74
	0.55 mg/kg/min	99.8 ±2.85	104.4 ±3.75	105.4 ±3.56*	100.8 ±5.03	103.4 ±4.07	105.5 ±3.83*	105.0 ±3.24*	103.8 ±4.02	108.8 ±2.42*	103.8 ±2.08	107.4 ±3.37*
	1.1 mg/kg/min	99.4 ±0.87	110.6 ±1.25*	112.0 ±2.72*	108.8 ±3.01*	114.2 ±1.88*	113.6 ±3.70**	110.8 ±1.28*	103.4 ±2.18	109.6 ±1.21*	107.4 ±1.78*	98.8 ±2.31
(A-V) Glucose (mg/dl)	0.15 mg/kg/min	4.2 ±0.05	4.2 ±0.10	4.8 ±0.16	5.0 ±0.12	5.0 ±0.08	5.6 ±0.12*	6.2 ±0.11*	7.6 ±0.20*	2.2 ±0.18	3.6 ±0.14	3.4 ±0.21
	0.55 mg/kg/min	4.2 ±0.14	5.4 ±0.09	9.6 ±0.13**	7.8 ±0.11*	11.2 ±0.23**	10.8 ±0.25**	15.8 ±0.17***	13.4 ±0.12***	15.2 ±0.27***	11.8 ±0.09**	10.4 ±0.18**
	1.1 mg/kg/min	3.4 ±0.08	21.8 ±0.13***	22.2 ±0.11***	18.2 ±0.16***	12.8 ±0.07**	12.0 ±0.14**	25.0 ±0.24***	12.0 ±0.28**	19.8 ±0.28***	22.0 ±0.26***	4.8 ±0.04

(*P ≤ 0.05, ** P ≤ 0.01, *** P ≤ 0.001)

Table 15: Effects of Galactose infusion on Arterial Blood Glucose Levels and (A-V) Glucose in Dogs
Values are expressed as mean ± SEM, (N = 5)

	Dose	0 min	5 min	10 min	15 min	20 min	25 min	30 min	45 min	60 min	75 min	90 min
Arterial Glucose (mg/dl)	0.15 Mg/kg/min	99.4 ±1.36	103.6 ±1.25	109.2 ±0.37*	108.8 ±0.58*	112.8 ±1.43*	110.8 ±2.96*	104.4 ±1.29	98.6 ±0.81	104.2 ±3.62	108.4 ±4.13*	104.2 ±3.25
	0.55 Mg/kg/min	93.2 ±1.16	103.2 ±2.97*	99.8 ±1.32	101.4 ±1.72	100.6 ±2.56	98.4 ±1.17	102.0 ±1.58*	100.8 ±1.20	95.2 ±2.48	92.0 ±5.68	91.0 ±2.77
	1.1 Mg/kg/min	96.2 ±1.16	102.6 ±1.50	106.4 ±1.29*	109.8 ±1.43*	105.2 ±1.39*	101.8 ±1.28	99.0 ±1.05	91.2 ±1.07	89.6 ±1.03	86.0 ±0.55	85.8 ±1.16
(A-V) Glucose (mg/dl)	0.15 Mg/kg/min	4.2 ±0.12	7.4 ±0.06	7.6 ±0.31	10.6 ±0.21*	10.2 ±0.18*	10.8 ±0.25*	6.6 ±0.14	7.8 ±0.35	10.0 ±0.17*	9.2 ±0.08*	7.0 ±0.22
	0.55 Mg/kg/min	4.2 ±0.11	8.8 ±0.16*	7.0 ±0.07	6.4 ±0.35	7.6 ±0.12	6.6 ±0.26	10.0 ±0.21*	9.2 ±0.16*	7.6 ±0.08	11.2 ±0.14*	9.0 ±0.13*
	1.1 Mg/kg/min	3.4 ±0.09	6.1 ±0.07	7.9 ±0.11*	12.0 ±0.20**	15.2 ±0.15**	11.8 ±0.16*	7.7 ±0.18	8.8 ±0.17*	7.1 ±0.13.	5.7 ±0.15	6.0 ±0.11

(* $P \leq 0.05$, ** $P \leq 0.01$)

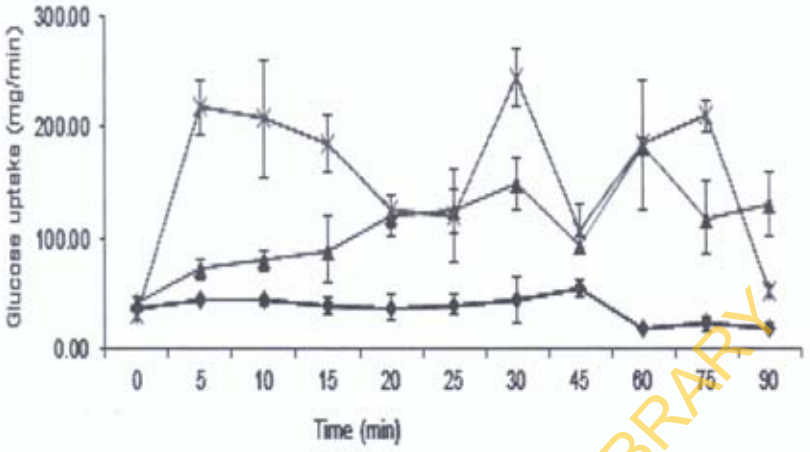

Fig. 13: Effects of intravenous infusion of fructose 0.15 (◆ - ◆), 0.55 (▼ - ▲), 1.1 (× - ×) mg/kg/min on glucose uptake.

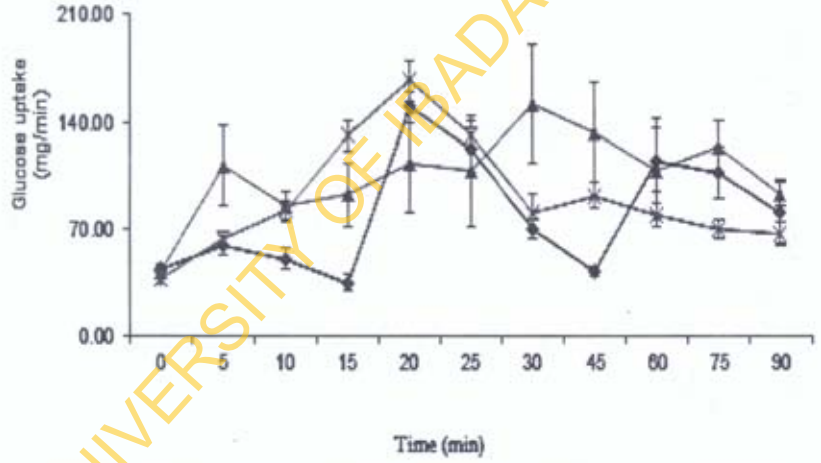

Fig. 14: Effects of intravenous infusion of galactose 0.15 (◆ - ◆), 0.55 (▲ - ▲), 1.1 (× - ×) mg/kg/min on glucose uptake.

The results from this study therefore led to the conclusion that gastrointestinal tract glucose uptake is largely in response to the increase in blood glucose level irrespective of the cause of the hyperglycaemia.

A Proximo-distal Gradient in Glucose Handling by the Gut

On the location of the part of gastrointestinal tract that is involved in glucose homeostasis, we have shown through a series of studies that apart from the upper jejunum (Grayson and Oyebola 1983; Alada and Oyebola 1996), the terminal ileum (Oyebola and Durosaiye 1988) and the colon (Alada et al. 2001) are involved. The upper part of the small intestine takes up the largest quantities of glucose in response to hyperglycaemia and the distal colon takes up the lowest quantities of glucose (table 16). There appears to be a proximo-distal gradient in glucose handling by the gut.

Table 16: Effect of Adrenaline on Glucose Uptake in Different Segments of the Gut

Part of GIT	Maximum GU in %	Reference
Upper Jejunum	700	Alada and Oyebola, 1996
Terminal Ileum	400	Oyebola and Durosaiye, 1988
Large Intestine	200	Alada et al. 2001

We have also been able to demonstrate the contribution of the gastrointestinal tract to glucose homeostasis in a smaller animal—the rabbit. For instance, following hyperglycaemia induced by adrenaline (Oyebola et al. 2011) or nicotine (Oyebola et al. 2009) in rabbits, there were significant increases in intestinal glucose uptake by 150% for adrenaline and 200% for nicotine.

The Role of Adrenergic Receptors in the Increased Glucose Uptake

Grayson and Oyebola (1983, 1985) showed that alpha and beta adrenergic receptors mediated the increased glucose uptake in response to adrenaline-induced (Grayson and Oyebola 1983) and nicotine-induced (Grayson and Oyebola 1985) hyperglycaemia. In our experiments, we also investigated the role of adrenergic receptors in increased intestinal

glucose uptake induced by adrenaline, glucagon, glucose, other sugars such as fructose and galactose or the negative glucose uptake in response to insulin induced hypoglycemia. The effects of alpha blockade, beta blockade and combined apha and bata blockade on glucose uptake in the canine gut are shown in figures 15, 16, 17, 20, 21 and 22.

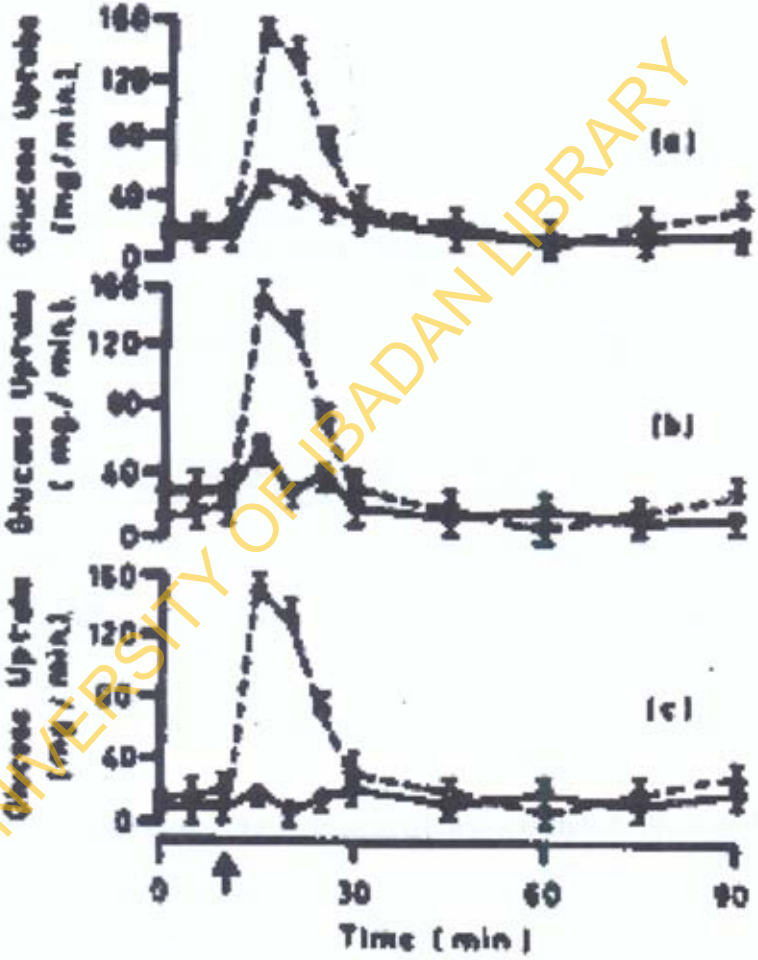

Fig. 15: Effect of i.v injection of adrenaline on intestinal glucose uptake during (a) α-block, (b) β-block and (c) α and β blockade. (0- -0- untreated, •—•-pretreated with blocker).

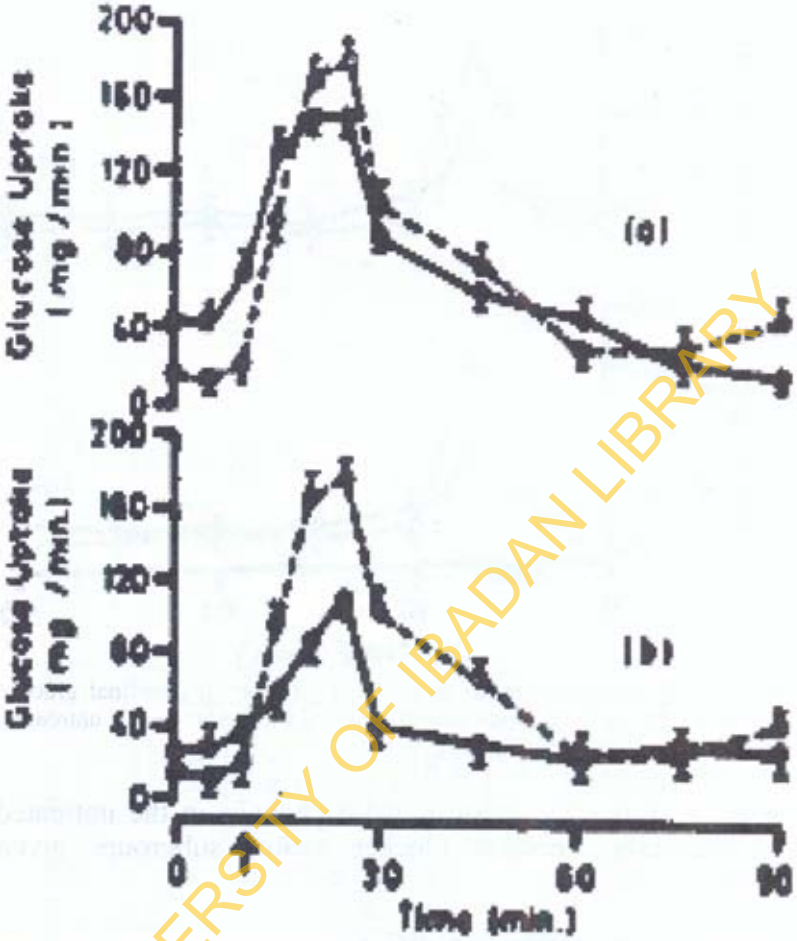

Fig. 16: Effects of i.v injection of glucagon on intestinal glucose uptake during a) β-block and (b) α and β blockade. (0- -0- untreated, •—•- pretreated with blocker).

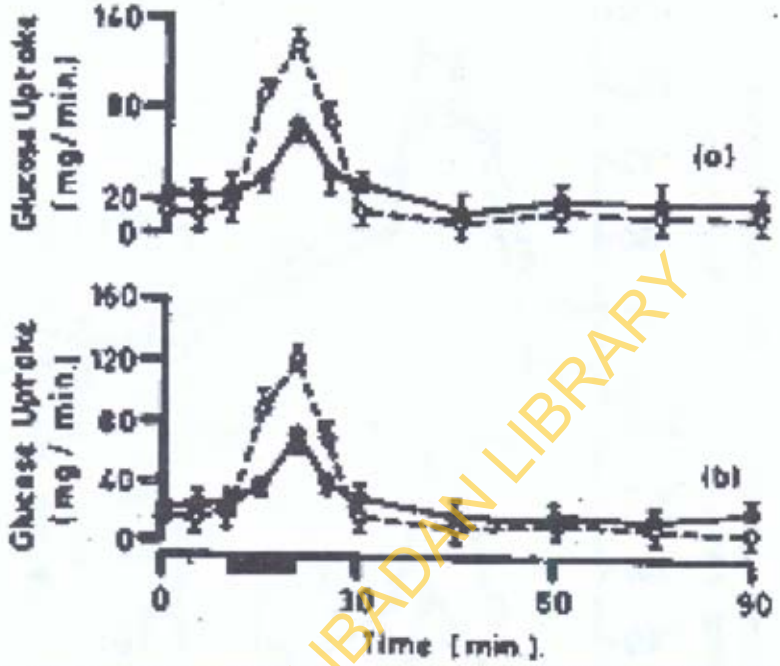

Fig. 17: Effect of intravenous infusion of glucose on intestinal glucose uptake during (a) β-block and (b) α and β blockade. (0- -0- untreated, •—•-pretreated with blocker).

Table 17 shows the blood glucose changes in the untreated and adrenergic receptor blocker treated subgroups given adrenaline injections.

Effect of Alpha Adrenergic Blocker

Prazosin, 0.2 mg/kg significantly reduced the adrenaline induced hyperglycemia (table 17). It also reduced the increase in intestinal glucose uptake following adrenaline injection (fig. 15a). Prazosin, however, had no effect on the increase in blood glucose induced by glucagon injection, glucose, fructose or galactose infusions. Prazosin also had no effect on the increased glucose uptake by the gut induced by glucagon, glucose, fructose or galactose administration. Pre-treating the animal with prazosin had no effect on insulin-induced hypoglycaemia and negative glucose uptake by the intestine.

Table 17: Effects of iv Injection of Adrenaline (5 μg/kg) on Arterial Glucose Levels in untreated α – blocked, β – blocked, and α and β blocked Dog (N = 5).

	0 min	5 min	10 min	15 min	20 min	25 min	30 min	45 min	60 min	75 min	90 min
Untreated (mg/dl)	107.50 ±11.16	106.50 ±15.11	113.00 ±14.33	179.25 ±12.78	182.25 ±10.99	173.00 ±12.08	115.25 ±15.57	138.50 ±8.92	127.25 ±16.20	118.25 ±10.36	115.50 ±8.22
Alpha-blocked (mg/dl)	106.80 ±8.76	105.00 ±10.21	108.53 ±11.84	113.82 ±10.66 ***	128.09 ±11.43 ***	130.55 ±11.68 ***	126.52 ±10.75	132.31 ±10.75	126.01 ±11.24	119.20 ±11.50	116.77 ±9.82
Beta-blocked (mg/dl)	*119.3 ±3.66	*119.54 ±5.50	112.63 ±8.24	121.70 ±10.67 ***	133.20 ±9.18 ***	125.41 ±8.31 ***	118.28 ±8.03 ***	122.00 ±7.95	119.16 ±8.64	120.50 ±6.10	113.36 ±7.48
Alpha and Beta Block (mg/dl)	106.20 ±8.04	106.00 ±10.60	107.10 ±6.50	110.35 ±7.75 ***	108.30 ±6.20 ***	111.62 ±10.89 ***	106.40 ±7.25 ***	108.64 ±9.70 ***	106.48 ±5.18 **	110.37 ±7.29	107.54 ±5.50

*- P < 0.05, **- P < 0.01, ***- P < 0.001

Effect of Beta Adrenergic Blocker

Propranolol, 0.5 mg/kg increased the resting blood glucose levels (table 17). It also increased the resting arterio-venous (A – V) glucose difference and glucose uptake. Propranolol significantly reduced the adrenaline-induced hyperglycemia. Adrenaline-induced increase in glucose uptake by the intestine was also significantly reduced by propranolol. The increase in glucose uptake decreased from 700% in untreated animal to about 90% following propranolol treatment (fig. 15b). Propranolol had no effect on blood glucose increase produce by glucagon. It however caused a significant decrease in glucagon-induced increase in glucose uptake (fig. 16a). Although the intestinal glucose uptake in propranolol-treated animals increased from 24.71 ± 4.17 mg/min to 72.81 ± 9.34 mg/min (about 300% increase) after infusion of glucose, this increase is significantly lower than that produced in untreated animals (fig. 17a). That is to say, propranolol significantly reduced the glucose uptake induced by glucose infusion. Figure 18 shows that propranolol abolished fructose induced increase in glucose uptake while figure 19 also shows that propranolol completely abolished the increase in glucose uptake produced by galactose.

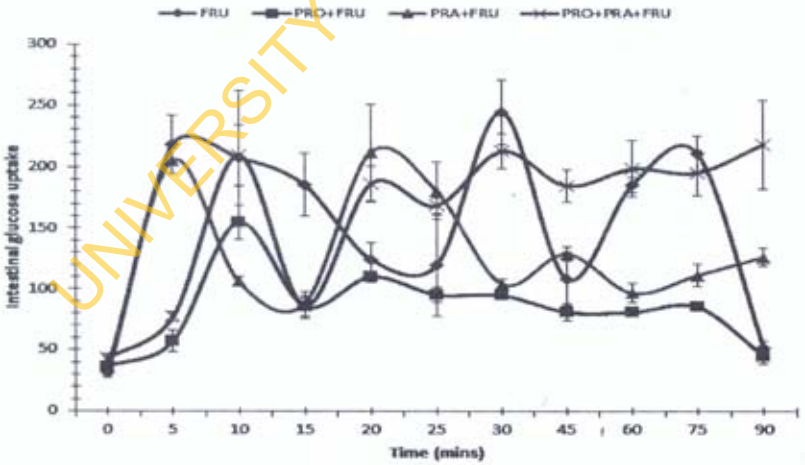

Fig. 18: Effects of fructose (FRU) infusion on intestinal glucose uptake before and after pretreatment with prazosin (PRA) and propranolol (PRO).

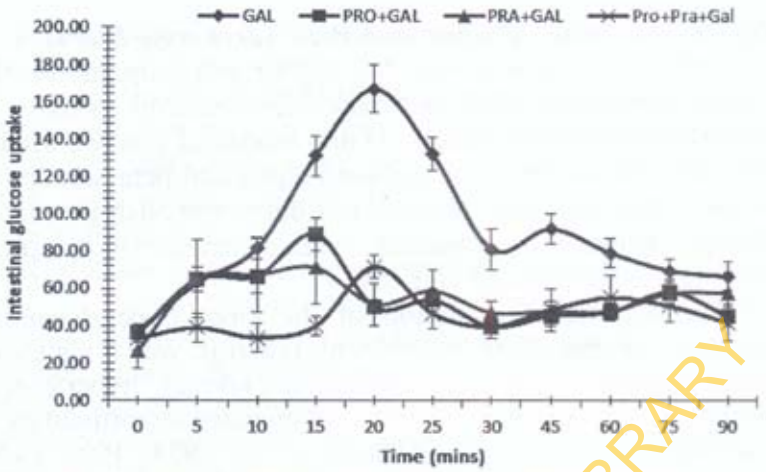

Fig. 19: Effects of galactose (GAL) infusion on intestinal glucose uptake before and after pretreatment with prazosin (PRA) and propranolol (PRO).

The effect of insulin in propranolol-treated dogs is shown in figure 20. Propranolol reduced significantly but did not abolish, the insulin-induced negative glucose uptake. From a value of -70.78 ± 6.16 mg/min, the negative glucose uptake was reduced to -34.15 ± 4.01 mg/min.

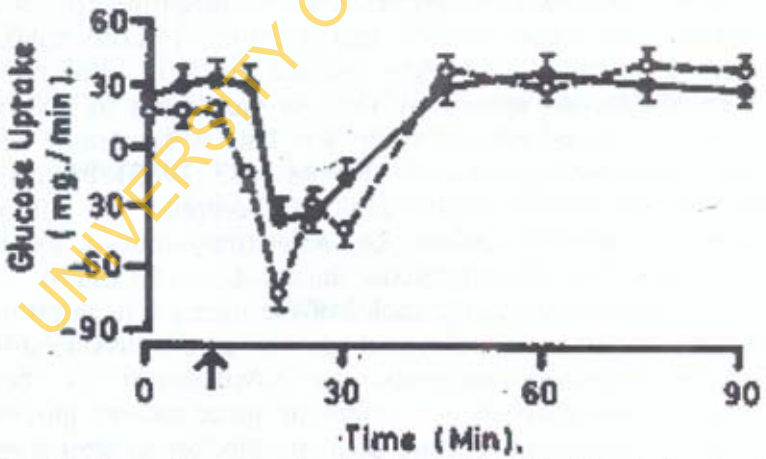

Fig. 20: Effect of i.v injection of insulin before (0- -0) and after (•—•) β blockade on intestinal glucose uptake.

Effects of combined Alpha and Beta Adrenergic Blockers

A combination of prazosin, 0.2 mg/kg and propranolol, 0.5 mg/kg completely abolished adrenaline-induced increase in blood glucose levels (table 17) and intestinal glucose uptake (fig. 15c). However, the combined alpha and beta adrenergic receptor blockers only reduced but did not abolish glucagon, glucose, fructose or galactose induced increase in intestinal glucose uptake (figs. 19 and 20).

The significant reduction of the large hyperglycaemic response to adrenaline injection by prazosin was a matter of great interest. Although studies in normal hypertensive patients receiving prazosin have not revealed abnormalities in carbohydrate metabolism (Thulin et al. 1974; Pitts 1974; Wibell et al. 1980), there is evidence which indicates that hepatic glycogenolysis in rats and some other animal species is mediated by alpha adrenoceptors (Sherline et al. 1972; Hutson et al. 1976; Blair et al. 1979). Other workers have shown that in man (Antonis et al. 1967), cat (Aljibouri et al. 1980) and rat (Oyebola and Alada 1993), hyperglycaemic response to adrenaline was abolished by a combination of alpha and beta blocking agents. The latter observation is consistent with the results of our study, whereby a combination of prazosin and propranolol abolished the effects of adrenaline on blood glucose and intestinal glucose uptake. The mechanism of adrenaline-induced hyperglycaemia and increased glucose uptake by the gut thus seem to involve alpha and beta adrenergic receptors. This is consistent with earlier reports (Grayson and Oyebola 1983, 1985). From the result of this study, alpha and beta receptors are almost equipotent in their effects on adrenaline-induced hyperglycaemia (table 17) and glucose uptake (figs. 15a and b).

The reduction by propranolol of the increase in intestinal glucose extraction and intestinal glucose uptake produced by glucagon injection suggests the involvement of beta adrenergic receptors in the effect of glucagon on glucose uptake by the bowel. Failure of alpha blocker to alter these variables shows the non-involvement of alpha adrenergic receptors in the response to glucagon.

Perhaps the most relevant result in this study on the mechanism of increased glucose uptake by the bowel is the effects of beta adrenergic blockade. While alpha adrenergic receptor blocker had no effect on glucose-induced hyperglycaemia and increased glucose uptake, propranolol significantly reduced the same. These findings suggest that the increase in intestinal glucose uptake in response to high blood glucose levels, irrespective of its cause is mediated partly by beta-receptors. Some other receptors are most probably involved since β-blockade alone did not abolish increased uptake. Alpha receptors, unlike in the adrenaline response are not involved in the increased glucose uptake induced by glucagon and glucose infusion. Also, the findings in the insulin experiments suggest that the beta adrenergic receptors mediated in part the increased negative glucose uptake induced by insulin. Again, alpha receptors are not involved.

Remarks and New Direction

It is becoming an accepted view that the gut may compliment the liver and the kidney in glucose homeostasis under different conditions, for example in diabetes in resting conditions or during fasting (Mithieux et al. 2004). In this presentation, I have presented evidence to show that the gastrointestinal tract plays a strong modulatory role in glucose homeostasis. This is similar to the role of the liver. Whether this finding could be related to the fact that the liver itself developed embryologically as an outgrowth of the gut (Deren 1968) is at the moment speculative. I have also shown that the glucose handling by the gut is mediated in part by beta adrenergic receptors. However, there are still questions that are begging for answers. For example, we still do not know the fate of the large quantities of glucose that is taken up by the bowel during the different hyperglycaemia. However, emerging information in the literature throws more light on the possible source of the glucose that is released from the bowel during insulin induced hypoglycaemia. Recent studies from different laboratories and using more

advanced molecular techniques including gene expression have confirmed that the intestine is a major gluconeogenic organ (Mithieux et al. 2004). That is, when the blood glucose level is very low, the intestine manufactures and pushes out glucose into the blood stream just as the liver and kidney do. In fact, gluconeogenic genes are strongly induced by the intestine of both fed and fasted rats (Chatelaine et al. 1998; Mithieux et al. 2004). It is not unlikely that important new insights into the role of the gut in glucose homeostasis and the overall carbohydrate metabolism will emerge in the future. This will most probably lead to the breaking of new grounds, especially with a view to finding solutions for a number of disorders such as diabetes mellitus.

Important Observation

Mr. Vice-Chancellor Sir, it is important for me at this stage to bring to your attention the state of our research facility at the University of Ibadan. To put it mildlly, it is not reseach-friendly and yet this University is supposed to be a research University! Every reseacher in the University is confronted with a myriad of challenges, from infrastructural decay to lack of basic research facility. Much as it is well known that a major underlying factor responsible for this state of decay is poor funding to the University, the University should give high priority within her limited resources to providing fund for infrastructure such as power and water supply and equiping the laboratories. I must however, commend the current Vice-Chancellor, Prof. I.F. Adewole on his initiaves of commencing a Research Foundation for the University. This is definitely a right step in solving this problem, but its impact on research activities is yet to be felt. Until it becomes a ready source of support for researchers, the Foundation should continue to gain the support of every administration.

Conclusion

Mr. Vice-Chancellor Sir, on a concluding note, I have regaled this audience with copious experimental data to prove that the

gut is much involved in glucose homeostasis. Based on experimental data that became available to us as recently as two decades ago, I have even ventured to describe the gut as a novel participant in glucose homeostasis. My guess however is that unknown to we inquisitive researchers, the gut most probably has been playing the role we now describe as novel since the beginning of time!

Charcot, the French physician, introduced us into the historical perspectives of diseases when he said that disease is from old and nothing about it has changed. It is we who change as we learn to recognize what was formerly imperceptible. Is it not possible that physiological processes also follow Charcot's postulate about diseases? Is it not most likely that most times a researcher shouts "Eureka" (that is, I have found it) when he stumbles on "new" information, he has just found what has always been there but was unknown to him or anyone else? That is, is it right to call what has probably always been there but unknown to anybody "novel" when it is eventually found? In other words, after all said and done, is the gut really a novel participant in glucose homeostasis?

I thank you for listening.

Acknowledgements

If it appears that I stand tall today, it is because I have received the support of many people too numerous to mention in the course of my journey through this life and in the various opportunities University of Ibadan has offered me to serve. However, I cannot forget to mention the following people:

- My parents, Barister and Alhaja I.A. Alada, both of blessed memory who did everything possible for all their children to acquire good education. May God continue to rest their gentle souls in perfect peace. Amen.
- My Teachers from primary school, through University even until this very moment. I am always indebted to

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- Members of staff, College of Medicine.
- Members of staff, Students' Affairs Division. I really appreciate your cooperation and support in the last three years which has contributed greatly to the peace we all enjoy on the campus. Please, keep up the good work.
- I also would like to express my appreciation to my colleagues – Wardens of our halls of residence – for

making a very ardous and seemingly difficult job, very easy for me.

- I also thank most especially every Students' Union leadership in the last three years for all their support in providing a peaceful and genial atmosphere that is conducive to learning. Aluta continua!
- I salute the courage and steadfastness of our union, ASUU's national and branch leaders. As a 'card carrying' member of our union, for almost 28 years, I have been impressed with the quality of leadership– incorruptible and a dogged defender of the University system and welfare of its members. You are indeed a great inspiration for upcoming generations.
- My numerous friends both within the University and outside. I thank you for being always there for me.
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- My darling wife and friend of almost twenty five years, Ayo Shafiat Alada. I thank you for your love and care all the times.
- To others I may have missed out, I say that you are greatly acknowledged by Almighty God and may you receive His favours at all times.
- I thank all of you who are here today. You have been a wonderful audience.
- My Creator, Almighty God who has done all these wonderful work through me and has sustained me till this very moment.

Mr. Vice-Chancellor, I thank you for this great opportunity!!

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BIODATA OF
PROFESSOR ABDUL RASAK AKINOLA ALADA

Professor Abdul Rasak Akinola Alada was born in Lagos on 3rd January, 1959 to the family of Barrister Ishola Alimi Alada and Alhaja Ashabi Alada (both of blessed memory). He had his primary education at All Saints Anglican Primary School, Yaba and Lagos Progressive School, Surulere, Lagos (1965 to 1971) and his secondary school at Eko Boys' High School, Lagos (1972 to 1976) where he passed his West African School Certificate in Division one. He worked briefly and thereafter relocated to Egypt where he got a scholarship award to study at the famous Cairo University in 1980. In 1985, he graduated from Cairo University with Bachelor of Science in Anatomy and Physiology with grade of Distinction and was on the university Honours list, having emerged as the best graduating student in his faculty. He returned to Nigeria in 1985 and had his compulsory National Youth service at School of Nursing, Katsina General Hospital, under Kaduna State. He was admitted into the University of Ibadan in November, 1986 and graduated MSc Physiology in April, 1988 and PhD Physiology in July, 1992.

Professor Akinola Alada was first appointed a Teaching Assistant in Department of Physiology in September, 1987. He was re-appointed an Assistant Lecturer in November, 1988 and was subsequently promoted Lecturer II, 1991, Lecturer I, 1994, Senior Lecturer, 1997, Reader, 2002 and Professor, October, 2005. He has successfully supervised four PhD theses, twenty two MSc dissertations and over ninety BSc Physiology projects. He has over 70 articles published in national and international journals, chapters in books and conference proceedings. He has served as external examiner at both undergraduate and postgraduate levels in many universities including Universities of Lagos, Benin, Ilorin, Jos, Calabar, Port Harcourt, Lagos State University, Obafemi Awolowo University, Usman Dan Fodio University, Nnamdi Azikwe University and University of Kwazulu Natal, South

Africa. He has also served on several NUC accreditation panels to many universities.

Professor Alada is a member of many professional bodies such Physiological Society of Nigeria (PSN), American Physiological Society (APS), The Physiological Society (TPS), London and West African Society of Pharmacology (WASP). He was at one time the Secretary General of the Physiological Society of Nigeria (2003 – 2007) and is presently the Editor-in-Chief, Nigerian Journal of Physiological Sciences which is the publication of PSN. He has also held appointments as visiting Professor at the University of Ilorin and Usman Dan Fodio University, Sokoto.

Professor Alada has served the University of Ibadan in many capacities. He was Pioneer Sub-Dean (BSc programmes), FBMS (2000 – 2001), Acting Head, Department of Physiology (November, 2001 – October, 2003), Chairman, Central Animal House, College of Medicine (2002 – 2008), Head, Department of Physiology (2010 – 2012) and Dean, Students' Affairs Division (June, 2012 to date). He has been a member of Senate (1998 – 2002, 2005 to date) and represented Senate on Court of Governors, College of Medicine (August 2003 – July 2004), Senate curriculum committee (2010 – 12), Senior Staff Disciplinary Committee and Otunba Tunwase National Hospital (2011 – 2014). He was nominated to represent the university community on the Internal Revenue Board (2011 – date). He also served as President, College of Medicine, Cooperative Investment and Credit Society (August, 2004 – July, 2008).

He is happily married to Mrs. Ayo Alada and the union is blessed with two children, Damilola Aishat and Bukola Fatimat.

NATIONAL ANTHEM

Arise, O compatriots
Nigeria's call obey
To serve our fatherland
With love and strength and faith
The labour of our heroes' past
Shall never be in vain
To serve with heart and might
One nation bound in freedom
Peace and unity

O God of creation
Direct our noble cause
Guide thou our leaders right
Help our youths the truth to know
In love and honesty to grow
And living just and true
Great lofty heights attain
To build a nation where peace
And justice shall reign

UNIVERSITY OF IBADAN ANTHEM

Unibadan, Fountainhead
Of true learning, deep and sound
Soothing spring for all who thirst
Bounds of knowledge to advance
Pledge to serve our cherished goals!
Self-reliance, unity
That our nation may with pride
Help to build a world that is truly free

Unibadan, first and best
Raise true minds for a noble cause
Social justice, equal chance
Greatness won with honest toil
Guide our people this to know
Wisdom's best to service turned
Help enshrine the right to learn
For a mind that knows is a mind that's free