HYPOGLYCAEMIA

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Preface

This book attempts to summarize contemporary knowledge of the aetiology, pathology, symptomatology, investigation and treatment of hypoglycaemia in man. Although it shares with the first edition this aim, as well as title and chapter headings, it has been completely rewritten. As with the first edition the major emphasis has been on spontaneous, rather than iatrogenic, hypoglycaemia since the latter is familiar to every clinician involved in the treatment of diabetes. This book should prove of value to clinicians in all disciplines, but particularly to those engaged in the practice of neurology, psychiatry, paediatrics and endocrinology, to whom most of the patients with spontaneous hypoglycaemia are referred, as well as to research workers interested in the various aspects of hypoglycaemia. Since much of what is known rests upon information gained from a study of only a small number of cases, and in some instances upon a single report, it was felt that adequate documentation was essential, so that the literature was extensively reviewed and critically evaluated in the light of our own experience. In general and where appropriate, we have cited recent works and apologize to the many colleagues whose work, though known to us, has been unquoted.

We wish to thank the many clinical and laboratory colleagues and friends who have referred patients to us and have freely given their advice and criticism, in particular Dr. Ellis Samols, whose help, advice and encouragement, especially in the early days of our collaboration, was of inestimable value. The exacting task of preparing the manuscript fell largely upon Mrs. Carmel Reynolds and Mrs. Penny Rayne to both of whom we are extremely grateful.

Vincent Marks

F. Clifford Rose

Autumn 1980

List of abbreviations

ACD	Acid–citrate–dextrose transfusion blood
ACTH	Adrenocorticotrophin
ADH	Alcohol dehydrogenase
ADP	Adenosine diphosphate
cAMP	Cyclic adenosine monophosphate
ATP	Adenosine triphosphate
A–V	Arterior–venous (difference)
C-peptide	C-peptide of pro-insulin
CRM	Glucagon cross-reacting material
^{13}C	Stable carbon isotope atomic weight 13
CSF	Cerebrospinal fluid
CoA	Coenzyme A
ECF	Extracellular fluid
^{2}D	Deuterium
DG	2-deoxyglucose
ECG	Electrocardiogram
EEG	Electroencephalogram
EMG	Electromyograph
FFA	Free fatty acids (see NEFA)
FSH	Follicle stimulating hormone
G	Gravitation force
Ga	Glucose appearance
Gd	Glucose disappearance
GIP	Gastric inhibitory polypeptide
GLI	Glucagon-like immunoreactivity
GMP	Cyclic guanodine monophosphate
IDM	Infants of diabetic mothers
IGF-I	Insulin-like growth factor I
IGF-II	Insulin-like growth factor II
IRG	Immunoreactive glucagon
IRI	Immunoreactive insulin
IRP	Insulin-releasing (gastrointestinal) polypeptide (including GIP and GLI)
GH	Growth hormone
HFI	Hereditary fructose intolerance
hGH	Human growth hormone
K^+	Potassium ion
LH	Luteinizing hormone
MEA (I)	Multiple endocrine adenomatosis (type I)
MEA (II)	Multiple endocrine adenomatosis (type II)
MSH	Melanocyte stimulating hormone
NAD	Nicotinamide-adenine dinucleotide
$NADH^+$	Reduced NAD
NADP	Nicotinamide-adenine dinucleotide phosphate
$NADPH^+$	Reduced NADP
NEFA	Non-esterified fatty acids (see FFA)
NSILAs	Non-suppressible insulin-like activity (soluble)
NSILAp	Non-suppressible insulin-like activity (precipitable)
NSILP	Non-suppressible insulin-like protein
PLC	Proinsulin-like components
PP	Pancreatic polypeptide
PTH	Parathyroid hormone
SGA	Small for gestational age
TSH	Thyroid stimulating hormone
UDP	Uridine diphosphate
UTP	Uridine triphosphate
VP	Vasopressin
VIP	Vasoactive intestinal peptide
VMA	3-hydroxy-4-methoxmandelic acid
WDHA	Watery diarrhoea, hypokalaemia, achlordydria syndrome (see Verner–Morrison and VIPoma)
2DG	2-deoxy-d-glucose

Contents

1 Introduction

Although hypoglycaemia was recognized as a biochemical anomaly in man during the early years of the present century, it was not considered of any clinical significance until the introduction of insulin therapy for diabetes in 1922. Overdosage with insulin is still the commonest cause of hypoglycaemia but, since its first description in 1924, there has been a growing recognition that endogenous (non-iatrogenic or spontaneous) hypoglycaemia is also important.

Interest in hypoglycaemia can be said to have begun with the experimental observation by Mann and Magath that cerebral dysfunction, with the production of symptoms reminiscent of acute intoxication, resulted from a fall in the blood sugar level produced by hepatectomy. Before this was known, attempts to reduce the blood glucose level in diabetic and normal animals with pancreatic tissue extracts had always been abandoned because of their liability to produce convulsions and apparent toxicity. Banting and Best, after having isolated insulin, showed not only that it lowered the blood glucose concentration but also that it caused signs of cerebral dysfunction which could be rapidly and completely reversed by restoring the blood glucose level to normal. The first clinical descriptions of the effects of hypoglycaemia in man appeared in 1922 concurrently with the description of the use of insulin for the treatment of diabetes. Shortly afterwards Seale Harris, having witnessed the symptoms of insulin in diabetic patients, postulated that similar symptoms, which he had previously observed to occur spontaneously in patients, might have a similar origin and be due to endogenous hyperinsulinism. This was later shown conclusively to be a cause of disease in man, but much confusion was caused, and still unfortunately persists, from the identification of hypoglycaemia with hyperinsulinism, so that the two terms were used interchangeably for many years.

Other causes of hypoglycaemia were recognized but considered either of minor importance or ignored. The distinction between hypoglycaemia which occurred during fasting and that which occurred only in response to the ingestion of carbohydrate was not made until Whipple, in 1936, pointed out that only patients with symptoms associated with fasting hypoglycaemia benefited from pancreatectomy; in these an islet cell tumour was invariably present.

Early observers of hypoglycaemia were hindered by the lack of accurate methods for measuring blood glucose and plasma hormone levels. Although practical clinical procedures for estimating blood sugar were first introduced in 1913, their limitations were only fully appreciated following the introduction of methods specific for glucose. Most of the blood sugar methods used formerly were reasonably precise and reproducible but were non-specific and too

inaccurate to give reliable information in the hypoglycaemia range, although adequate in the normoglycaemic and hyperglycaemic ranges.

Much of our knowledge concerning the clinical manifestations of hypoglycaemia is derived from observations made on patients overtreated with insulin, either accidentally in diabetes, or deliberately in schizophrenia, or experimentally in volunteers. It is impossible under these circumstances to distinguish between effects due to the lowered blood glucose concentration and those directly due to insulin. Recognition that, during prolonged fasting and in some types of endogenous hypoglycaemia, the brain can utilize endogenous substrates,

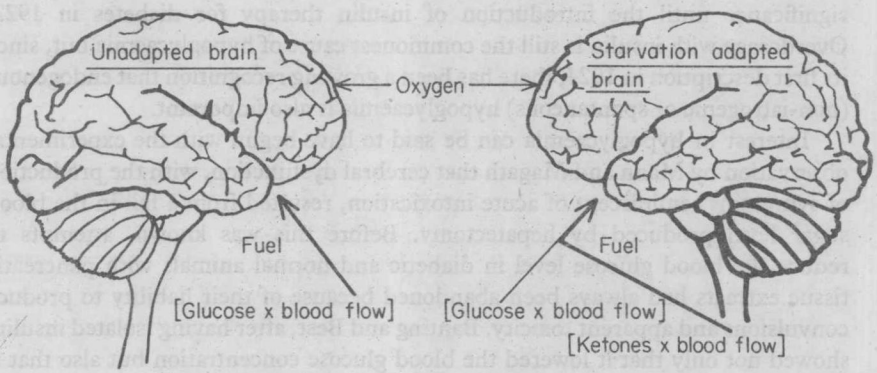

Fig. 1.1 Fuel utilization by the human brain.

notably the ketone bodies, β-hydroxybutyrate and aceto-acetate, as alternative sources of energy to glucose (Fig 1.1) helps to explain the often poor correlation observed between glucose levels and the severity of symptoms.

2 The regulation of blood glucose

The total amount of glucose in the body is small; it is unevenly distributed and virtually confined to the extracellular fluid (ECF) and liver cells. These together comprise a body pool of glucose to which glucose molecules may be either added or subtracted. Extrahepatic tissues do not ordinarily contain free glucose except for cells of the islets of Langerhans, kidney, nervous system and erythron.

Under basal conditions the concentration of glucose in interstitial fluid and plasma (whether arterial, capillary or venous) are equal and reflects the size of the body glucose pool. By means of ^{14}C or ^{3}H glucose injected or infused into the blood, estimates [1,2,14] can be made of (a) the size of the glucose pool, i.e. the amount of glucose which dilutes the radiolabelled glucose; (b) the turnover rate of the glucose pool; and (c) the glucose space, i.e. the hypothetical fluid volume which would contain the glucose pool at the same concentration of glucose as in plasma water.

Estimates of the glucose space in man vary from 25–35% of total body volume, values that are slightly larger than the ECF and so in keeping with the concept that the body glucose pool represents the glucose of the blood, the interstitial fluid and the free intracellular glucose of the liver.

The glucose pool in the resting subject averages about 15–20 g (83–110 mmol) and glucose turnover varies between 120–180 mg (0.66–1.0 mmol/l) per minute which corresponds to about 170–260 g per day[2] of which between one half and one third is accounted for by the brain.[7]

The plasma half-life of glucose, in the fasting subject, is in the region of 60–80 minutes or, put differently, the blood glucose concentration would fall to roughly half its fasting level within an hour or so if, during fasting, glucose inflow from the liver were suddenly to cease but outflow into the tissues continued uninterrupted. Glucose turnover rate is halved during prolonged fasting and increased many times by eating. It is a tribute to the enormous capability of the body for homeostasis that a glucose load up to ten times larger than the glucose pool can be added to it, within a period of two hours, with only a doubling or less of the pool size. These adjustments are brought about mainly by alterations in insulin activity on the liver and peripheral tissues, although other factors undoubtedly play a part.

The blood glucose concentration in the post-absorptive subject remains remarkably constant, indicating that glucose inflow into the glucose pool (glucose appearance—Ga) exactly balances glucose outflow (glucose disappearance—Gd) into the tissues. If glucose outflow temporarily exceeds glucose inflow, the blood glucose concentration falls, i.e. the glucose pool contracts;

conversely, if inflow temporarily exceeds outflow the blood glucose concentration rises. This means that *changes* in blood glucose concentration invariably reflect an imbalance between processes which add, and those which subtract, glucose molecules from the glucose pool. Contrary to what is often believed, they give no information on the rate of glucose turnover, nor do they indicate which process is primarily responsible. For the purpose of discussion, the two processes are considered under separate headings but they occur simultaneously and independently. Although studied in the past mostly by means of unstable radioisotopes, they have more recently been investigated using either glucose labelled with the stable isotopes ^{13}C and ^{2}D[4,5] or by selective venous catheterization.[6] The former techniques are non-invasive and can be used over prolonged periods without even the remote possibility of producing a radiation hazard such as accompanies the use of ^{14}C and ^{3}H, but they are technically demanding and require expensive detection and measuring equipment. Experience with them is still extremely limited but can be expected to increase knowledge and throw considerable light upon alterations in glucose dynamics in disease that can, at present, only be inferred from physiological changes observed in volunteers and selected patients.

GLUCOSE OUTFLOW

Entry of glucose into the cell

At normal blood glucose concentrations, the only drain upon the glucose pool is assimilation of glucose by the tissues. For this to occur, glucose must first enter the cell where it becomes available to be acted upon by enzymes. Few types of mammalian cells are readily permeable to glucose, the most important being those of the liver, brain, islets of Langerhans, kidney, intestinal mucosa and erythrocytes. In these tissues glucose exists free in the cell-sap and, within minutes, is in equilibrium with glucose in the ECF. Most tissues, particularly striated muscle, fat and connective tissue, appear to possess, at the cell membrane level, a system for the regulated transfer of glucose from the ECF into the cell. In tissues of this type, the rate at which glucose enters the cell determines the rate of glucose assimilation, i.e. cell permeability is rate limiting. Consequently, free glucose is generally not demonstrable in the intracellular fluid of these tissues which together constitute the bulk of body mass. The rate of glucose entry into the cell is determined mainly by the effective concentration of insulin in the ECF and by the glucose concentration. Until the concentration of glucose in the ECF exceeds a certain value, glucose assimilation is virtually zero.[7] As the glucose concentration in the ECF rises, the rate of glucose uptake increases until a maximum value is achieved above which no increase in uptake occurs, despite further elevations in ECF glucose and insulin concentrations. These upper limits far exceed those encountered under normal physiogical conditions.

The tissue threshold for glucose is close to the fasting blood glucose concen-

tration and may be an important factor in its determination.[7] Insulin lowers the glucose threshold in muscle, adipose tissue, and probably most other tissues, thereby greatly facilitating the entry of glucose into the cells. A similar effect is produced by muscular work,[8] anaerobiosis and drugs which uncouple oxidative phosphorylation[9] such as salicylate and dinitrophenol.

At blood glucose concentrations below the tissue threshold glucose assimilation is wholly accounted for by non-threshold tissues such as brain, liver, kidney and the islets of Langerhans; at blood glucose concentrations above this an increasingly large role in glucose assimilation is assumed by muscle, adipose and other threshold tissues.

Intracellular metabolism

The glucose molecule, after entering the cell, is incorporated into the intracellular metabolic pool. The first step involves phosphorylation to glucose-6-phosphate by *hexokinase* with ATP as co-factor and high energy phosphate donor.

$$\text{GLUCOSE} + \text{ATP} \xrightarrow{\textit{Hexokinase}} \text{GLUCOSE-6-PHOSPHATE} + \text{ADP}$$

This reaction is irreversible. Liberation of free glucose from glucose-6-phosphate requires another enzyme, *glucose-6-phosphatase*, which is present in appreciable amounts only in the liver and kidneys.[110]

$$\text{GLUCOSE-6-PHOSPHATE} \xrightarrow{\textit{Glucose-6-Phosphatase}} \text{GLUCOSE} + \text{Pi}$$

Glucose-6-phosphate can be considered the starting point of many intra-cellular metabolic pathways. Depending upon which pathway is followed, it may lead to (Fig. 2.1):

(a) formation of glycogen—the storage form of carbohydrate in animals
(b) glycolysis with production of lactate or pyruvate and with eventual entry into the Krebs cycle
(c) direct oxidation through the hexosemonophosphate shunt
(d) glucuronic acid
(e) hexosamine production and ultimately mucopolysaccharide formation.

The factors that determine by which pathway a glucose molecule will be metabolized are complex and depend, in large part, upon the type of tissue, its redox state and the availability of other substrates. Only the salient features of the more important pathways will be considered here.

GLYCOLYSIS

Glycolysis (Fig. 2.2) is the main process by which glucose is degraded and leads to the formation of two molecules of pyruvate from one of glucose. The further

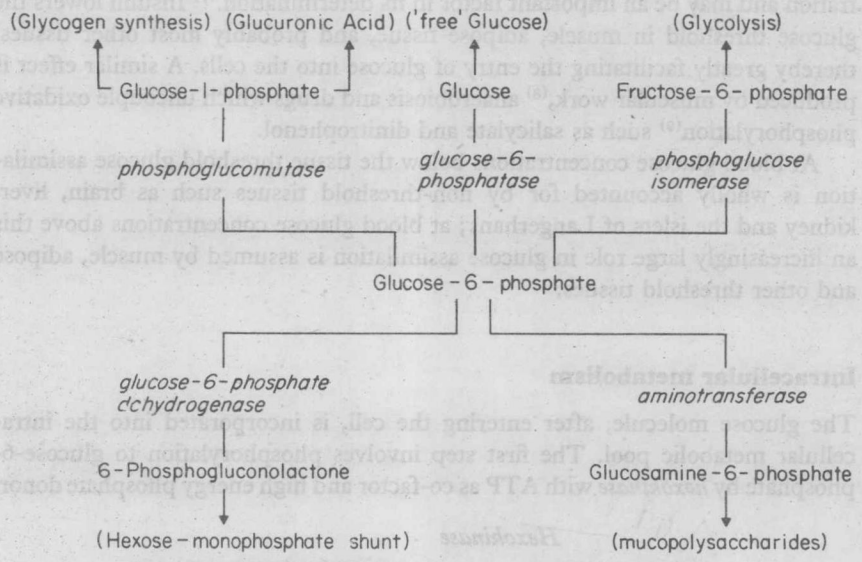

Fig. 2.1 Intracellular pathways available to glucose-6-phosphate.

metabolism of pyruvate depends on a host of factors which have recently been reviewed[11] and need not be further discussed here.

All the enzymic reactions involved in glycolysis are reversible, except for two: the conversion of fructose-6-phosphate to fructose 1-6-diphosphate and of phosphoenolpyruvate to pyruvate. For this reason, although many of the steps involved in gluconeogenesis (literally new glucose formation) are brought about by the same enzymes as are involved in glycolysis, the two processes are not the reverse of each other.

The rate limiting step in glycolysis is the conversion of fructose-6-phosphate to fructose 1-6-diphosphate by phosphofructokinase—an enzyme whose activity is generally lower in liver than in most other tissues.

Glycolysis occurs in most, if not all, tissues and in some, such as brain and skeletal muscle, is essentially the only glucose catabolic pathway. It is, in itself, a poor source of energy but serves to produce substrates such as pyruvate, which can be completely oxidized to provide energy, or glycerol phosphate which, by combining with fatty acids to form triglycerides, become important constituents of the cells.

Not all of the pyruvate formed during glycolysis is oxidized. Some is reduced to lactate by reaction with NADH formed during glycolysis, and some is converted by transamination into alanine. Much or all of the lactate and alanine formed in this way diffuses out of the cells into the blood in which it is carried to the liver to provide an important source of new glucose molecules.

Although the liver is capable of both glycolysis and gluconeogenesis, it is doubtful whether, under physiological conditions, it ever exhibits a net flow in

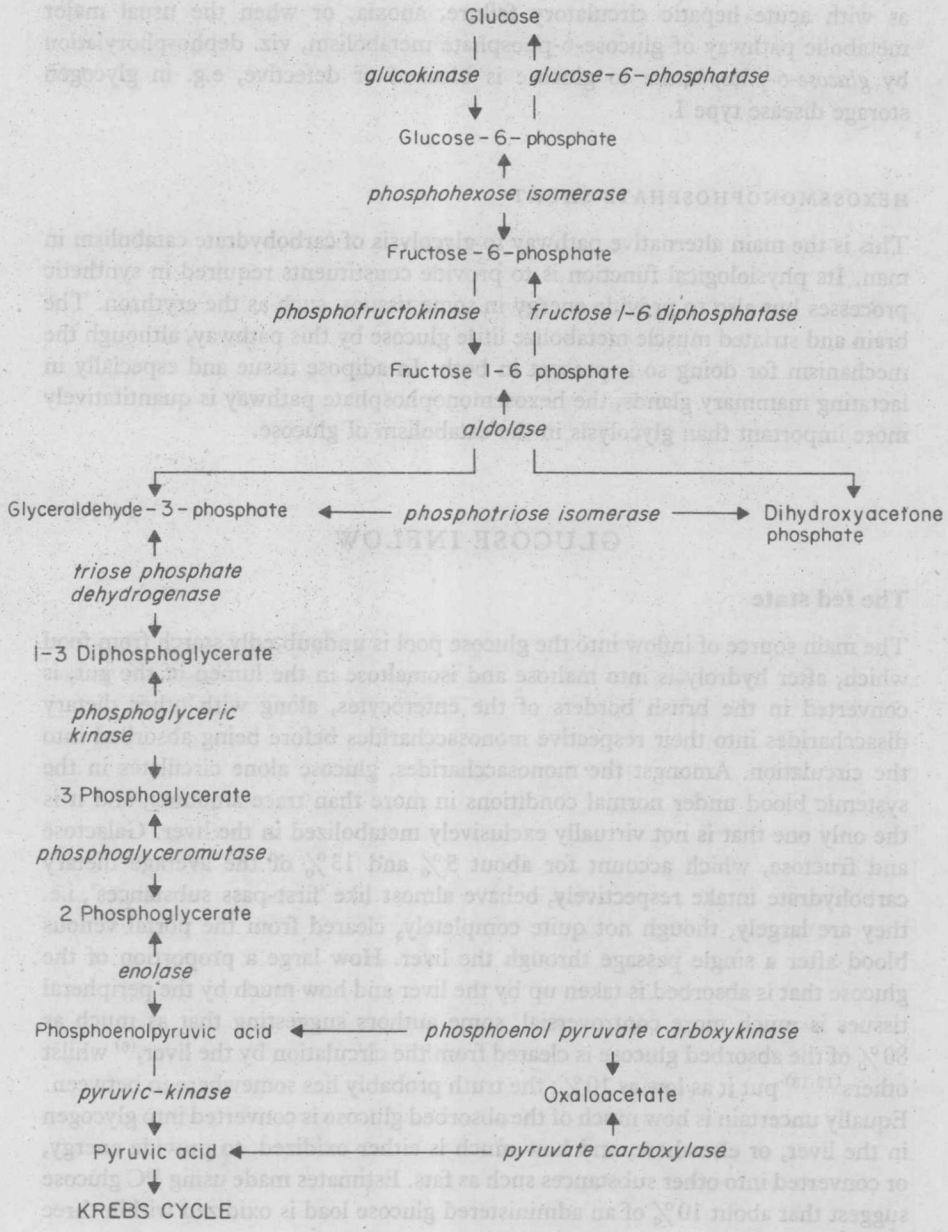

Fig. 2.2 Glycolytic and gluconeogenic pathways.

the direction of glycolysis since, even under resting conditions, lactate (and other glycogenic precursors) are released into the circulation by peripheral tissues and must be cleared by the liver and reconverted into glucose. The situation is different when the redox potential of the liver changes dramatically,

as with acute hepatic circulatory failure, anoxia, or when the usual major metabolic pathway of glucose-6-phosphate metabolism, viz. dephosphorylation by *glucose-6-phosphatase* to glucose is blocked or defective, e.g. in glycogen storage disease type I.

HEXOSEMONOPHOSPHATE SHUNT

This is the main alternative pathway to glycolysis of carbohydrate catabolism in man. Its physiological function is to provide constituents required in synthetic processes but also to provide energy in some tissues, such as the erythron. The brain and striated muscle metabolize little glucose by this pathway, although the mechanism for doing so is present in both. In adipose tissue and especially in lactating mammary glands, the hexosemonophosphate pathway is quantitatively more important than glycolysis in the catabolism of glucose.

GLUCOSE INFLOW

The fed state

The main source of inflow into the glucose pool is undoubtedly starch from food which, after hydrolysis into maltose and isomaltose in the lumen of the gut, is converted in the brush borders of the enterocytes, along with other dietary disaccharides into their respective monosaccharides before being absorbed into the circulation. Amongst the monosaccharides, glucose alone circulates in the systemic blood under normal conditions in more than trace amounts, and it is the only one that is not virtually exclusively metabolized in the liver. Galactose and fructose, which account for about 5% and 13% of the average dietary carbohydrate intake respectively, behave almost like 'first-pass substances', i.e. they are largely, though not quite completely, cleared from the portal venous blood after a single passage through the liver. How large a proportion of the glucose that is absorbed is taken up by the liver and how much by the peripheral tissues is much more controversial, some authors suggesting that as much as 80% of the absorbed glucose is cleared from the circulation by the liver,[6] whilst others[12,13] put it as low as 10%; the truth probably lies somewhere in between. Equally uncertain is how much of the absorbed glucose is converted into glycogen in the liver, or elsewhere, and how much is either oxidized, to provide energy, or converted into other substances such as fats. Estimates made using ^{13}C glucose suggest that about 10% of an administered glucose load is oxidized within three hours of ingestion.

The fasting state

Feeding in man is intermittent and for some of the time the supply of glucose from the gut is below the requirement for glucose by the body as a whole. The

proportion of time that a person is effectively fasting depends upon the frequency of feeding, the size and composition of the meals and the rates of gastric emptying and intestinal absorption. For many individuals, fewer than nine hours in any twenty-four are spent in the genuinely fasting state, mostly between midnight and seven a.m.

While all tissues participate in removing glucose from the blood only the liver, and to a lesser extent the kidneys, have the capacity to add glucose to it. The ability of the liver to maintain blood glucose levels constant in the absence of glucose inflow from the gut was first observed by Claude Bernard who, in 1853, wrote 'sugar is manufactured in the liver which must therefore be considered an organ which produces or secretes sugar'. This statement was accepted by many but rejected by others until 1922 when Mann and Magath produced hypoglycaemia in the dog by hepatectomy, proving conclusively that the liver normally adds glucose into the blood.

The unique position occupied by the liver as the pivot about which glucose homeostasis is balanced can be largely attributed to three properties of the liver cell not shared to any appreciable degree by others, except those of the kidney.

1 Free permeability to glucose, i.e. glucose inside the cell and glucose in the ECF are in equilibrium; when the concentration of glucose in the intracellular water exceeds that in the ECF glucose diffuses out into the blood; conversely, when the concentration of glucose in the extracellular fluid is higher than in the intracellular water, as occurs during absorption of glucose from the gut, it diffuses in.

2 The presence of a high concentration of *glucose-6-phosphatase*, the enzyme which cleaves glucose-6-phosphate into glucose and inorganic phosphorus. Most other tissues are deficient or completely lacking in *glucose-6-phosphatase* and are unable to liberate glucose from glucose-6-phosphate, whether formed from glucose by *hexokinase* or from glycogen by glycogenolysis.

3 The ability to synthesize glucose from simpler, smaller molecules, i.e. gluconeogenesis, because of the presence of the three key gluconeogenic enzymes, *fructose 1-6-diphosphatase*, *pyruvate carboxylase* and *phosphoenol pyruvate carboxylase*.

Glucose uptake and glucose release by the liver[1] occur continuously and simultaneously, their relative rates determining whether there is overall net glucose uptake, net glucose release, or 'equilibrium'. One of the factors determining this is the blood glucose concentration although the most important is undoubtedly the portal venous insulin concentration. Whether glucagon plays any significant role in man is doubtful.

The level of blood glucose at which the changeover occurs from net glucose release to net glucose uptake is close to the fasting blood glucose concentration and is an important determinant of it. It used to be thought that the control of glucose inflow and outflow from the glucose pool was auto-regulatory or, in engineering jargon, that the liver exercised narrow range glucostatic control. This is no longer thought likely and it seems probable that control is largely exerted

by insulin—which encourages glucose uptake by the liver and depresses its output—and by other agencies—including the autonomic innervation to the liver and possibly glucagon—which do more or less the opposite.

Glucose released from the liver between meals is derived from two sources: (1) glucose absorbed in excess of requirements during the phase of temporary hyperglycaemia after eating, and deposited as glycogen; (2) by gluconeogenesis, i.e. from glucose precursors brought to the liver from the extrahepatic tissues. It has been estimated that by morning after an overnight fast, the two processes are making roughly equal contributions to glucose inflow from the liver.

GLYCOGENESIS AND GLYCOGENOLYSIS

Since carbohydrates are not readily stored as such, most of the excess sugar absorbed from the food which is not immediately used as fuel, is converted either into fat or stored as glycogen. Whether the actual glucose molecules absorbed are converted into glycogen or, as seems more likely[15], they facilitate the formation of glycogen by glucose molecules produced from continuing gluconeogenesis is unsettled but largely academic.

The amount of glycogen in the liver is determined to a large extent by the preceding diet and varies widely. Examination of biopsy specimens taken from healthy volunteers suggests that the average glycogen content of the whole liver is only 44 g (range 15–80 g) after an overnight fast, and not much greater after feeding. After 36 hours without food, liver glycogen stores may fall as low as 4–8 g but do not change much thereafter, even if fasting is continued for several more days. Parenthetically, it may be mentioned that the glycaemic response evoked by glucagon reaches its lowest level—virtually zero—normally after 48–72 hours without food, but then rises back to almost basal levels if fasting is continued.[17,18] Glycogen never disappears completely from the liver except in extremes and may be an obligatory intermediate in the production of glucose by the gluconeogenic pathway. Indeed, it has been suggested, in some species at least, that hepatic glycogen is formed exclusively through gluconeogenesis and that only a very small percentage of the glucose absorbed from the gut actually enters the circulation as such, rather than as glucose metabolites and/or hepatic glycogen precursors.[16]

Chemically glycogen is a complex, highly branched homopolysaccharide containing only beta-glucosyl units joined in alpha 1–4 and alpha 1–6 linkages. Its molecular weight varies, depending upon the method of isolation, between 1 and 100 million daltons. Glycogen is found in nearly all tissues, especially liver and muscle, but significant amounts are also present in brain, heart, kidneys and adipose tissue. Its deposition is associated with storage of about twice its own weight of water.

Both the synthesis and breakdown of glycogen are brought about by an extremely complex series of reactions, which are interrelated through their joint dependence upon *protein-kinase* but which otherwise utilize totally different sets of enzymes.[19] Glycogen formation is brought about by *glycogen synthetase*,