tion. Of the other hormones, catecholamine and growth hormone concentrations did not alter, while plasma cortisol concentration showed a small increase but not until 18 h after glucagon had increased. Furthermore, the rise in cortisol concentration showed no correlation with ketone bodies or FFA. Gerich, Lorenzi, Bier, Schneider, Tsaklikian, Karam & Forsham (1975, New England Journal of Medicine, 292, 985) have confirmed the probable importance of glucagon by infusing somatosta-
tin (GH-RH) into patients at the same time as insulin was withdrawn. There was a much-delayed and depressed rise in blood 3-hydroxybutyrate and plasma glucose concentrations while plasma glucagon concentration decreased by 50%.

It seems, therefore, that glucagon is important in the pathogenesis of diabetic ketoacidosis even when the cause seems to be simple insulin deficiency. In infection glucagon probably plays a major role in precipitating ketoacidosis, while in other acute disease states ketoacidosis results from an imbalance of insulin and gluca-
gon concentrations with cortisol and catecholamines also contributing to the lipolytic and ketogenic drive.

D. THE METABOLIC RESPONSE OF NERVOUS TISSUE TO ALTERATIONS IN ACID–BASE STATUS
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tal, Lund, Sweden

There is a mutual relationship between the acid–base and the energy metabolism of the brain. On one hand,hyper-
capnia and hypocapnia induce changes in carbohydrate and amino acid metabolism which, by altering the buffer base concentration, aid in regulating intracellular pH. On the other hand, changes in metabolic production of acids alter the intracellular pH and secondarily influence the CO₂ tension.

There are two main types of metabolic changes in-
duced by hypercapnia. First, the acidosis affects pH-
dependent equilibrium reactions, e.g. the creatine phosphokinase and the lactate and malate dehydrogenase reactions. As a consequence, the phosphocreatine concentration is decreased and the lactate/pyruvate and malate/oxaloacetate ratios are increased. However, since the contents of ATP, ADP and AMP are unchanged, hypercapnia, even if excessive, does not alter the balance between production and utilization of energy. Second, there is inhibition of phosphofructokinase which, by reducing the delivery of pyruvate, induces a state of relative substrate deficiency. As a result, citric acid cycle intermediates and amino acids are mobilized as substrates. In hypocapnia changes are usually in the opposite direction and acid production limits the increase in intracellular pH. When marked, hypocapnia appears to induce mild tissue hypoxia due to its effect on cerebral blood flow. As a result, lactic acid production is further enhanced and intracellular pH returns to normal, or subnormal values.

Cerebral hypoxia leads to activation of phospho-
fructokinase and other rate-limiting glycolytic enzymes. The resulting increase in pyruvate delivery, and the redox change, seem to determine the changes observed in citric acid cycle intermediates and amino acids. Changes in the opposite direction are observed when acid production is inhibited by barbiturate anaesthesia or by insulin-induced hypoglycaemia. The results allow the conclusion that the pyruvate concentration determines the size of the Krebs cycle pool and that changes in this pool strongly influence the flux of carbon atoms between the Krebs cycle and the amino acid pools.

E. CLINICAL AND EXPERIMENTAL ASPECTS OF LACTIC ACIDOSIS
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Clinical lactic acidosis may be divided into two cate-
gories: Type A, the variety commonly seen in shock, and Type B, in which there is no clinical evidence of poor tissue perfusion or hypoxia. Older views on the patho-
genesis of lactic acidosis were mainly centred on the possibility of overproduction of lactic acid by the tissues, and, particularly in Type A lactic acidosis, this is likely to be present. More recently interest has arisen in the possibility of defective removal of lactate and hydrogen ions from the circulation. In resting man the liver and kidneys are the major sites of lactate uptake. Studies on the isolated perfused rat and guinea-pig liver have shown that acidosis itself inhibits lactate uptake, probably because of a mutual interdependence of hepatic intracellular pH and lactate uptake. A fall in hepatic lactate uptake results in a lowering of intracellular pH, which in turn depresses lactate uptake further. Phenformin, the most common causal agent of clinical Type B lactic acidosis has been shown to lower both hepatic cell pH and lactate uptake. The clinical efficacy of alkalinization in lactic acidosis may be due to correction of hepatic intracellular acidosis. In contrast to the situation in the liver, the absolute renal contribution to lactate removal increases markedly in acidosis, and the kidneys may potentially compensate for depression of hepatic lactate uptake. It is likely that metabolism of lactate must be depressed in both liver and kidneys in order for lactic acidosis to occur; this may be the situation in both shock and in phenformin-induced lactic acidosis.

F. METABOLIC COMPLICATIONS OF INTRA-
VENOUS FEEDING WITH SOLUTIONS CON-
 TAINING FRUCTOSE AND AMINO ACIDS
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The choice of a substrate whose metabolism can provide energy to support the synthesis of tissue constituents during intravenous feeding has often been influenced by the observation that a particular compound is metabolized by man more rapidly than glucose. During the past 3 years, some attention has been paid to serious metabolic complications arising as a direct result of the rate and pathways of metabolism of fructose, sorbitol and xylitol. In particular, lactic acidosis and hyperuricaemia have
occurred during fructose and xylitol infusion. The rates of metabolism have often been determined in fit subjects or in patients undergoing standard elective operations to the upper gastrointestinal tract, such as vagotomy and pyloroplasty. Less is known of the effects of serious illness on substrate utilization. In a series of patients undergoing intravenous feeding because of Crohn's disease or ulcerative colitis, determination of blood metabolites before the start of intravenous feeding reveals increased blood lactate concentrations in most patients. When fructose or sorbitol are infused the lactate concentration can rise sufficiently to disturb acid–base status. There is evidence that the rate-limiting steps in the utilization of sorbitol occur after its initial oxidation to fructose and thus to advocate the use of sorbitol on the basis of its rapid disappearance from blood is open to criticism.

COMMUNICATIONS

1. THE UNDERLYING GENETIC DEFECT IN THALASSAEMIA, A COMMON HEREDITARY ANAEMIA

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Thalassaemia is a common hereditary anaemia, caused by a decrease in the synthesis of either α- or β-globin. An inherited disease due to the malfunctioning of a single gene could be due to one of a number of causes. The gene for the protein affected could be deleted, or a point mutation could occur in the gene which prevents its transcription into messenger RNA. Alternatively, a remote mutation could affect the control of transcription. Finally, messenger RNA coding for the protein might be made, but for some reason cannot be expressed in the cell, either because it is defective itself due to a mutation, or because some other component of the process of protein synthesis is not functional.

Techniques recently developed allow the isolation of pure messenger RNAs for specific proteins. Using these methods globin messenger RNA has been obtained from human reticulocytes. An exact copy of the messenger RNA was prepared enzymatically (globin complementary DNA) using the viral enzyme reverse transcriptase. This radioactive probe was then used to search for gene sequences in homozygous α-thalassaemia and in cases of β-thalassaemia in which no β-globin is synthesized.

In the case of the α-thalassaemia, the genes for α-globin are deleted, and this is clearly the primary genetic defect. The β-thalassaemia lacked detectable β-globin messenger RNA, but the gene is apparently present. Therefore, at least in this case, β-thalassaemia is a point or control mutation preventing transcription rather than a complete deletion.

These techniques have also been used to determine directly the number of each globin gene present, and the results agree with those predicted from genetic data.

2. NORMAL DISTRIBUTION AND POSTPRANDIAL RELEASE OF GUT HORMONES

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Several new gastrointestinal hormonal peptides have been isolated in the last few years including vasoactive intestinal peptide (VIP), gastric inhibitory peptide (GIP) and motilin. However, there is relatively little information on their distribution in the gut and their possible release by physiological stimuli. We have measured the concentrations of gastrin, pancreatic glucagon, secretin, GIP, VIP and motilin in each of nine anatomical divisions of the GI tracts of seven freshly slaughtered primates (four baboons, three monkeys). The hormones were solubilized by three separate tissue homogenizations in acid alcohol and solids removed by centrifugation. The solutions were then neutralized, dried down and re-dissolved for radioimmunoassay. In baboons the greatest amounts of gastrin were found in the antrum (10 ± 1 µg), pancreatic glucagon in the gastric fundus (1.1 ± 0.03 µg) and pancreas (259 ± 32 µg), enteroglucagon in the ileum (66 ± 8 µg), secretin in the duodenum (3.6 ± 0.3 µg), GIP in the jejunum (29 ± 4 µg), VIP in the colon (235 ± 84 µg) and motilin in the jejunum (31 ± 3 µg). The hormone distribution was identical in the monkeys.

Ten healthy volunteers were studied during a normal hospital lunch. Blood samples were taken from a soft intravenous catheter in the left antecubital fossa before and for 5 h after the meal. Gastrin rose to a peak of 10 ± 3 pmol/l at 50 min, pancreatic glucagon fell by 3 ± 1 pmol/l at 150 min, while enteroglucagon rose steadily to a peak of 58 ± 20 pmol/l at 240 min. Secretin and VIP showed no change (detection limit ± 0.5 pmol/l). GIP showed a big rise to 41 ± 5 pmol/l at 75 min while motilin was variable showing a mean rise of 18 ± 7 pmol/l at 20 min but a later mean fall of -3 ± 5 pmol/l at 90 min. The development of sensitive gut hormone assays has allowed accurate production of hormone 'maps' of the gut and definition of normal hormone responses to physiological stimuli and these are essential first steps in the understanding of gastrointestinal endocrinology in human pathology.

3. A TRIAL OF HYPOTENSIVE TREATMENT IN PREGNANCY

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It is not clear whether mild to moderate chronic hypertension in pregnancy should or should not be treated with antihypertensive drugs. One small trial of methyl dopa suggested possible benefit for the foetus (Leather et al., 1968, Lancet, ii, 488).

We report a trial of alpha methyl dopa (Aldomet) for the treatment of hypertension in pregnancy involving 277 women. Hypertension was diagnosed if two blood pressure readings taken under standardized conditions using a London School of Hygiene sphygmomanometer to avoid observer bias equalled or exceeded 140 mmHg.