MEDICAL RESEARCH SOCIETY

A meeting of the Medical Research Society was held on Friday and Saturday, 11 and 12 July 1975, at Oxford. The following Symposium and Communications were presented.

SYMPOSIUM: Clinical Disorders of Intermediary Carbohydrate Metabolism

A. A NEW EFFECT OF METHIONINE ON LIVER METABOLISM

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B. METABOLIC CHANGES DURING STARVATION

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The metabolic response to starvation may be characterized as biphasic in which an initial or 'gluconeogenic phase' and a delayed or 'protein-sparing phase' may be identified. The early response to starvation is concerned with the maintenance of adequate glucose release from the liver so as to meet the on-going needs of the brain. This is achieved by stimulation of hepatic glycogenolysis and gluconeogenesis. The hormonal signals responsible for these adaptive changes are a drop in circulating insulin and a rise in glucagon. Since cerebral glucose utilization occurs at a rate of 150 g/day and inasmuch at liver glycogen stores amount to 70-90 g, it is clear that glycogenolysis becomes a progressively less important source of blood glucose as fasting extends beyond 18 h. On the other hand, augmented peripheral release and hepatic extraction of glucogenic amino acids, notably alanine, become progressively more important in the maintenance of glucose homeostasis. This augmented rate of gluconeogenesis occurs, however, at the expense of body protein stores, which undergo dissolution at the rate of 60-80 g (8-10 g of urinary nitrogen) per day.

As fasting progresses beyond 1 week and extends for periods of 3-6 weeks, the rate of nitrogen loss declines to less than 5 g/day. This delayed response may thus be characterized as 'protein-sparing'. Since protein-derived amino acids represent the sole precursors available to mammalian tissue for de-novo glucose synthesis, a reduction in protein catabolism must be accompanied by a decline in gluconeogenesis. Glucose homeostasis is maintained in the 'protein-sparing phase' via a reduction in glucose utilization as well as glucose production. During starvation, ketone bodies progressively accumulate in blood reaching levels of 6-8 mmol/l. In prolonged fasting ketones are extracted by the brain, thereby reducing glucose utilization by 60-70%. Hepatic gluconeogenesis shows a simultaneous decline of equal magnitude. This is achieved by means of a reduction in output of glucogenic amino acids, particularly alanine, from muscle.

These changes in protein catabolism and muscle alanine output in prolonged fasting cannot be accounted for on the basis of alterations in the secretion of insulin, glucagon, or other gluco-regulatory hormones. Recent studies, however, indicate that hyperketonaemia may itself reduce the output of alanine from muscle and decrease the rate of protein catabolism. Infusion of 3-hydroxybutyric acid in fasting may result in a fall in blood alanine and a decline in urinary nitrogen excretion. Thus ketones may have a dual role in the 'protein-sparing phase' of starvation: as a substrate for the brain, and as a signal to muscle limiting alanine output and protein catabolism.

C. THE PATHOGENESIS OF DIABETIC KETOACIDOSIS

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Severe diabetic ketoadidosis remains a potentially lethal condition with mortality rates ranging from 5 to 10% in good centres to 25% elsewhere. Knowledge of the precipitating factors and biochemical genesis of ketoacidosis should improve prevention, recognition and logical treatment of the condition.

The major causes and precipitating factors of ketoacidosis are: (1) infection, (2) failure to diagnose new diabetes, (3) decreased insulin administration, and (4) other acute disease states such as myocardial infarction, cerebrovascular accidents and trauma (Hockaday & Alberti, 1972, Clinics in Endocrinology, 3, 751). Some of these factors are associated purely with insulin deficiency but in infection and other acute conditions patients may be taking their normal insulin dose but still become ketoadidotic. In such states the circulating concentrations of the 'stress' or catabolic hormones are increased and it has been assumed that this results in a relative insulin deficiency. High plasma concentrations of these catabolic hormones (glucagon, catecholamines and cortisol) have frequently been reported in severe diabetic ketoacidosis but it has not been known whether these are late sequelae of the condition or are of pathogenic significance.

Recent work has clarified the role of these hormones. In two separate studies (Alberti, Christensen, Iversen & Ørskov, 1975, Lancet, in press; Gerich, Tsalikian, Lorenzi, et al., 1975, Journal of Clinical Endocrinology and Metabolism, in press) hormonal and metabolic changes have been measured after insulin withdrawal from insulin-requiring diabetic patients. Blood glucose rose rapidly to a plateau while blood ketone body and plasma FFA concentrations rose more gradually. Plasma glucagon concentration showed an early rise and correlated strongly with the rise in ketone body concentra-