Summary of Discussion

Dr. Franz M. Matschinsky considered that neurological mechanisms may play a major part in the secretion of insulin; during the ingestion of food there is increased electrical activity in the afferent nerves from the liver and gut, and in the hypothalamus. *Dr. David M. Kipnis* agreed and noted that vagal stimulation in vivo and cholinergic drugs in vitro are known to cause increased insulin release. In his own laboratory it has been shown that theophylline and cyclic AMP introduced into the lateral ventricle of the sheep stimulate insulin secretion which is quite independent of glucose concentration in the blood. Thus, neurological mechanisms might well play a major role in preparing the body for "the assault by food." It is also possible that the "basal adrenergic state" of β cells may influence the resting level of circulating insulin.

Dr. Rolf Luft reported briefly on studies which show that insulin responses measured in blood taken from peripheral veins do reflect what occurs in the portal circulation. He infused subjects with glucose for one hour through the brachial vein and sampled blood from both the portal and brachial veins. The profile of changes in insulin concentrations seen in the two veins were the same, but the absolute levels found in the portal vein were about three times those occurring in the brachial vein. This was true in groups of high and low (prediabetic) responders studied by his group.

Several speakers reported their observations of responses to amino acids. Dr. Matschinsky found that high concentrations of leucine (20mM) cause a biphasic secretory response which was similar to that induced by glucose. *Dr. Daniel Porte, Jr.,* observed a similar response in dogs infused with arginine. *Dr. Gerold M. Grodsky* found no clear evidence of a multiphasic response in the rat pancreas perfused with arginine in the presence of varied concentrations of glucose. In man, *Dr. Stefan S. Fajans* found two peaks in plasma insulin concentration during infusion of arginine (30 gm.) over varying periods. The first of these peaks occurred after five to ten minutes and, unlike that induced with glucose, could be elicited in both normal and mildly diabetic subjects. He concluded that the action of arginine must therefore differ qualitatively from that of glucose. Dr. Luft did not consider the small first peak seen by Dr. Fajans in response to arginine to be comparable with the much larger one produced by glucose at a slightly later stage in his own patients. He thought that Fajan's reported peak might well be an artifact due to initial distribution of secreted insulin. Dr. Fajans disagreed, since he had seen this peak at all rates of arginine infusion without the period of previous priming used by Luft. Dr. Kipnis commented that he could not get any insulinogenic response to glucagon in hypoglycemic children when the blood sugar level was 40 to 50 mg./100 ml. However, if the glucose level was first raised to about 100 mg./100 ml. by infusion of alanine, an insulinogenic response to glucagon could then be obtained. Dr. Fajans had postulated that the effect of arginine upon insulin secretion is independent, but he had observed, as had others, that the magnitude of the response to this amino acid does increase with the increasing concentrations of glucose in the blood. *Dr. Philip J. Randle* suggested that the first peak induced by arginine might, in fact, be due to glucose if this amino acid increases the sensitivity of the islets to glucose or, as he put it, moves the insulin response curve "to the left." *Dr. Willy J. Malaisse* had observed such a shift in response to glucose when arginine was added to media containing incubated rat pancreatic tissue. In reply to *Dr. Robert H. Williams,* Dr. Fajans proposed that the second peak induced by arginine was not due to an indirect effect secondary to induced glucagon secretion.

Dr. Porte, commenting on Dr. Kipnis' report, noted that the resting plasma insulin levels of normal Japanese subjects are the same as those seen in normal Americans. When fed a predominantly fat-containing diet, as in the case of the Sumo wrestlers, they become markedly obese and their resting insulin levels rise. He was convinced that diet does influence resting insulin levels and illustrated this with studies of subjects who had fasted for three days. After this time, the levels of plasma insulin had fallen in both normal and obese subjects but the absolute levels in the obese subjects were still high. Alcohol given after the period of fasting lowered the blood sugar and the insulin levels, but again the insulin levels remained higher in the obese than in the normal subjects. Dr. Porte also reported the results of a study in one moderately obese and mildly diabetic patient who was fed on an isocaloric diet containing from 5 to 85 per cent carbohydrate and 15 per cent pro-

tein. Blood sugar and plasma insulin levels tended to be higher when the diet contained low proportions of carbohydrate. Dr. Kipnis was concerned by any comparisons between allegedly normal Japanese and American subjects. He pointed out that the normal Japanese has a plasma cholesterol level of about 125 mg./100 ml. and a lower incidence of coronary disease than, for example, the normal American subjects studied at Framingham, who had cholesterol levels of the order of 225 mg./100 ml. Only if one were to study strictly comparable groups in the two countries would it be possible to know whether the "normal" insulin levels are the same. He also pointed out the limitations of acute studies in obese patients. It is true that fasting does cause lowering of the plasma insulin level, but failure to reduce the level of an obese subject to that of a fasting normal subject may have nothing to do with reduction in carbohydrate intake. The changes produced by many years of dietary abuse cannot be reversed during a short period of dietary control. Chick and Like, for example, have shown that the hypertrophy induced in islets of primates and subprimates with cortisone takes many months to resolve. Thus, if a similar phenomenon applies to the obese subject, such short periods of dietary control may alter the response of individual islets to a stimulus but not that of the islet tissue as a whole. Therefore, one might not expect to find any major change in the basal plasma insulin level. As far as insulinogenic response is concerned, glucose has its maximal effect at concentrations between 75 and about 150 mg./100 ml. At the level (120 mg./100 ml.) reported in his patient by Porte, the basal insulin level (22 μU./ml.) is much lower than that normally found in obese subjects (30 to 50 μU./ml.) and suggests that the pancreatic β cells are under intense stimulation but show impaired response. Under such conditions, and as Porte reported, acute perturbations of diet are not likely to induce major changes in the basal insulin level.

Dr. E. F. Pfeiffer reinforced Dr. Kipnis' remarks upon the effects of diet in obese subjects. In his experience, only a small proportion of obese subjects could be restored to an ideal weight by dietary means, but in such cases the resting level of insulin and the reactive increases in plasma insulin following glucose stimulation are both reduced to normal. If they are then fed on a diet containing more than 25 per cent carbohydrate, they gain weight again. In the initial stages of fasting, obese subjects show lowered levels of circulating triglycerides and glucose but their plasma insulin levels remain elevated. He agreed that the glucose content of the diet is important. In his own laboratory, Dr. Pfeiffer had shown that the response of the perfused rat pancreas to arginine is much greater when the rat has been fed on a diet containing sucrose than when starch is the source of glucose in the diet. He also agreed that subjects used for comparison should be well chosen. A cyclist whose excessive weight is due to increased muscle mass should not, as was done once, be compared with an obese subject of similar weight. Also, dietary intake should not be the sole criterion. Those who live in the tropics may take in only 2,000 calories, mainly in the form of carbohydrate, but they perform different amounts of physical work and may not take other necessary dietary components, which would distinguish them from apparently similar subjects living in other lands. Finally, in patients with chronic pancreatitis, the insulinogenic response to oral glucose is not greater than that to intravenous glucose and the patient does not respond to either pancreozymin or secretin.

—PETER H. WRIGHT, M.D.