Insulin and Carbohydrate Metabolism.

ALTHOUGH the main outline of the action of insulin on the metabolism of carbohydrate is now fairly clear, the actual details of the chemical transformations occurring in the synthesis and combustion of sugar in the body are still only known in part. The view that insulin transforms glucose into some reactive form, although still maintained by some investigators, has not been confirmed by others. Either there is a failure to find any change in the rotation of the glucose under the influence of muscle tissue and insulin (A. B. Anderson and A. Carruthers, *Biochem. Jour.*, vol. 20, p. 556; 1926), or discrepancies between the polarimetric and copper reduction values of the extracts examined are considered to be explicable rather on the basis of the presence of other optically active or reducing substances in addition to the glucose (H. F. Holden, *ibid.*, p. 263, and G. S. Lund and C. G. L. Wolf, *ibid.*, p. 259). Anderson and Carruthers have also found that the polarimetric value of dialysates or extracts of blood varies according to the reaction of the solution at the time of estimation.

It appears certain that phosphorus plays an essential part in the utilisation of glucose; and the formation of a hexosephosphate may be regarded as an essential link in the chain, probably both to synthesis and degradation. An exception, however, appears to be provided by blood, the corpuscles of which break down, *in vitro*, glucose into lactic acid, without the intervention of the phosphorus molecule (J. T. Irving, *ibid.*, p. 1320). The reduction in the blood-sugar under the action of insulin is always accompanied by a parallel reduction in the inorganic phosphorus, which, however, is later excreted from the body, any hexosephosphate formed not being stored but rapidly broken down again.

The development of convulsions when the blood-sugar has fallen to a low level, and their abolition by the administration of glucose, has provided a useful means of investigating further the details of carbohydrate metabolism by observing what compounds have the same favourable effect as glucose. The convulsions appear to be caused by disturbances in equilibrium, the symptoms being similar to those observed after unilateral labyrinth extirpation or other lesion to the vestibular apparatus (W. Russell Brain, *Quart. Jour. Exp. Physiol.*, vol. 16, p. 43; 1926). Thus the animal (rabbit) holds its head rotated to one side, and the whole body may be rotated on the pelvis. Later, rolling movements occur towards the side to which the head is rotated, sometimes also to the opposite side. On the other hand, the preliminary symptoms of apprehensiveness and shying at the movement of an observer suggest a heightened irritability of the whole of the central nervous system, which perhaps one might suggest to be correlated with the fall in the sugar of the blood.

The brain, and presumably also the rest of the nervous system, depends for its glucose upon that brought to it in the blood; although reducing substances are present in the brain tissue, they appear to consist chiefly of creatinine and pentoses (Barbara E. and E. G. Holmes, *Biochem. Jour.*, vol. 19, p. 492; 1925; and vol. 20, p. 595; 1926). These authors, in their investigations into the metabolism of the brain, have found that this tissue forms lactic acid from glucose in the absence of oxygen, and that the acid is removed if oxygen is afterwards admitted. Examination of rabbit's brains *post mortem* shows that they contain lactic acid, the amount of which does not increase on anaerobic incubation unless glucose is also present. From their series of experiments, the conclusion may be drawn that the amount of lactic acid found in the brain *post mortem* depends on the level of the blood-sugar at the time of death, and is roughly proportional to it: thus it is increased following the administration of an anæsthetic and decreased after an injection of insulin. It bears no relationship to the reducing substances in the brain, which, as we have seen, are not glucose, or apparently to the glycogen, which remains remarkably constant after a variety of experimental procedures, such as depancreatisation or the injection of a convulsive dose of insulin.

The formation of lactic acid from the blood glucose must be a highly active process, since it appears to be complete in the few minutes elapsing between death of the animal and removal and cooling of the brain: in the rabbit the amount found is of the order 0·1 gm. per cent. Insulin has no direct effect on the lactic acid metabolism of the brain, but influences it solely by producing hypoglycæmia: moreover, following depancreatisation, the brain can convert both blood and added glucose to lactic acid under anaerobic conditions and remove it again in the presence of oxygen, and to the same degree as a normal brain (*ibid.*, vol. 19, p. 492; 1925, and p. 836; vol. 20, p. 1196; 1926; and vol. 21, p. 412; 1927).

It appears, then, that insulin plays no part in the conversion of glucose to lactic acid and the subsequent removal of the latter in the brain as in skeletal muscle, but the work throws no light on why hypoglycæmia should produce convulsions: the lactic acid in the brain tissue itself is reduced when the blood-sugar falls, but, following the convulsions, the blood lactic acid increases, owing to the escape into the circulation of some of the acid set free during the violent muscular movements.

Since Herring, Irvine, and Macleod investigated the remedial effect of various sugars upon insulin convulsions (*Biochem. Jour.*, vol. 18, p. 1023; 1924), numerous other investigators have studied the same problem, using a variety of sugars or their possible metabolites in the hope of discovering some of the stages through which carbohydrates pass in their metabolism in the body. Recovery has been produced by the administration of glucal (Winter) and dihydroxyacetone (Kermack, Lambie and Slater, Laufberger, Hewitt and Reeves, Markowitz and Campbell, etc.), whilst the following compounds have been found to be inactive: glucosan and desoxyglucose (Winter), methyl glyoxal, lactic acid, glycerol, sodium citrate and pyruvate, and rhamnose (Lambie and co-workers), hexosedi- or mono-phosphate (Marks and Morgan), glyceric aldehyde (Hewitt and Reeves), and glucosone (Hynd) (L. B. Winter, *Biochem. Jour.*, vol. 20, p. 668; 1926; and vol. 21, p. 54; 1927; W. O. Kermack, C. G. Lambie, and R. H. Slater, *ibid.*, vol. 20, p. 486, and vol. 21, p. 40; Lambie and Frances A. Redhead, *ibid.*, vol. 21, p. 549; H. P. Marks and W. T. J. Morgan, *ibid.*, vol. 21, p. 530; V. Laufberger, *Publ. de la Faculté de Médecine*, Brno, Czechoslovakia, vol. 4, p. 1; 1926; J. A. Hewitt and H. G. Reeves, *Lancet*, vol. 2, p. 703; 1926; J. Markowitz and W. R. Campbell, *Am. J. Physiol.*, vol. 80, p. 548; 1927; A. Hynd, *Proc. Roy. Soc.*, vol. 101, B, p. 244; 1927).

Various points of interest emerge from this work. Glucal is presumably effective owing to the similarity of the molecule to that of glucose. More interest attaches to the place of dihydroxyacetone in carbohydrate metabolism. Laufberger has shown that its behaviour in the body is the same as that of glucose (*Pub. de la Faculté de Médecine*, Brno, Czechoslovakia,

vol. 2, p. 83; 1923–24), and Lambie and his co-workers have adduced evidence indicating that it acts by being directly oxidised and not by being converted into glucose first: in which case they suggest that the reaction which is facilitated in the organism by insulin, and fails to proceed satisfactorily in the diabetic, is the transformation of glucose into dihydroxyacetone. Thus they have found that in the decerebrate eviscerated preparation, the latter will not maintain the blood-glucose at a constant level when infused, nor does it accumulate in the blood, the inference being that it is immediately oxidised: in other experiments its administration has failed to give so marked a rise in the blood-sugar as that of glucose itself: it raises the respiratory quotient and increases the metabolism more quickly and to a greater extent than glucose: and the fall in the inorganic phosphate of the blood parallels the intensity of the metabolic change, so that it appears that dihydroxyacetone causes a more rapid formation of the phosphoric acid ester than glucose.

These authors suggest that the reactions which occur may be similar to those postulated, from theoretical considerations, by A. L. Raymond (*Proc. Nat. Acad. Sci.*, vol. 11, p. 622; 1925). Glucose reacts with phosphoric acid to form a hexosemonophosphoric ester, which then splits into a molecule of triose and one of triosephosphate: two molecules of the latter condense to form a hexose diphosphate, which is hydrolysed back to hexose and inorganic phosphate. The triose may be dihydroxyacetone itself or closely related to it. In a further discussion, Lambie points out that lævulose, like dihydroxyacetone, is both more easily oxidised and a better glycogen former than glucose, yet only glucose can be obtained from glycogen on hydrolysis: it is therefore possible that dihydroxyacetone may be a common intermediary between lævulose and glucose and glycogen. Lævulose, however, does not cause recovery from insulin hypoglycæmia so readily as glucose or dihydroxyacetone: possibly it may be converted into the latter without the aid of insulin, being more closely related to it than glucose. In insulin hypoglycæmia, however, the conversion of glucose into dihydroxyacetone under the influence of the excess of insulin might be even more rapid than the transformation of lævulose, so that glucose would be more effective in causing recovery than the latter.

This hypothesis of the mechanism of action of insulin and of the rôle of dihydroxyacetone in metabolism has, however, been controverted by Markovitz and Campbell, who maintain that this compound is not a normal metabolite of glucose, but must be converted into the latter by the liver before the body can make use of it, and adduce experimental evidence in support of this view. The ultimate decision between these two views must be withheld until further work, which will be awaited with interest, has been carried out on the rôle of dihydroxyacetone in carbohydrate metabolism.

In conclusion, attention may be directed to some interesting observations which may possibly lead to a satisfactory explanation of the cause of insulin convulsions. Mention has been made of the fact that methylglyoxal cannot produce recovery from them: Lambie and his co-workers have also noticed that after an injection of this compound, glucose or dihydroxyacetone may also be ineffective: in other words, methylglyoxal appears to exert some toxic action on the animal. Hynd has gone even further, and observed that an injection of glucosone (a body closely related to glucose from which methylglyoxal might possibly be derived) produces a condition similar to insulin hypoglycæmia, which, however, differs from the latter in that glucose cannot bring about recovery. He suggests that insulin may cause the production of glucosone from glucose in the body.

These observations suggest that the convulsions are caused by some intermediary metabolite in the combustion of glucose: it appears reasonable to suppose that this compound is always being formed in small quantities in the body, but is immediately further broken down. Following an injection of insulin, the amount produced is considerably increased and the oxidising mechanism fails to keep pace with this increased production, so that the compound set free in the body is enabled to exert its toxic effects. In this connexion the work of Dakin and Dudley may be recalled: they found that most tissues contained an enzyme, glyoxalase, which was capable of converting methylglyoxal into lactic acid. However, the relationship between the curative effect of an injection of glucose or dihydroxyacetone upon insulin convulsions, and the possible presence of glucosone or methylglyoxal in excess as their direct cause, appears to require further investigation before one of the different hypotheses outlined above can be considered definitely established.

Marine Biology in Ceylonese Waters.

DETAILS of the marine biological research carried out by the Ceylon Government are contained in the Administration Report of the Government Marine Biologist for 1926. (Part 4: Education, Science, and Art (F), by Dr. Joseph Pearson. Pp. F29. Colombo: Government Record Office. 65 cents.) In this report there is an account by Mr. A. H. Malpas, the assistant marine biologist, on the present state of the pearl oyster, the window-pane oyster, and the chank (a gastropod, *Turbinella pyrum*, Linn.) fisheries. It would appear that there is no likelihood of a large pearl oyster fishery for at least four years, whereas an experimental fishery on the lines advocated by Dr. J. Pearson, the marine biologist, may be held in 1928. The essence of the new system is the elimination of the sale of oysters to the public, by which means all the pearls would come into the hands of the Government.

The window-pane oyster fishery at Lake Tamblegam in 1926 was very successful. Although the Government received a revenue of only Rs.18,000.0 for two million oysters, it is stated that the lessee's returns from the fishery were between one and two lakhs of rupees, but the sum was more probably nearer Rs.50,000.0. There is a curious anomaly in the control of the chank fishery in the Palk Strait. On the Indian side the fishery is under the control of the Madras Fisheries Department, and hence the Government made a net profit of Rs.46,367.0.0 in 1922–23 on 466,540 chanks. On the Ceylon side chank fishing is open to all comers, and the only revenue that accrues to Government is that derived from the export duty. In 1923, the Ceylon Government made a profit of Rs.12,065.0 on 2,419,786 chanks. From these figures it is clear that although the Ceylon chank fishery is about five times as large as the Madras fishery, yet its value as a Ceylon Government asset is almost negligible.

A considerable amount of fisheries research has been carried out by Mr. A. H. Malpas and Mr. M. Gomez. It is very gratifying to note that, as a direct outcome of the trawling experiments carried out by the Government Marine Biology Department, a company has been registered in Colombo to modernise