Aspects of Carbohydrate Metabolism.

III. Some Relationships with Phosphorus Metabolism.

IT is now well known that esters of carbohydrate and phosphoric acid play an important part as intermediates in carbohydrate metabolism in both animals and plants. They were first obtained in the alcoholic fermentation of yeast; later they were found to play a part in the metabolism of muscle and other tissues. Phosphorus occurs in animal tissues in several other forms; for example, as ortho- and pyro-phosphate, as a constituent of nucleo-proteins, and in combination with creatine in muscle. It is proposed in this review to discuss only certain aspects of the metabolism of phosphoric acid esters; the formation of hexose phosphate as a step in the production of lactic acid from starch by skeletal muscle has already been mentioned in a previous article (Nov. 8, p. 740). P. Eggleton has published a review on the rôle of phosphorus in muscular contraction, in which reference is made to the hexose phosphates (*Physiol. Reviews*, vol. 9, p. 432; 1929).

Resting muscles do not contain hexose diphosphoric acid; they can, however, glycolyse it and, in the presence of sodium fluoride and glycogen, synthesise it. The ester formed appears to be the same as that isolated by Harden and Young from yeast fermentations. W. T. J. Morgan has investigated its chemistry (*Biochem. Jour.*, vol. 21, p. 675; 1927; with R. Robison, *ibid.*, vol. 22, p. 1270; 1928). The first step was the formation of the methylhexoside-diphosphates, which were then separated into the α and β forms. The barium salts were hydrolysed with bone phosphatase (to which further reference will be made below), when the phosphoric acid was split off; further investigation, including estimations of the rotations before and after acid hydrolysis of the hexosides, and determinations of the methoxy group, indicated that the hexose present is fructose, probably γ-fructose. A tetramethyl hexose, having the same rotation as tetramethyl-γ-fructose, was also prepared; the constitution of the original acid is probably γ-fructose 1 : 6 diphosphoric acid.

J. Pryde and E. T. Waters have confirmed the presence of the diphosphate in muscle press juice after carrying out the fermentative re-synthesis; when this step was omitted, only a monophosphate was isolated, from the muscle of the rabbit, donkey, and goat, and this appears to be the ester of normal resting muscle (*Biochem. Jour.*, vol. 23, p. 573; 1929). The amount present in the muscles of the larger animals was less than in those of the rabbit, in which the yield was 0·13 per cent; it is possible that it is connected with the speed of contraction of the muscle. By oxidation of the hexose group with bromine and removal of the phosphoric acid by hydrolysis with weak sulphuric acid, a hexonic acid was obtained which was identified as gluconic acid. Ninety per cent of the hexose is an aldose, 10 per cent a ketose; from the formation of gluconic acid the former is presumably *d*-glucose.

The presence of phosphoric esters in different tissues suggests the presence of enzymes to synthesise and hydrolyse them; in fact, phosphatases are very generally distributed throughout the body, according to H. D. Kay (*Biochem. Jour.*, vol. 20, p. 791; 1926; vol. 22, pp. 855 and 1446; 1928). The enzymes can be extracted with chloroform water from the ground-up tissues, the extract being filtered through cotton-wool before use. They act upon hexose phosphates, glycerophosphates, and nucleotides; for quantitative estimation it is convenient to use sodium glycerophosphate in glycine-sodium hydroxide buffer at *p*H 8–9: the amount liberating 1 mgm. phosphorus in two hours at 38° may be called one unit. The enzyme is found in highest concentration in the mammal in the kidney and the mucous membrane of the small intestine: there is a close parallelism between its distribution and that of ereptase. Study of the reactions with the different substrates led to the conclusion that the same enzyme is responsible for the hydrolysis of each. In the case of the kidney, the enzyme is chiefly present in the cortex; there is more in the infant soon after birth than in the fœtus, and thereafter its concentration does not change much to adult life. It is capable of acting upon part of the phosphoric ester in the blood plasma. It has been suggested that its function is to hydrolyse this ester, which is then excreted as inorganic phosphate in the urine; but Kay, with R. T. Brain and P. G. Marshall (*ibid.*, vol. 22, p. 628; 1928), found that the excretion of phosphate was controlled by the level of the inorganic phosphate in the plasma, and not by that of the ester phosphorus. The low level of the latter in the plasma cannot be raised by administration of ester by mouth, though a temporary increase can be brought about by intravenous injection. On the other hand, the amount present in the kidney varies with its functional efficiency: thus it is markedly reduced in chronic nephritis in man and in acute uranium nephritis in rabbits (Brain and Kay: *ibid.*, vol. 21, p. 1104; 1927).

Both intestinal and kidney extracts show synthetic activity, provided high concentrations of the alcohol are used; sodium glycerophosphate was successfully isolated from the reaction mixture after allowing duodenal contents to act on sodium phosphate and glycerol for a week.

It may be mentioned that Kay has also found a pyrophosphatase in many mammalian tissues, with a distribution similar to that of the phosphatase described above; it hydrolyses pyrophosphate to orthophosphate. Its optimum *p*H is 7·2–7·8, in contrast to the range 8·8–9·3 of the orthophosphoric esterase.

The true phosphatase is of considerable interest; it can be conveniently extracted from young bones (rabbits) by soaking the split bone in chloroform water for some days, and filtering and evaporating the extract (M. Martland and R. Robison: *Biochem. Jour.*, vol. 23. p. 238; 1929). It can be purified by precipitation from water with alcohol and ether and extraction of the precipitate with 50 per cent alcohol; it cannot be dialysed or ultra-filtered, and is easily adsorbed. Its optimum *p*H is about 8·4; the initial rate of hydrolysis of glycerophosphate, however, increases up to *p*H 9·4, but at the same time inactivation of the enzyme is accelerated. It hydrolyses the phosphoric esters of the plasma. Small amounts of inorganic phosphate but not of glycerol retard the hydrolysis of glycerophosphate; in the presence of high concentrations of the alcohol it is capable of bringing about esterification of phosphate (Martland and Robison: *ibid.*, vol. 20, p. 847; 1926: vol. 21, p. 665; 1927).

H. B. Fell and Robison have investigated the phosphatase activity of embryonic avian femora, cultivated *in vitro* (*ibid.*, vol. 23, p. 767; 1929). They found that the tissue synthesised the enzyme during cultivation; the amount in the bone increased to a maximum and then declined, corresponding to the phases of histological differentiation followed by degeneration. The course of development was similar

to that occurring normally *in vivo*, but the degree of development attained was less. The enzyme is confined to bone and ossifying cartilage; it is absent from small-celled, non-hypertrophied cartilage. It presumably plays some part in calcification: it has been shown that it is capable of causing the deposition of calcium phosphate from calcium glycerophosphate in the complete absence of inorganic phosphate (for example, Robison, *ibid.*, vol. 20, p. 388; 1926).

T. H. Milroy examined the processes of fatigue and recovery in normal and diabetic muscle and found that fatigue was characterised by the entrance of water, the loss of some phosphate, depletion of the glycogen store, and increase in lactic acid, together with loss of the power of esterification of phosphate under the influence of sodium fluoride (*Quart. Jour. Exp. Physiol.*, vol. 17, p. 161; 1927). In recovery the reverse changes were observed; with muscle taken from a depancreatised cat, the recovery processes were much slower, especially the storage of glycogen and the ability to synthesise hexose phosphate.

D. Stiven has recently investigated in detail the part played by phosphoric esters in the formation of lactic acid from glycogen or starch, using a muscle extract: muscle from a cat perfused with Ringer's solution after killing instantaneously was extracted, after mincing, with cold sodium chloride and bicarbonate solution; the extract was obtained by pressing through muslin and concentrated by freezing out water; the *p*H was adjusted by adding phosphate and bicarbonate (*Biochem. Jour.*, vol. 22, pp. 867, 874, and 882; 1928: vol. 23, p. 583; 1929: vol. 24, pp. 169 and 172; 1930). Under anaerobic conditions, the extract produces lactic acid from glycogen, starch, or glucose, though at somewhat different rates. With glycogen as substrate, the changes in phosphoric esters were followed in detail and found to be of three types: in the first, there is no ester accumulation or change in phosphate until all the glycogen has been used up, when phosphate increases; in the second, no ester accumulates for the first 30–40 min. of incubation, but thereafter accumulation is rapid; in the third, ester accumulates at the commencement and is then broken down. The actual course depends in part on the concentration of glycogen and the extract used. In any event, there is no molar relationship between lactic acid production and phosphoric ester accumulation or breakdown.

Addition of hexose diphosphate under certain conditions inhibits lactic acid formation and increases the formation of phosphoric ester; at the same time the glycogen decreases more rapidly than when the addition is not made. Stiven has also found that a sterile cell-free muscle extract prepared from a cat or wild rabbit will convert glucose to lactic acid without the addition of any activator; the glycolysis occurred in the early stages of incubation and was certainly due to the muscle enzymes and not to any infection.

Although the rate and extent of lactic acid formation from glucose are usually greater than from glycogen, the ester accumulation is much greater in the case of the latter. Again, the rate of lactic acid production and ester accumulation is greater with glycogen than with soluble starch in the earlier stages of the reaction, although finally the lactic acid formation is the same with both. Irradiation of the muscle extract with ultra-violet rays from a quartz mercury vapour lamp for short periods increased the rate of lactic acid production from glycogen; at first ester accumulation increased, but later decreased, coincident with the maximum rate of formation of the acid; longer exposures destroyed the enzyme. These results differ in some respects from those obtained by previous observers, and further work will be necessary before the details of the chemical changes produced by muscle or muscle extracts upon carbohydrates are finally and completely elucidated.

The Psychology of Adolescence.

THE psychology of adolescence has not received from psychologists that attention which its popularity with novelists, poets, and painters would seem to merit. It is, therefore, a matter of interest that, at the Bristol meeting of the British Association, Section J (Psychology) devoted the whole of a morning's session to hearing and discussing four papers on this subject.

In his paper on "The Basis of Social Adjustment", Dr. R. G. Gordon maintained that the problems of adolescence were largely problems of adjustment to society, and that the success of such adjustment depended on the formation of a sentiment of a social self which should in large measure dominate the other sentiments in the personality. The organisation of this sentiment, he said, depended on certain emotional dispositions or instincts: suggestibility, passive sympathy, imitation, and the herd instinct—the last of these being of first importance. These, however, were not enough, for the mentally defective often exhibited them in no small degree and yet was almost totally ineducable: he showed no particular peculiarities in respect of the instinctive bases of social adjustment; he was, for example, no more suggestible than normal people. Nor was the tale completed by the sex instinct. "To describe social intercourse as a manifestation of sexuality", said Dr. Gordon, "is, to my mind, a mistake. What the sex instinct does is to give a tremendous impulse to extraversion: it directs the individual's interest away from himself." He made the interesting suggestion that differences in the strength of the herd instinct were largely responsible for differences between the introvert and the extravert. These emotional dispositions, he said, had to be controlled and organised, and the individual had to learn to discriminate between what met with social approval and what did not. This control, integration, and discrimination depended on the acquisition of knowledge, the organisation of beliefs, and the development of the power of making sound judgments. It was in these respects that the mentally defective was lacking. They were associated with the proper development of the cerebral cortex; so social adjustment had to be regarded as of gradual development and only coming to fruition with a full functional activity of the cortex.

Dr. Gordon made an interesting distinction between the control, integration, and discrimination implied in social adjustment and what is commonly called intelligence, and suggested that some intelligent people never developed the capacity for social adjustment, because they were lacking in the special cortical development necessary for the integration of their instincts and the formation of the social sentiments: they were aments in spite of their intelligence. Such people might compensate either by an intense integration of the ego-centric sentiment, as in the typical epileptic personality, or by failure to adjust to life, as in many psychasthenics and chronic hypochondriacs, who preferred illness to health, finding