Fletcher, W. M., Hopkins, F. G. RESPIRATORY PROCESS IN MUSCLE AND THE NATURE OF MUSCULAR MOTION. [Proc. Roy. Soc. Biol. Sci., Series B, Vol. 89, No. B, 619.]

The authors review the importance of muscular activity as the means of knowing the modes of energy discharge by the living cell and the relation of these to the specific chemical processes of life.

It was held at the end of the last century that muscular energy sprang from a more or less explosive breakdown of a molecular complex which had been made "irritable" by the inclusion of oxygen in the cell while at rest, lactic acid and carbon dioxid being liberated. The idea that this irritability was dependent upon combustion was disproved, since it was found that carbon dioxid took place in the temporary absence of oxygen, lactic acid being also produced. This led Hermann to assume the existence of "inogen" as an unstable precursor in which the necessary combustion took place to yield the energy of contraction, and that fresh carbon bodies and perhaps lactic acid entered into a newly oxygenated molecule of inogen. This inogen theory, extended to the so-called anabolism and catabolism in the chemical processes of life in all cells, rested on two bases. (1) It was believed that the oxygen was already present and therefore combustion could take place with a simultaneous fresh production of lactic acid and carbon dioxid in the absence of an immediate oxygen supply. (2) The increase in the instability of the inogen molecule and in the rate of production of the lactic acid and carbon dioxid with rise of temperature was recognized, as well as the fixation of the molecule without yielding either substance if the muscle were scalded suddenly with hot water. Later experiments of the authors with advance in technic prove however that the contemporary and immediate supply of oxygen does affect the products due to contraction and that the hypothesis of a previous inclusion of oxygen is insufficient. In regard to the second basis of Hermann's theory it was found that rapidly scalded muscle yields a large volume of carbon dioxid but practically no lactic acid. The carbon dioxid yield is also from two sources, one displaceable by acid, the other by heat. Lactic acid and carbon are therefore separately expelled.

It was found furthermore that the carbon dioxid yield is much increased in the presence of oxygen and yet the irritability is not more quickly exhausted but longer maintained. All irritant gases quicken the production of lactic acid, which in turn expels preformed carbon dioxid. At the same time lactic acid is the most obvious cause of fatigue and stiffening of muscle, yet these two conditions are inhibited by oxygen. Qualitative estimations made under conditions which eliminated disturbing influences showed that fatigued muscle contained more lactic acid than resting muscle but less after resting in an oxygen atmosphere. Lactic acid was found to increase after mechanical injury, and the output of undamaged muscle increases in increase of temperature under

conditions where the discharge had been spontaneous, while in oxygen there is no evidence of such output. Instead there is a decrease of lactic acid when fatigued muscle containing lactic acid is left at rest in an oxygen atmosphere. Marked rise of temperature overcomes this effect of oxygen, and so does severe mechanical injury. It is plain then that oxygen enters the muscle substance for the purposes of an immediate combustion and not to prepare material for explosion. Experiments upon heat production in muscle show that the oxidations which are always associated with muscular activity are separated in time from the moment of liberation of mechanical energy. They have to do with a restoration process, not with stimulation. Lactic acid instead of being regarded as a toxic product is probably an essential agent in the machinery of contraction itself. The muscle fiber itself seems to yield lactic acid by a non-oxidative molecular rupture, heat being given off. The accumulation of the acid produces fatigue, but the presence of oxygen removes this after each contraction and each successive stimulus with its associated breakdown is followed by a normal contraction. Successive experiments lead to the belief that it is the lactic acid itself which is not removed by the oxygen but is oxidized again into the muscle with a yield of carbon dioxid and that at least part of the heat of lactic acid combustion is stored in potential form in the muscle as it returns to rest. The potential energy required for the act of contraction probably lies in a particular condition of a physicochemical system. In a system of colloidal fibrils, or of longitudinal surfaces, into relation with which H-ions of lactic acid are ready to be brought, there is a potential of energy which may be discharged by a change in state of tension. Then upon recovery by oxidative removal of the lactic acid, the energy of combustion is partly discharged as heat and partly returned to the muscle in the restoration of the potential. The acid ions will be separated from the colloidal fibrils, so that the fibrils return to their former tension—that of rest. Carbohydrate is accepted as the reservoir of this energy for the muscle. The conception of this change in the physicochemical system of colloid fibrils accounts for the small energy change necessary to the breakdown of carbohydrate to lactic acid. This energy is demanded for the contractile act which also uses, perhaps, to a greater degree, the energy derived from the oxidation of the lactic acid, residing in the physicochemical system of the muscle, which was produced in the previous contraction. It would seem that the evolution of muscle has taken advantage of the acid phase of carbohydrate degradation and that thus lactic acid is given, through appropriate arrangement of the cell elements, a position in which it can induce those tension changes upon which animal movement depends. There is then no need to assume an unknown unstable chemical substance as the source of contractile energy. It is simpler, these investigators believe, to accept the existence of the potential energy in the relatively permanent physicochemical system of

the muscle which is obtainable as a result of changes in the physical configuration. Then sugar, at least, of the foodstuffs, may be considered the chemical mechanism handling the contractile energy.

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McCrudden, Janney, Goodhart and Isaacson. MUSCULAR DYSTROPHY AND THE VEGETATIVE NERVOUS SYSTEM. [Arch. Int. Med., 1918. Ed. B. M. J.]

Hypoglycemia, due to disturbance of the ductless glands is among the causes of muscular dystrophy, is the general conclusion of both these papers. McCrudden, who gives a summary of the available data, says that the myasthenia of progressive muscular dystrophy is due to hypoglycemia, which together with the fatty infiltration depends on impaired glycogenesis, the carbohydrate of the food being probably changed largely into fat instead of glycogen, and that this impaired glycogenesis is the result of disease of the adrenals or other endocrine glands. The article by Janney, Goodhart, and Isaacson, already commented on in this JOURNAL, contains, in addition to a critical review of the subject, the details of the observations on the metabolism of nine cases of muscular dystrophy, the patients being supplied with a creatinine-creatine-free diet from a special kitchen and kept in separate rooms under constant supervision by nurses trained in metabolic work. These patients showed a disturbance in the creatinine-creatin metabolism; the urinary creatinine was diminished in all the cases and was usually reduced in proportion to the severity of the cases; moderate amounts of creatine, which is not normally present, in the urine were found in all the cases, and in eight out of the nine cases the quantity of creatine exceeded that of creatinine. There was also constant hypoglycemia with impaired utilization of carbohydrates, or essentially the same metabolic picture as that recorded in myxedema, hypopituitarism, and Addison's disease, which are undoubtedly due to insufficiency of the ductless glands, and in animals after experimental removal of the thyroid or adrenals. Nearly all the patients gave skiagraphic evidence of bony changes, which the authors contend are not necessarily due to disuse, and other manifestations of disturbances of the ductless glands, such as pigmentation and dryness of the skin, hypertrichosis, unusual distribution of the subcutaneous fat, and both hypertrophy and arrested development of the genitals, were noted. Hypothyroidism was the most prominent condition, but the pituitary was unquestionably affected in one case, and the pineal possibly in two others. The conclusion drawn is that muscular dystrophy may in reality be only a symptom-group due to deficient function, not of one but of several endocrine glands separately or coincidently affected. This endocrine failure causes hypoglycemia, and from the consequent interference with their normal carbohydrate supply the muscles weaken, atrophy and degenerate, and creatine appears in the