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Studies on the Phosphate Metabolism in Multiple Sclerosis

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In order to elucidate the pathological processes of MS on the basis of the anatomo-pathological events it was attempted to gain insight into the patho-physiological processes of the organism in the various phases of the disease.

To elucidate the metabolic changes of the organism of MS patients different loadings were used (ACTH, Corticoids, exptl. fever, etc.).

The results concerning the change of energy rich phosphate esters in the erythrocyte with different loadings are presented. In the case of experimental febrile loads at 38°C the inorganic phosphate content shows an increasing tendency in the blood of most of the MS patients, whilst in that of the controls it decreases.

The change of the energy rich phosphate ester content of the cells is the opposite to the change of the inorganic P of the blood inasmuch as with febrile loadings the energy rich phosphate ester content of the erythrocytes of MS patients decreases, as compared to that of the controls which rather show an increasing tendency.

The amount of other organic phosphate esters does not vary significantly in the case of the MS patients as compared to that of the controls.

Following ACTH administration the same significant differences were obtained as when applying febrile loads.

The conclusion can be drawn that the erythrocytes of the MS organism cannot produce the energy rich phosphate esters corresponding to the energy requirements of the experimentally enhanced metabolism. The significance of these metabolic disturbances is discussed.

The pathological process in multiple sclerosis (MS) with its focal and essentially selective attack on the myelin sheaths, seems to be peculiar to the disease. On the basis of the pathomorphological picture these types of reaction are usually termed demyelinisation reactions or leukoencephalitides. In general they can be considered as a disease of the white matter. Among the different demyelinating diseases multiple sclerosis is a special disease of humans, it cannot be transferred to animals. Thus, the pathochemical processes of the damaged nervous tissue cannot be studied directly. We are completely dependent upon clinical human material, blood, cerebrospinal fluid, urine, etc. This fact naturally limits the possibilities to elucidate in details the pathological processes of the organism.

At the elaboration of our research plan relating to the pathology of MS the following aspects were taken into consideration:

1) In view of the fact that this illness is essentially the disease of the central white matter of the brain it seemed an important task to obtain as many data as possible relating to the normal biological and biochemical processes of the white matter[1–5].

2) On the basis of the anatomo-pathological events we attempted to gain insight into the patho-physiological processes of the organism in the various phases of the disease: acute, reparative and stationary[9–14].

3) We attempted to elucidate the metabolic changes of the organism according to an integrated view of the fundamental correlation of the structure, function and metabolism. Only later, after recognising many details of the pathological chain reactions taking place in the organism, we shall be able to gain information about the causative factors of this disease[15].

The organisation of the resting and functional structures of the cells are controlled by the energy producing oxidation processes of the cells. Any disturbance in the function of the oxido-reduction system may induce a structural damage of the cells. Thus the impairment of the myelin sheath with its very complex components and strictly organised layers may be produced by disturbances in the nutrient[8] or oxygen[6,7] supply respectively, as well as by the disturbance of the function of any catalyst of the oxido-reduction system. In every cell the decomposition and synthetic processes must be in equilibrium; if the decomposition processes increase at the expense of the synthetic processes structural damage ensues.

Glucose is the main energy source of the grey and white matter of the central nervous system[1]. Acetylcholine, cholesterols and the different long chain fatty acids of the nervous tissue are built up by the intermediary products of the glucose metabolism. Thus our attention was focussed on the carbohydrate metabolism in patients suffering from multiple sclerosis.

It is most important to bring the evaluation of laboratory results into correlation with the different phases of the illness. As the active, reparative and stationary periods of the disease cannot always be well differentiated clinically, the correct evaluation of the laboratory data obtained is also difficult. The many discrepancies contained in the literature may partly be due to this fact. Taking these considerations into account it seems preferable to examine the responses of the organism to various well-defined loads. If loads are applied to pathologically impaired or less efficient enzyme systems the functional or metabolic disturbances ensue earlier in the region of the pathological enzyme system. Owing to the above considerations therefore, instead of concentrating our attention on the various chemical changes occurring in the blood in the different phases of the disease we have rather observed the various alterations resulting from varying loads. Patients suffering from different phases of this disease were submitted to various loads: ACTH, corticoids and fever induced by milk. These proved to be the most suitable means. On examining the different metabolites, electrolytes and enzyme activities at a temperature of 38°C (the blood samples were taken at this temperature) it could be established that the organism of MS patients reacts not only quantitatively but also qualitatively differently as compared to the controls[13,14].

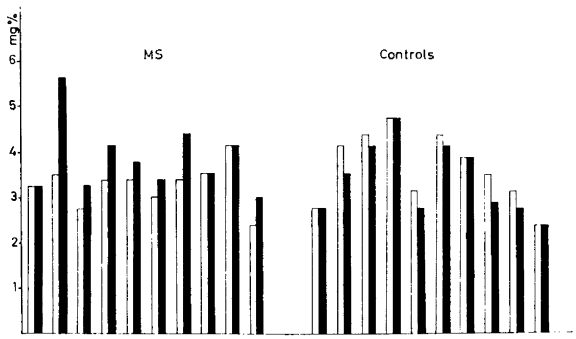

Fig. 1. Changes in the inorganic phosphate level of the blood induced by fever loads. MS: $0.02<P<0.05$; controls: $P>0.05$. □: before fever ■: at a temperature of 38°C.

Concerning the keto body formation we could establish that whilst the keto body content of the blood of MS patients in a resting state does not show a significant difference as compared to the controls, in the case of a febrile load (at 38°C) far more keto bodies and lactate form in the MS patients than in the controls. The keto body formation runs parallel with the activity of the disease. In a febrile state the metabolic processes are enhanced. The sugar utilization also increases[15].

The enhanced keto body and lactate production of MS patients in a febrile state points to the fact that there is some disturbance in their carbohydrate metabolism. And if this is the case some disturbance may be assumed in the related phosphate metabolism too. Owing to these considerations the next task was to examine the phosphate metabolism in different loading states.

METHOD

After three to six days of rest fasting blood samples were taken and then 10 ml sterile milk was administered intramuscularly. The patients were not allowed to move during the examination. Normal subjects, acting as controls, were submitted to the same procedure. In order to perform hormonal loadings 20 units of ACTH was administered intramuscularly, or 25 mg Di-Adreson-F aquosum (Organon) intravenously. The blood samples were taken at a temperature of 38°C; after the ACTH injections twice in intervals of 2 hours and following Di-Adreson-F aquosum administration 4 times every hour. For the inorganic phosphate determinations the method of Lohmann and Jendrassik[16] was applied. The different acid soluble phosphate esters were estimated according to Lohmann[17].

RESULTS

Fever loads: In the case of febrile loads at 38°C the inorganic phosphate content shows an increasing tendency in the blood of most of the MS patients, whilst in that of the controls it decreases (Fig. 1).

The change of the energy rich phosphate ester (acid soluble phosphate esters hydrolysable in 7 min) content of the blood cells is the opposite to that of the blood inorganic P content, inasmuch as with febrile loadings the energy rich

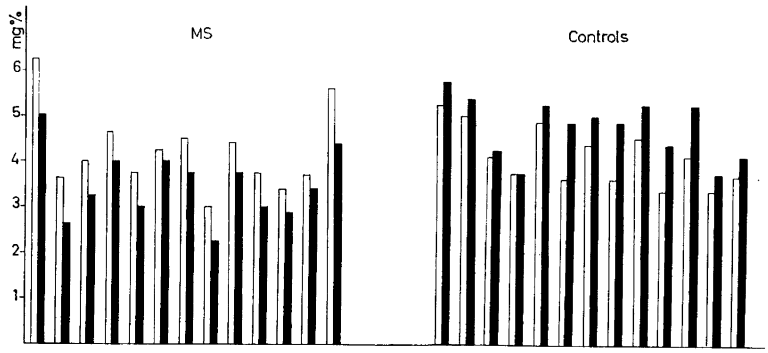

Fig. 2. Changes in the energy-rich phosphate ester content of the blood after fever loads. MS and controls: $0.02<P<0.05$. □: before fever ■: at a temperature of 38°C.

phosphate content of the cellular elements of MS patients decreases, while that of the controls rather shows an increasing tendency (Fig. 2).

The amount of other acid soluble, hydrolysable and nonhydrolysable phosphate esters does not show any significant difference in the case of the MS patients as compared to that of the controls.

Hormonal loads: Every load – also a febrile one – increases the activity of the hypophyseo-adrenal system. The ACTH production is enhanced. Hence we examined the effect of the experimentally administered ACTH and corticoids too.

Following ACTH administration the same significant differences could be observed in the energy rich phosphate ester content of the blood as on applying fever loads. The significant changes could be observed 2 hours after the administration of the ACTH (Fig. 3).

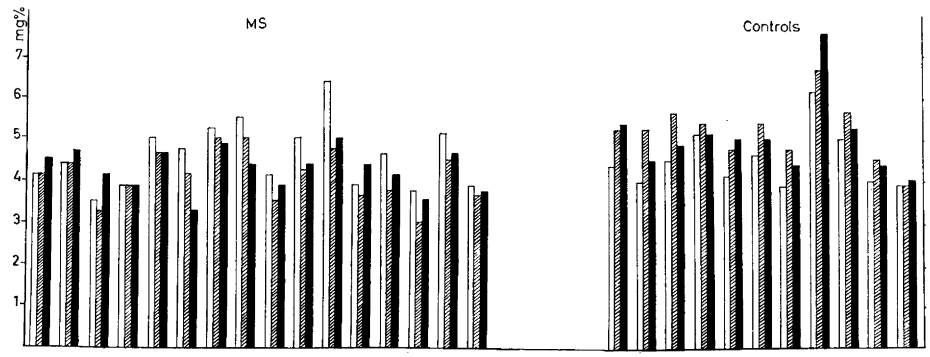

Fig. 3. Changes in the energy-rich phosphate ester content of the blood after administration of ACTH. MS (16 cases) and controls (11 cases): 2nd h: $0.02 < P < 0.05$; 4th h: $P > 0.05$. □: before ACTH ▨: 2nd h after ACTH ■: 4th h after ACTH.

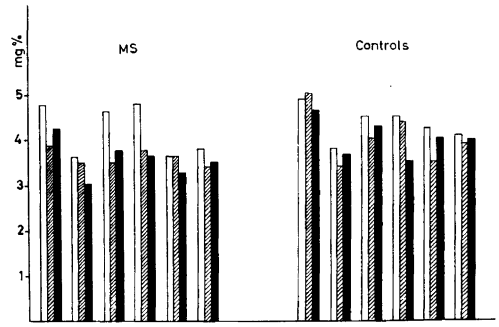

Fig. 4. Changes in the energy-rich phosphate ester content of the blood after administration of Di-Adreson-F aquosum. MS: 1st h: $0.02<P<0.05$; 2nd h: $P>0.05$; controls: 1st and 2nd h: $P>0.05$. □ : before Di-Adreson-F aquosum ▨ : 1st h after injection ■ : 2nd h after injection.

On administering a glucocorticoid (Di-Adreson-F aquosum), (Organon) the energy rich phosphate ester content of the blood decreased in the first two hours in both the MS patients and the controls, but the change was only significant in the case of MS patients (Fig. 4).

DISCUSSION

The conclusion may be drawn that the erythrocytes of normal individuals can produce the energy rich phosphate esters corresponding to the energy requirements of the enhanced febrile metabolism, whereas the cellular elements of the blood of MS patients fail to do this. The cause of the decreased energy-rich phosphates in the blood of MS patients in a febrile state as compared to the controls might be attributed partly to the weakness of the processes generating energy rich phosphate esters and partly to the increased ATP-ase activity in such conditions.

Examinations to establish whether the cause of the metabolic disturbances of the erythrocytes of MS patients mentioned above should be sought for in the enzyme system of the erythrocytes themselves, or whether the composition of the surrounding plasma exerts a damaging influence on the metabolism of the otherwise normal erythrocytes are in progress.

The question seems justified how the metabolic changes described above can be brought into correlation with the etiologic factors of MS. We assume that as a causative factor is not involved, but that the above metabolic loads indicate a disorder of the general adaptation mechanism in MS. They can, on the other hand, explain the well known clinicopathologic facts that the state of every MS patient deteritorates as a result of physical or metabolic loads. Namely, as has already been stated in the case of experimental metabolic loads (fever, ACTH) one of the tissue elements of the MS organism: the red blood cell is not able to produce the energy rich phosphate esters in amounts corresponding to the enhanced metabolic requirements. This can of course have an unfavourable effect on the restitutional processes.

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