TREATMENT OF RHEUMATOID ARTHRITIS WITH ADENOSINTRIPHOSPHORIC ACID (ATP)

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In papers published between 1940 and 1945 we reported the results of an investigation on the intermediary metabolism in rheumatoid arthritis, and showed that adenosintriphosphoric acid (ATP) has a beneficial effect on the course of this disease. In the present paper we propose to give a brief review of these investigations and to consider the results in relation to the observations made by Hench and others (1949).

We have found that in some cases of rheumatoid arthritis, vitamin B therapy has a certain, although in many instances rather unsatisfactory, effect, which is sometimes intensified by simultaneous phosphate therapy. On these observations we based our working hypothesis that the cause of rheumatoid arthritis is probably to be found in disturbances of carbohydrate metabolism.

Carbohydrate Metabolism

In order to clarify this question we made quantitative determinations on whole blood of some intermediary products of the metabolism of carbohydrates, chiefly on pyruvic acid and citric acid, with the patient at rest, and also after exertion. At rest the mean value for citric acid, in tests on an empty stomach, was lower in rheumatoid arthritis (1.366 mg. per 100 c.cm.) in about one hundred cases examined than normal (1.835 mg. per 100 c.cm.), and the deviation was statistically significant. For pyruvic acid the mean value (0.909 mg. per 100 c.cm.) was higher than normal (0.835 mg. per 100 c.cm.), but the deviation was not statistically significant. After exertion the values for citric acid in whole blood were lower in rheumatoid arthritis than normally, with statistically significant difference.

Determination of serum iron was done in fifty-two cases of rheumatoid arthritis and showed lower values (0.039 mg. per 100 c.cm.) than normal (0.114 mg. per 100 c.cm.), with statistically significant deviations. On electrophoresis, serum from ten cases of rheumatoid arthritis showed unchanged albumin-globulin ratios with increased content of globulin, particularly γ -globulin.

ATP Therapy

As these examinations seemed to indicate a lowered metabolism of carbohydrates, we considered it justifiable to try a therapy that would stimulate the conversion of carbohydrates. For this purpose we first used muscle adenylic acid, but changed later to ATP. One hundred and forty-four cases of rheumatoid arthritis were treated with ATP. Of these, about 66 per cent. showed marked improvement or recovered completely for longer or shorter periods immediately after the treatment. In about 19.4 per cent., however, the recovery was such that we are not able to state definitely whether it was a result of the ATP treatment. Only 14.6 per cent. showed no apparent response.

After the completion of the treatment with ATP, the blood was examined in the same manner as before the treatment. In those cases where there was clinical improvement, all the values for citric acid, before as well as after exertion, showed a statistically significant rise. In the cases where there was no recovery, on the other hand, there was no elevation of the citric acid values. The values for pyruvic acid showed a tendency to decrease, but the deviation was not statistically significant. The immediate effect of treatment with ATP was a decrease of citric acid and an increase of pyruvic acid. The values for serum iron rose to normal level after treatment with ATP, which was followed by clinical improvement. The albumin-globulin ratio was also normalized, in that the albumin increased and the globulin, particularly the γ -globulin, decreased.

It seems to us reasonable to presume that the deviations from the normal of the values for citric acid and pyruvic acid in the blood in rheumatoid arthritis are evidence of a disturbance, most likely a lowering, of the metabolism of carbohydrates. This presumption is also borne out by the fact that treatment with ATP, which from a biological point of view is of importance mainly in the enzymatic phosphorylation, has a beneficial effect in cases of rheumatoid arthritis, and that the blood values for citric acid and pyruvic acid return to normal

simultaneously. The tests for serum iron, and electrophoresis tests of blood serum, show that there are concurrent disturbances in the conversion of iron and proteins.

Liver Function and Rheumatoid Arthritis

Hench and others have pointed out that inter-current hepatitis with jaundice in patients who have rheumatoid arthritis often causes a temporary remission of the articular symptoms. This has been verified in our investigations. It is a known fact that in hepatitis there is often a rise in the values for citric acid and serum iron. In rheumatoid arthritis, on the other hand, these values are lower than normal, as shown in the foregoing. In our opinion these facts suggest that there may be a connexion between rheumatoid arthritis and changes in the function of the liver. For this reason we made a close study of the pathological anatomical picture of the liver in this disease. In ninety-three autopsy cases of rheumatoid arthritis fatty changes in the liver were demonstrated in 42 per cent., amyloid degeneration of the liver in 8 per cent., and cirrhosis of the liver in 10.7 per cent. The corresponding figures for an average autopsy material are 2 per cent., 1 per cent., and 3 per cent. respectively. In view of the high incidence of changes of the liver in rheumatoid arthritis, it seems to us very probable that there is some connexion between the two.

The disturbance in the intermediary metabolism of carbohydrates, which in all probability is present in rheumatoid arthritis, may presumably be associated with the appearance of fatty liver, just as fatty liver is a result of diabetes mellitus. In animals there are diseases caused by inadequate conversion of carbohydrates, which regularly involve fatty degeneration of the liver and which respond favourably to ATP. Lehninger in his experiments has shown that the oxidation of fatty acids in the liver requires the presence of ATP. The fatty degeneration of the liver in rheumatoid arthritis would thus be further evidence of the lack of active ATP in the organism.

In 1942, on the basis of these investigations, we wrote as follows:

"In recent years the opinion that rheumatic diseases are due to disturbances in the metabolism of carbohydrates (Pemberton, Wille, and others) has gained an increasing number of supporters. This concept need not be opposed to other concepts. It lies, so to speak, on a different plane. Toxic changes in the tissues, meteorologic factors, allergic changes in the reaction of the mesenchymal tissue and disturbances in the internal secretion may naturally give rise to or consist in

disturbances in the metabolism of carbohydrates. In a great number of rheumatic diseases of various types we have been able to demonstrate disturbances in the metabolism of carbohydrates, and we have also been able to treat these diseases effectively with biogenic substances which have biochemical effects, in that they are in one way or another active in the metabolism of carbohydrates. This seems to be clear evidence in support of the opinion that disturbances in the metabolism of carbohydrates play a decisive part in the appearance of pathological changes in the tissues in these diseases. It may obviously be presumed that in those rheumatic diseases that are affected favourably by ATP the result is due to the fact that those glands of internal secretion which produce enzymes active in the phosphorylation (for example sexual glands, adrenal glands, hypophysis)—as a result of intoxication, physiological or pathological changes—degenerate or atrophy, or that their function is otherwise affected, with consequent disturbances in the metabolism of carbohydrates."

Compound E

These conclusions have been confirmed recently by the important investigations of Hench and others, which show clearly that hormones from the adrenal cortex (Compound E) as well as from the hypophysis (ACTH) induce prompt remission of nearly all symptoms in rheumatoid arthritis. We do not as yet know how the effect of these hormones is accomplished in the organism. Judging from the size of the required doses (100 mg. of Compound E), it is not a matter of actual substitution therapy. Vogt (1944), on the other hand, has demonstrated that the adrenal glands of a 10 kg. dog, which together weigh about 1 mg., in twenty-four hours excrete the same amount of 17-ketosteroids as that present in 17 kg. of adrenal glands. This seems to indicate that the doses given should not be considered as physiologically too large.

A remarkable fact is that those 17-ketosteroids that mainly regulate the conversion of electrolytes have no therapeutic effect in cases of rheumatoid arthritis. Compound E, which influences principally the metabolism of carbohydrates and also of proteins, has hitherto been found to be the only definitely effective agent. Zeller, who at present is studying these problems at the Mayo clinic, has expressed the opinion that Compound E can hardly be effective in any other way than by influencing enzymes, in the first place those enzymes the active group of which is ATP.

Treatment with Compound E would thus stimulate the metabolism of carbohydrates, which would explain the therapeutic effect. The principal cause of rheumatoid arthritis would thus be a reduction in the power to convert carbohydrates, which in its turn is due to functional disturbances

in the adrenal cortex or the hypophysis. It does not seem improbable that the sexual glands would also be involved, partly because rheumatoid arthritis in many cases appears in connexion with the menopause and parturition and is aggravated by menses, partly because the sexual glands produce hormones which are closely related chemically to the hormones of the adrenal cortex. This is in accordance with our comment of 1942.

The satisfactory results that we have obtained from treating rheumatoid arthritis with ATP seem to bear out Zeller's opinion. The explanation of the relatively slow but more constant effect that we have obtained by ATP treatment is perhaps to be found in Vogt's (1949) recent observation that ATP directly stimulates the secretion of the adrenal cortex. It is possible that the increased activity of the adrenal cortex does not appear until after some time; but when it has started it often becomes more permanent.

Our next task will be to investigate whether the conversion of ATP in the organism is disturbed in rheumatoid arthritis, and whether it is affected by the treatment.

Summary

It seems reasonable to presume that the results of our earlier investigations into rheumatoid arthritis show evidence of a disturbance (most likely a lowering) of the metabolism of carbohydrates. This presumption is also borne out by the fact that treatment with ATP, which from a biological point of view is of importance mainly in the enzymatic phosphorylation, has a beneficial effect in cases of rheumatoid arthritis.

It is known that in hepatitis there is often a rise in the values for citric acid and serum iron. In rheumatoid arthritis, on the other hand, these values are lower than normal. There may thus be a connexion between rheumatoid arthritis and changes in the function of the liver. In material from ninety-three autopsy cases of rheumatoid arthritis, fatty changes in the liver were demonstrated in 42 per cent., amyloid degeneration of the liver in 8 per cent., and cirrhosis of the liver in 10.7 per cent.

The important investigations of Hench and others

have clearly shown that hormones from the adrenal cortex as well as from the hypophysis induce prompt remission of nearly all symptoms in rheumatoid arthritis. Our treatment with ATP is discussed in view of the investigations of Hench and his co-workers and also in view of other new researches.

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Traitement de l'Arthrite Rhumatismale par l'Acide Adénosintriphosphorique (ATP)

RÉSUMÉ

On se croit justifié de supposer que les résultats de nos investigations antérieures sur l'arthrite rhumatismale apportent des preuves en faveur d'un dérangement (le plus probablement diminution) du métabolisme des hydrates de carbone. Cette supposition se voit également supportée par le fait que le traitement par l'ATP—qui du point de vue biologique, joue un rôle important dans la phosphorylation enzymatique—produit un effet favorable dans l'arthrite rhumatismale.

On sait que dans la hépatite les chiffres de l'acide citrique et du fer dans le sérum se trouvent souvent augmentés. Par contre, dans l'arthrite rhumatismale ces chiffres sont diminués. Il est bien possible qu'il y ait un rapport entre l'arthrite rhumatismale et les altérations de la fonction hépatique. L'examen du matériel d'autopsie de 93 cas d'arthrite rhumatismale a révélé dans le foie la dégénérescence graisseuse dans 42 pour cent, amyloïde dans 8 pour cent, et la cirrhose dans 10.7 pour cent des cas.

Les importantes investigations de Hench et coll. ont montré clairement que les hormones de la substance corticale de la surrénale et ceux de la glande pituitaire font disparaître rapidement presque tous les symptômes de l'arthrite rhumatismale. On discute notre traitement par l'ATP à la lumière des recherches de Hench et coll., et aussi à la lumière des autres investigations récentes.