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Has the Time Come to Bridge the Gap between Basic and Clinical Research in the Field of Diabetes?

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The relation between basic and applied research is a problem of an almost philosophical nature and the solution is likely to vary within different fields of research. I shall confine myself to the significance of phosphate in the diabetes disease. A closer collaboration between basic research and the clinics cannot be expected to take place simply because some research council or other authority instruct free scientists what to do. Representatives of basic research are perhaps more individualistic than others and work best on problems which attract them. However, in all development there is one quite simple principle which has the advantage of being universal. What has to come to pass will come to pass.

At this moment when clinical diabetes research is about to take a new path, it is possible that new issues will arise and stand out as inescapable and challenging to basic research. One new path is the treatment of all diabetics with phosphate supplementation, introduced by Dr Jörn Ditzel at Aalborg in 1976. He is doing this for reasons arising from his own research. But he is by no means a pioneer in this respect. On the contrary phosphate treatment has existed for a long time, always recurring for as good reasons as have been available at that time. Phosphate deficiency in rickets was discovered in 1920 and as there seemed to be certain similarities between rickets and diabetes, for instance stunted growth, the use of phosphate injections was initiated in Germany before the discovery of insulin. Both Elias et al. (7) and Friedländer and Rosenthal (9) noted reduced blood and urine sugar and sometimes a decrease would continue for three days after only one injection. But then the whole matter was abandoned and forgotten after the discovery of insulin. During the sixties I was working on a hypothesis dealing with the observation that diabetes begins with increased and not with reduced concentrations of insulin. One of the functions of insulin which has long been overlooked is the stimulatory effect on phosphate and potassium uptake. If the concentration of phosphate drops, the increase of insulin can be interpreted as an adaptation, to preserve phosphate uptake. In the long run the increased production of insulin may lead to β-cell exhaustion and diabetes. My hypothesis was entitled: "Is phosphorus

deficiency a primary and insulin insufficiency a resultant secondary factor in the etiology and pathogenesis of diabetes?"

During this work I was much surprised to come across a few lines in small print in the Presse Medicale where P. Le Gac stated that lack of phosphate ions renders the insulin ineffective. The year of publication was 1950 but neither previously nor later could I find any article on the matter. As I discovered here a confirmation of my own ideas I wrote a letter to Le Gac who turned out to be a Professor of Pharmacology at Rennes and received a kind reply and some reprints from provincial French periodicals (11). Strangely enough it appeared that also his view of the diabetes problem originated from his knowledge of veterinary medicine to which phosphate deficiency was a current problem already in the thirties. Le Gac thought he could see similarities between the frequent acetonemia in cattle and the diabetic crisis in man and acetone vomiting in children. These conditions are severe acidoses leading to heavy losses of phosphate. Consequently it becomes imperative to rephosphatize the patient. This is precisely what Le Gac was doing already at the end of the thirties by the administration of a daily dose of 3-4 g sodium phosphate.

Guest and Rapoport (10) reported in 1941 that oral and parenteral administration of phosphate accelerates the recovery from different forms of acidosis, like experimental ammonium chlorid acidosis, gastroenteritis in children and diabetes. In the USA, treatment of diabetic coma with phosphate injections was initiated in 1948 and the results were better than with conventional alkali treatment. Despite their apparently beneficial effects on the disease these early experiments have neither influenced today's therapy of nor concepts about diabetes.

One-sided view of the insulin effect

Is it possible that the lack of interest in the role of phosphate is due to the fact that too much attention has been focused on the effect of insulin on glucose uptake? Scientists have enjoyed the concept of glucose dancing to the tune of the insulin long enough. But there is another piper calling the tune..

Not until the sixties was there any proof that insulin stimulates phosphate and potassium uptake. Studies on erythrocytes established that insulin, without affecting the uptake of glucose, caused complex changes in the phosphate metabolism involving synthesis of phosphorylated products. At high concentrations of glucose phosphorylation is a rate-limiting metabolic step (6). Glycolysis would consequently require that sufficient amounts of phosphate are present when insulin stimulates glucose uptake. It is possible that this demand for phosphate can only be satisfied by the utilization of both the anion present in the cell and that taken up. Decreased phosphorylation could consequently result from low serum phosphate or depletion of intracellular phosphate, e.g. during

acidosis. One extreme situation with intracellular depletion is the diabetic crisis when blood phosphate is often as high as 7-8 mg% and exceptionally 17 mg%. If you then, like Franks et al. (8), inject sodium phosphate, the metabolism will restart and the result is said to surpass the customary alkali treatment. The method is still not generally accepted. The remarkable observation that the large amounts of extracellular phosphate do not respond to insulin whereas exogenous phosphate does, remains to be explained.

Under physiological conditions insulin prevents the efflux of phosphate from cells (15). Unsufficient or discontious insulin administration to diabetics may consequently explain why these patients have a somewhat raised blood phosphate and lose more phosphate with the urine than healthy individuals (1). Astrug (1) points out that in this disease so much phosphate can be mobilized that one must suspect increased parathyroid activity.

Metabolic changes due to phosphate deficiency

In normal subjects, but not diabetics, there is a substantial reduction of blood phosphate during glucose tolerance tests (3). This is analogous to the effect of insulin which in healthy subjects leads to a rapid and sustained reduction of phoshate whereas a smaller effect of short duration is obtained with diabetics (4). Another difference is that lipid phosphorous increases in normal subjects after a carbohydrate meal, but decreases in the diabetics. The phosphate metabolism is consequently anomalous in diabetes (14). Even if blood phoshate is normal or increased and the uptake disturbed there is a phosphate deficiency in a physiological sense. Experimental studies have shown that the ATP-synthesis decreases during phosphate deficiency (2,16). This observation may indicate a disturbance of glucose phosphorylation as well as other phosphorylation processes resulting in metabolic acidosis. Since the acidosis facilitates phosphate elimination with the urine, phosphate deficiency may be self-aggrevating. Also other diseases than diabetes with increased losses of phosphate in the urine can be improved by phosphate treatment (13).

The blood phosphate level can be adjusted by food supplementation

My hypothesis on diabetes as mentioned earlier was based on the idea that phosphate deficiency could be regarded as a primary factor in the pathogenesis. In those days, the sixties and the beginning of the seventies, this idea was unacceptable since a condition of phosphorus deficiency in man was unheard of at the time. Today the situation is different because it has now been shown that such deficiency not only does exist but also is fairly frequent. This fact is still not universally recognized.

Let us now return to Jörn Ditzel whom I met at the International Workshop on Phosphate in Heidelberg 1976, where he showed that an increase of phosphate

improves the defective oxygen binding of red blood cells in diabetes. He has successfully continued his studies of the significance of 2,3-diphosphoglycerate (2,3-DPG), begun 15 years ago. The ratio 2,3-DPG/hemoglobin should be high in order to achieve on optimal oxygen supply for the tissues. The synthesis of 2,3-DPG increases with blood phosphate which in turn can be enhanced by a phosphate supplemented diet. He believes that it may be possible to prevent the vascular lesions of diabetes in this way (5). For my part and starting from a different basis I treated some diabetics already in the fifties. The effect of treatment was healing of ulcers and the insulin dose could be reduced by about 30%.

It should also be mentioned that when making experiments in 1979 with normal rats on a phosphate-deficient diet, I was surprised to find that the time of coagulation was drastically reduced. Is phosphorus deficiency a new coagulation factor and can normalization of the phosphate level prevent thromboses in the capillaries? Here again is a problem which shows the clinics' need of support from basic research.

Clinical diabetes research takes up the phosphate issue

At the 1979 Workshop on Phosphate in Strasbourg, a group of physicians and biochemists led by S. Ljunghall (12) presented an investigation of 2000 healthy middle-aged men, divided into two groups, one with high the other with low blood-phosphate. The former group had less blood glucose and insulin than the other. Even in healthy individuals a relative phosphate deficiency thus shows an effect on blood glucose and insulin which, if aggravated, would result in a diabetic condition.

If and when phosphate treatment of diabetes becomes generally accepted and put into practise, one can expect a reduced insulin requirement. We do not yet know for certain whether vascular complications can be controlled. An alert six-year-old phosphate-oriented research programme is now taking up the problems of the nearly sixty-year-old diabetes research. Perhaps the old dream of a closer collaboration between basic clinical research will come true after all.

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