New Dynamics of Preventive Medicine, 1974

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Mineral Transporters

Hans Nieper, M.D.

I feel preventive medicine is the most important guideline at the moment to come to with less effort and less money to better results in the prevention and the protection of our health. So far as emerges out of my limited understanding of the American situation, my feeling is that if people would go more often for a preventative check-up they would, less frequently, run into trouble.

I think a few of you have already heard of the concepts of active mineral transports in directed therapy. I will give you a tour of horizons of what active mineral transport is and what it can do and how it is to be explained.

Late in the 1950s it was discovered that cells of the female breasts becoming malignant are going to lose magnesium so we thought why not conceive an extra-active transport of principle to take magnesium into these cells with the help of phenylalanine and paraminobenzoic acid. At the same time, Hans Selye's book on the prevention of myocardial necrosis with the help of potassium and magnesium chloride was published and so we developed, in fulfilling the requirements of more active transport of potassium and magnesium into the cell, the potassium-magnesium aspartate in 1957-1958. This became quite successful world-wide as a medicament for the protection of myocardial necrosis, enhancement of liver functions and the detoxification of digitalis. Since this has been so successful, we followed this concept of active mineral transport and we changed as well the mineral which had to be transported as also the molecules which are suitable to transport mineral into a cell by means of artificially created active transport. So the most important transporters we have today are aspartic acid, 2-aminoethylphosphoric acid and orotic acid; 2-aminoethylphosphoric acid (AEP) is a substance which plays a role as a component in the cell membrane and at the same time has the property to form a complex with minerals. You may replace the calcium by

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magnesium, potassium, iron or whatever. This substance goes into the outer layer of cell membrane, is decomposed there, incorporated into the cell membrane and releases the ion upon metabolization. The second substance, the aspartates, especially the L-aspartate, goes to the inner layer of the outer cell membrane and there, upon metabolization, releases the mineral to become the ion. The third substance which interests us enormously is orotic acid which forms a high complex salt with any mineral and which has no metabolic affinity to the outer cell membrane but penetrates the outer cell membrane even in the form of a complex salt and is only metabolized at the site of the membranes of the mitochondria and of the structures found in the cell plasma. Only here the mineral will be released to the form of an ion.

So we have three different kinds of transporters: The AEPs (outer layer of the outer cell membrane), the aspartates (inner layer of the outer cell membrane) and the orotates (cell plasma organelles). All three substances are officially on the market in Germany and they play an important role in cardiology and hepatology for the aspartates. In the prevention and the treatment of multiple sclerosis, for the AEP, calcium potassium magnesium AEP is officially declared in Germany as the only active substance in the treatment of multiple sclerosis. The myelin is a multilayer of cell membrane and AEP goes there, fits as a membrane component in the damaged membrane in the case of multiple sclerosis, releases the calcium at the same time which shields against aggression by antibodies. The orotates are officially on the market for the treatment of numerous diseases, especially decalcification and immune aggression toward the cell. Keep this in mind: different transporters go to different structures inside the cell.

We will direct ourselves to calcium orotate. Calcium orotate really performs clinical effects in various diseases connected with decalcification and injury of bones which can rapidly be improved by means of the application of calcium orotate by using this new concept of active mineral transport since we know, especially in studies run in Zurich, that all formation of bone, more or less, is controlled by cell membrane and that the microgranules of apatit have to be formed inside the osteoblast and then released through the cell membrane again.

A patient's leg was sliced off with all the attendant injuries of vessels. It was almost impossible to heal him by conventional means. He received calcium orotate for two years and he is now able to walk around. He telephoned me recently and said he is in excellent shape. This is one of the accidents and injuries which really needs calcium orotate to achieve the best results which obtained today in my opinion.

Bone fractures have been treated unsuccessfully for several months and years without formation of callus or healing. The bone fractures were due, in one case, to an immune arteriolitis. Upon application of calcium orotate, within six weeks the patient returned to normal functions and had no more complaints.

Especially in Europe, more than in this country, decalcification has to do with the higher carbohydrate intake. In Germany we have a tremendous amount of, more or less, severe damages in the dorsal spine. A 28-year-old patient suffered with juvenile decalcification and severe osteochondrosis. There was no help for this patient, not by hormones or conventional calcium. However, upon treatment with calcium diorotate he became normal in every respect within a few weeks and is still without any complaints.

Now here I have to stress a little bit the aspects of the transport by the orotates. The orotic molecule is mostly taken up by mesenchymal tissue and by bradytrophic tissue, especially by cartilage tissue and also by the vessel walls, by the blood-brain barrier and by the matrix of the bone. It is much less taken up by epithelial tissue such as liver epithelium glands, and so on, or mucosa, in contrast to the AEP, for instance. We learned, during the months and years, that the improvement which we observed in dorsal spine complaints upon the application of calcium orotate, obviously had not so much to do with an improvement of the recalcification, or the improvement of the density of the bone tissue, but with the protection given to the tissue and cartilage surface by means of active calcium transport into cartilage tissue with the help of orotic carrying molecule. The orotic acid plays a very important role in so-called pentose pathway metabolism which accounts for the metabolism in cartilage tissue and especially for all organs which account for aging. There, the ribose coupling needs orotic acid and therefore obviously the orotic carrying molecule has a high affinity to this kind of tissue, like cartilage which, so far, we were unable to influence and which experienced even more damage under the influence of cortisone. Therefore, calcium orotate seems to me to be one of the most important substances to prevent cortisone side effects in, eg, rheumatoid arthritis. This is very important.

I could speak much longer on this problem. However I want you to have a certain impression. During the following years in which you will stay healthy with the help of orotates, you will be able to learn more and more about this. A 14-year-old girl, unsuccessfully treated so far with every imaginable medication, was entirely relieved with calcium orotate, because the calcium orotate goes into this connective tissue which

develops in the frame of this disease, as well as in Perthes disease, as in Schlatter disease and in Recklinghausen's disease.

By the way, I have quite a few patients who after the intake of contraceptive pills developed cartilage damage. The application of calcium orotate allows the continuation of the intake of baby pills.

A patient with a severe osteochondrosis was almost entirely immobilized. After six weeks of treatment, there were no more complaints. Astonishingly enough, there is no parallel between the lack of increasing density of bone tissue and improvement, which again points into the direction that the origin of pain in spinal syndrome has to do with cartilage behavior less so with osteoporosis as such. A 64-year-old lady with severe decalcification and in severe pain had a disc slipped off a vertebra. She was treated unsuccessfully for years and is now without any complaints for two years. Although without any radiological improvements, she is fine. In the case of severe osteochondrosis in an 18-year-old patient, she was almost immobilized two years ago. She has now absolutely no complaints and is mobile, despite the fact that there is no change in roentgenologic finding.

What we see in Europe in dorsal spine deformation is alarming. I do not know if you have a parallel in the United States. From the literature, I learned that decalcification problems in Europe play a much more important role than in this country because in the United States the protein intake is, on the average, higher.

We learned recently that Bechterew disease is an autoimmune disease related to rheumatoid form and astonishingly enough as well as the intravenous application of calcium AEP as the application of calcium orotate gives very important relief in these patients. We have the feeling that the application of the orotates blocks the immune processes which lead to an abnormal and ectopic calcification in these patients. They become partly remobilized and we have patients who gained about 20 degrees in upright position. Especially, there is no more pain. I have quite a series of Bechterew disease patients and they were always very much helped by this kind of treatment, where previously all other imaginable treatment failed. One patient had this disease for about 13 years and after 11 years of ailing we started the treatment with calcium AEP intravenously and calcium orotate; there were no more complaints, she resumed normal housekeeping and gained about 20 degrees of an upright position. Another patient was an 82-year-old lady with excellent activity. Only in upright position she had unbearable pain and when lying down had no pain at all. This is a typical symptom for chondrosis. Upon impact on the cartilage the pain developed. After the treatment with calcium

diorotate (3 gm/day) she had no more pain at all. She is going around in a Fiat sports car at 82 years of age.

Arthrosis of the hip shows good results with the treatment of calcium orotate. Of course, you cannot replace damage and lesion. However, we have the feeling that once the first signs of osteochondrosis develop, the long-time treatment with calcium orotate helps a lot and at least stretches out the time until eventually the arthrosis will have developed to become a surgical problem. The protection of the cartilage layer really is the mechanism which accounts for the prevention of osteochrondosis and of arthrosis.

We have quite a series of patients with severe osteoporosis with arthrosis on both sides who underwent operations and were previously, for about six months, treated with calcium AEP and calcium orotate. Surgeons reported a very important hardening of the spongiosal structure of the bone and all over it seems that the results, especially upon the implantation of the metal, seem to be much better after such a pretreatment than without it.

In Houston, Texas, four years ago at the Cancer Congress, I presented a series of patients who had developed metastatic disease, mostly breast cancers with bone metastases. We started about five years ago. This was the first clinical step with calcium orotate to try to recalcify these metastases. We found that calcium orotate has no side effects at all. It is more successful than sodium fluoride in the calcification of bone metastases and we had excellent and reliable success in about 40% of all metastatic disease in the bone system. One patient had very severe lesions in the left hip. After treatment with calcium orotate for about eight weeks this patient was free from any complaints, the lesions were mostly recalcified. This patient, too, went around in a Fiat sports car without having any complaints.

Another patient came with 200 parts per million of serum calcium pretreatment with important doses of conventional calcium which resulted in hypercalcemia, a dangerous situation concerning the heart rate and heart metabolism, with thousands of metastases and practically in a terminal situation. After about four months of treatment with calcium orotate there was almost entire recalcification. The results speak for themselves: no more complaints.

This is calcium orotate, it's effect on recalcification of bone metastases, on cartilage tissue and also on osteoporosis. Without any doubt, clinically, it is obvious that there is no calcium compound known which affects cartilage tissue and which prevents damage on pentose pathway tissue such as cartilage. I feel this is quite a bit of progress in

preserving our health and especially in preventing aging of tissue.

Another mineral transporter is the zinc aspartate which is officially on the market in Germany and offered as a medicament for the improvement in diabetes and of immune defense. It seems that the production of insulin is enhanced by actively transported zinc. Heinitz made quite an extensive report on this. In his study, diabetics received 40 units of insulin alone and in combination with zinc aspartate. The sugar tolerance becomes much better in the combination of 40 units of insulin and zinc aspartate than without the zinc aspartate. In the problem of diabetes, this is an important observation.

In a study out of our hospital, there are borderline diabetics, mostly early detected. They are treated exclusively with zinc orotate, no insulin. I feel that in the management of diabetes, a basic treatment with an actively transported zinc preparation, such as zinc orotate, should be a must because it takes off the peaks of the ups and downs in the control of the diabetes. We have zinc orotate officially on the market in Germany as a substance which helps to overcome immune fatigue in cancer patients because zinc orotate activates the thymus gland and the formation of T informed lymphocytes. Zinc plays the role of a spark plug in cell bound desaminases which are actually the tool of the T lymphocyte to fight cancer cells. Therefore, we test all cancer patients for zinc levels. All cancer patients get actively transported zinc to protect the immune system from fatigue.

Now, again, let us come to another field, to cardiology. As I have pointed out, potassium-magnesium-aspartate, in many countries, with the exception of the United States, plays a very important role in the management of metabolic heart disease. Here is an outlook on the mortality from heart infarct or coronary disease at different times. We now have in Germany about 105,000 people who die each year from heart attack, much increased since the late 1950s (7,000 deaths per year). This was from a study by Bansi in Hamburg, Germany. However, it was found that the arteriosclerotic lesions stayed static, so obviously there is no important or no essential interrelationship between arteriosclerotic behavior of the vessel and death rate from cardiac infarct and cardiac necrosis.

We had a very interesting cardiological congress in Baden-Baden, Germany, last year, with participants including Laboris of Paris, France, and Baroldi of Milan, Italy, and from Houston, and Erhardt from Stockholm, who pointed out that the coronary thrombus develops only after the cardiac necrosis and not before in practically all cases. One came

to the conclusion that occlusion in coronary vessels accounts for, at the most, 20% of the different factors which cause myocardial necrosis, and that they are mostly metabolic factors which lead to heart attack and cardiac necrosis. Baroldi, the former pathologist who worked with Dr. Denton Cooley in Houston, pointed out that despite occlusion of the coronary system there is sufficient collateral supply of all cardiac tissue so that there is no major reason to expect a necrosis to develop from insufficient blood supply.

We feel that there are other factors than arteriosclerosis and occlusion which account for the high incidence of cardiac infarcts. We know by now that potassium magnesium aspartate decreases very much the death rate from cardiac infarct. Our own study, taken over seven years' time, shows a decrease of about 84%. This seems to be in line with an Australian study. In other words, under constant treatment with potassium magnesium aspartate we come back to the death rate from cardiac infarct that we had 20 years ago in Germany. Also, magnesium orotate prevents cardiac necrosis and so does potassium orotate, as Bujust pointed out. However, potassium orotate is not available on the market, for reasons of stability.

In a study of magnesium orotate, it was seen that magnesium goes into vessel walls, as I pointed out, with the help of the orotic molecule. We just recently completed a study which shows that increasing of vessel elasticity is best after treatment with magnesium orotate after one year or 1½ years treatment. This substance is followed by the so-called EPL which means "Essential Phospholipid Substances," which are on the market in Germany. In arteriosclerosis we found a 94% success rate with magnesium orotate, about 60% success rate with EPL substances and almost no improving effect of clofibrate on vessel elasticity!

I conclude that just a laboratory cosmetic effect in decreasing cholesterol has nothing to do with the improvement of vessel elasticity. On the other hand, magnesium orotate activates cholesterol esterases and mobilizes cholesterol. We observe quite often that in the beginning the cholesterol levels increase as the vessels are cleaned more and more, and only after 1½ years do they go down to normal. In a study done in Munich, Germany, with magnesium orotate, there was an improvement in cholesterol lipids levels. Also, iron orotate is sold on the market in Germany now, it is a cell going ion transporter, and by the way it is manufactured by an American firm in Germany.

One of the most important factors in overcoming muscular fatigue and potential risk of muscular necrosis in the myocardium and to overcome an overspill of the lactate pool is to increase the formation of ATP. In a

Japanese study it was shown that potassium magnesium aspartate enhances ATPases before and after potassium aspartate. In the gastrocnemic muscle, the formation of ATP is very much enhanced upon the application of potassium magnesium aspartate. For the same reason, potassium magnesium aspartate today plays an important role in the enhancement of the host defense in the cancer patient: more formation of ATP. The Japanese thought of a decrease in the use of ATP but we found recently that we have to deal with more formation of ATP. This is very important, it is a key phenomenon in the understanding of the effect of potassium magnesium aspartate. The ions potassium and magnesium transported to the inner layer of the outer cell membrane activate the respective enzymes, which then result in the formation of more ATP.

Potassium magnesium aspartate was given to improve abnormal levels of alpha-keto-glutaric acid and lactic acid which develop upon the application of glycosides such as ouabain and Digoxin. This was one of our first studies and is now 14 years old. This study resulted in the fact that today many big firms in Germany, including Bayer, offer digitalis in combination with potassium magnesium aspartate in order to improve the tolerance of digitalis. This has been a very important observation. In several patients with a history of cardiac necrosis and respective complaints the lactate level is mostly improved by the application of potassium magnesium aspartate.

Now we come to a very important observation. A few years ago it was reported in Germany that the oral intake of ouabain resulted in a decrease in angina and, obviously, an important decrease in the death rate from heart attack. This observation was very controversial. This again resulted in very extensive studies which are mostly carried out in Dresden by the cooperative of Manfred von Ardenne. It came out of these studies that the decrease of the pH in the myocardium as a result of metabolic deficiencies and of metabolic damage and increase of lactate due to a decrease of blood supply and many other different factors, that this decrease of the pH results sooner or later in the labilization of lysosomes. As a matter of fact, the big myocardial necrosis develops only upon the release of lysozymes in the form of a chain reaction, in which lysosome enzymes again labilize other lysosomes so that an important release of the lysosomal enzymes results in a big necrosis. The Ardenne people were able to really point out that this mechanism has a very high likelihood. Or, on the other hand, that the increasing of the pH and the decreasing of the acidity, by decreasing lactate, for instance, results in a potential protection of lysosomes and therefore results in protection from cardiac necrosis. As a matter of fact

these chain reactions, which develop by the lysosomal enzyme mediated labilization of other lysosomes, manifolds the lysosomal activity, and this has been shown experimentally. I refer you to the original papers which came out, especially in Germany, in *Acta Cardiologica*.

A very interesting experiment has been widely reported. The Ardenne people have special electrodes to measure in vivo the pH levels in myocardial tissue in the rat. Upon a ligation of a coronary artery, there is a decrease of the pH, which, as I said previously, may result in lysozymal activity. And upon the application of oral ouabain, there is again an increase of the pH, which may result in better protection. This is an experiment which may explain the observation that oral ouabain as well as potassium magnesium aspartate as well as magnesium aspartate protect one from potential cardiac necrosis.

Minerals, electrolytes and electrolyte transport play a role in sustaining the normal function of the myocardium. In contrast to skeletal muscle, the cardiac muscle gets about 48% of its energy from fat. That's why it survives in famine and hunger. The mobilization of energy from fat is performed by enzymes which are mostly controlled by calcium. Therefore, an active transport of calcium is very important to the myocardial muscle. We know by now that in the aging muscle there is a deficiency in transit of calcium. This has been shown by Fleckenstein and by Kaufmann. We know that calcium orotate in the aging heart muscle very importantly activates the release of energy from fat and from triglycerides. Therefore, it decreases triglycerides, converts them into energy. Most importantly, since there is no release of calcium ions from calcium orotate in the cell membrane, there is no electric disturbance on the myocardium upon the application of calcium orotate. This is a very important observation. There is not even a complication from toxic side effects when digitalis is given at the same time. However, in Switzerland, studies on 14-year-old dogs were done on a 14% slope. These dogs had on the average about 14 meters of walking way, then they had to arrest. Upon treatment with digitalis, these 14 meters increased to 15 or 16 meters. A combination of digitalis and potassium magnesium aspartate resulted in about 40 meters of running. And the combination of digitalis and potassium magnesium aspartate plus calcium orotate resulted in no arrest after more than 500 meters. This was a very important observation which has to do with the improvement of defective calcium transit into aging myocardium or into hypertrophic myocardium. This may give you a certain idea of how ions which work a spark plug in an automobile engine play a role in sustaining normal function of myocardium metabolism.

Potassium magnesium aspartate has an effect on supraventricular extrasystoles. This therapy very often results in an improvement of the clinical finding.

The ductile system of the myocardium is not a nerve system but rather a transformed muscle, cardiac muscle system, which is mainly based on pentose pathway or direct oxydation metabolism. This is exactly the tissue where the orotates go. I have the feeling that the prevention of potential danger to the ductile system of the myocardium will be one of the major indications of the orotate therapy. A patient had tachyarrhythmia, more than 1,000 mg% of triglycerides. Upon treatment of 4 gm of calcium orotate together with digitalis, there was a striking improvement. First, no complication of the combination of digitalis and calcium carrier because there is no membrane calcium deliberated. Second, the decrease of the triglycerides down to 400 because the conversion of the triglycerides to energy was very much improved. I think that this is a very modern aspect of protective myocardiology, very new and very recent. I have not read of this elsewhere so far.

In another study from a hospital in Mannheim, Germany, a patient with posterior wall infarct received potassium magnesium aspartate. A few days later they ran out of their magnesium potassium aspartate supply. The infarct pattern reappeared. And then they got a new supply into the hospital. And, again there was improvement.

You can substitute minerals and ions to either become active factors in enzyme metabolism or to become a component of structure, cell membrane, or bone. We can also think of using the release of ions in order to protect membranes and surfaces from immune aggression. This is a very old theory. Injection of calcium for the treatment of allergies. This mechanism of course can be manifolded by the application of an active transport principle. The Büchi cell membrane model shows two different pores. One is the active transport pore which accounts for the active transmembranal transport of nutritive substances like amino acids, sugars, hormones, etc. The other one is the free lipid pore which may allow the entry of unwanted material like infective agents, antibodies, toxins, especially when insufficient electrostatic compression of the cell membrane keeps these pores open. The 2-amino-ethylphosphate complex salts react with the membrane at the entrance of the free lipid pores and there release their ion, eg, calcium. We feel that this is an imaginable mechanism which explains the powerful shielding effect of calcium AEP of membranes against immune aggression. This is so in gastritis, multiple sclerosis, nephritis, blood-brain barrier encephalitis disseminata and in pancreatitis.

An electron microscopy study performed in Muenster, Germany, by Moeminghoff, works with peroxidase injected into capillaries.

Granules, oxidase granules, are released into the micro villi. They penetrate the capillary membrane and penetrate into the micro villi. This shows that there is no sufficient shielding of the membrane to prevent the transit of peroxidase granules of active peroxidase.

For the test the system has been pretreated with calcium AEP. Thereafter there is no more transit of peroxidase into the micro villi. However, the exchange of nutritive substances is unchanged. Therefore, only the unwanted transit of unwanted substances will be blocked, but nutritive substances will not be kept out. This has to do with the phenomenon that the cell membranes have two different pores, one active transport pore, which accounts for the active transport and which is not affected by the release of calcium ion and of AEP, and then an uncontrolled exhaust, which can be controlled by calcium AEP in order to prevent the transit of unwanted material – viruses, antibodies, or, as in this particular case, peroxidase.

The same thing can be achieved, by the way, with the aspartates. It is lesser, but it is also effective for shielding of the capillary membrane against transit of unwanted materials.

Today the application of active calcium carriers is playing an increasing role in the treatment and management of immune disease. There was a three-year study of the effect of calcium orotate on chronic aggressive hepatitis. Some of these people were terminal cases. Included also are 12 cases of cirrhosis of the liver with ascites. The result is that after a treatment of about six weeks or up to 1½ years, all aggressive hepatitis and all liver cirrhosis showed normal function and had no more sign of effective aggression. You are the first to learn about this because this is the first time that I have released this information to the public. We have at this moment a Volkswagen Grant to look into this problem further. The mechanism seems to be the following: According to the research done especially by Deborah Doniach, the mechanism of chronic aggressive hepatitis and practically all forms of liver cirrhosis is based upon the aggression by antimitochondrial antibodies, not on cell antimembrane antibodies. The calcium ion out of calcium orotate is released on the membrane of the mitochondria; at least this seems likely. The constant release of calcium ions at this specific site in the cells, and especially of the liver mesenchyma, results in an inhibition which slowly turns down the vicious circle of immune aggression and antigen release. After a certain time there is no more effective humoral aggression against the liver. This

seems to be very effective and in addition to this since calcium orotate prevents side effects from cortisone, the combination of cortisone and calcium orotate gives an even better aspect.

Now, a few months ago, we started research work using lithium orotate. Lithium orotate, also of course, goes in the blood-brain barrier and into pentose pathway tissue, especially into the glia, but also into the membranes of mitochondria and especially of lysosomes. What we have observed is the following: the release of the lithium in the membranes of lysosomes results in a depletion of sodium and the dehydration of lysosomal membranes. This means stabilization of lysosomal membranes so that there is no more release of aggressive enzymes. With the help of the combination of calcium orotate and lithium orotate, we are able to perform, within about four days, what we formerly were able to see in about one year using calcium orotate alone. Obviously, the treatment with lithium orotate results in an entire stop of the release of aggressive enzymes in chronic hepatitis. And after about four days or one week, or two weeks, the patients report healthy behavior and healthy feeling and there is no more sign of hepatitis. This problem is now being further studied in various hospitals and clinics in Germany. My feeling is that the continuous aggression of antimitochondrial antibodies may result in the labilization of these membranes. And once the labilization has developed, another principle becomes active: the release of aggressive enzymes. Chronic hepatitis is a two-step phenomenon. With the help of calcium orotate, in addition to lithium orotate, we probably will be able to control both situations and both conditions. I feel that we have made quite a step forward in the control of this disease, which, in Germany, plays a very important role.

I would like to make it perfectly clear how the mineral transport substances work. They release an ion at a site where we want it to be released. Hans Selye said once ten years ago in Hannover, Germany: We are able to write an address on the mineral, on the potential ion, and have it go where we want it to go so that it can exert its function. Either by activation of enzymes or by restoring structure or by sealing against potential aggression. It is a very simple, extremely harmless, but yet active principle.

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The anti-inflammatory and immune-inhibiting Effects of Calcium Orotate on bradythrophic Tissues

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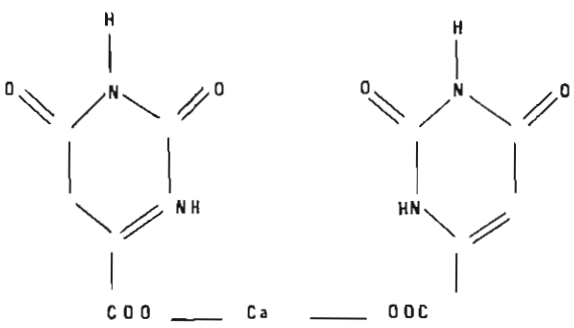
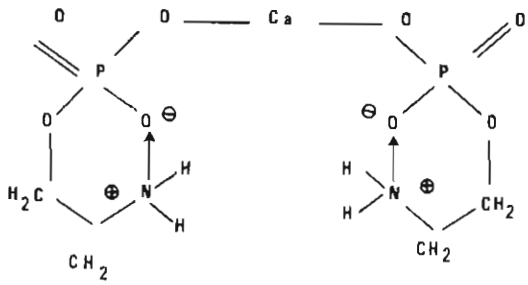
During preliminary work on electrolyte carriers, based on aspartic acid (NIEPER and BLUMBERGER, 1966) nicotinyl-aspartic acid, serine and 2-aminoethanol phosphoric acid (NIEPER, 1967), KÖHLER and NIEPER had considered the possibility that orotic acid could also be an appropriate electrolyte carrier molecule. This the more so since orotic acid penetrates very easily into the cell and in addition it is an aromatic substance with salts that possess high complexing power.

However, further studies on orotic acid as electrolyte carriers were abandoned at that time since according to some 600 outstanding articles in the literature, orotic acid should be considered as a nucleic acid precursor and such a carrier molecule could not offer sound clinical application as an electrolyte carrier.

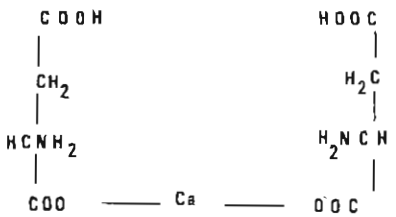
But later on it was proven that this first opinion was erroneous. In one instance, BAJUSZ (1967) had been able to demonstrate that potassium orotate was just as suitable to prevent idiopathic myocardial necrosis in certain hamster breeds as potassium aspartate, while KCl does not produce the same effect. This observation appeared to indicate that orotic acid could be a useful electrolyte carrier. Following this, a few single observations seemed even to indicate that the hypothesis, according to which the action of orotic acid is based on its role as pyrimidine precursor and should therefore be considered as a nucleic acid percursor, may not be accurate (MATSUDAIRA, NAKAMURA and HISHIKAWA, 1968). A few clinical investigations in 1966 with an original new magnesium orotate (Hippocras, Kavaform) induced us ultimately to addopt a drastically new orientation in our concept of the action of orotic acid and orotates. It was demonstrated that in the mobilization of cholesterol esters and in the activation of cholesterol turnover, Mg-orotate is basically more efficient in mobilizing cholesterol esters than any other activator of cholesterol metabolism that we had used so far, such as sitisterole, EPL substances, nicotinic acid, Mg-nicotinate, K-Mg nicotinyl aspartate, Mg-oleate, heparinoid, K-Mg-aspartate and Mg-2-aminoethanol phosphate. [Exception : Regelan (ethyl-alpha-p-chlorophenoxyisobutyrate) decreases more markedly serum cholesterol level. However, the clinical effect of Regelan appears to be limited]. This even more so since Mg-orotate reaches its full activity even when administered in such relatively small doses as 200 to 600 mg daily. This is a much smaller dose than that with which H. VON EULER and WINDMÜLLER (1967) were able to produce fatty livers in the rat (with free orotic acid). In addition, in the course of one year of clinical experimentation with Hippokras at a dose of 1-2 tablets daily in three patients whose livers were punctured, no development of fatty liver was observed.



Calcium orotate



Calcium EAP (Ca-2-amino-éthylphosphate)



Calcium aspartate.

Quite frequently patients with angina pectoris requested spontaneously additional Mg-orotate (Hippokras) treatment since its action on angina pectoris conditions is unusually good. It is most probable that this action is connected with the protective effect on cardiac metabolism, particularly in the light of the above mentioned work of BAJUSZ and the numerous publications on the mechanism of action of K,Mg-aspartate.

This remarkable effect, particularly on cholesterol metabolism is in contradiction with the concept that orotic acid be only a nucleic acid precursor. Thus the only acceptable interpretation would be that Mg-orotate acts through some metabolic mechanism in which orotic acid plays an important part. This seems to point on the pentose pathway since orotic acid plays there an essential role by activating riboses (ARVIDSON, 1949).

The pentose pathway is a very old phylogenetic form of metabolism with direct oxidation. Appreciation should be awarded to Dr. LABORIT and his collaborators for their untiring and revolutionary work (1962-1968) on the fundamental functional principles of cellular metabolism which has permitted to clarify progressively the importance of the pentose pathway. Actually, not enough attention is paid to the therapeutic promises that its activity conceals, particularly since the pentose pathway — a more fundamental and phylogenetically older element of cellular metabolism than the Krebs cycle — offers new possibilities for the solution of some geriatric problems.

The following tissues: glia, myeline sheath, cartilage, vessel walls (media?). both arterial and venous, and including the blood-bran barrier (BBB) are for their existence, assimilation and functioning mainly depended on the pentose pathway and are therefore particularly resistant to any lack of actively transported erythrocyte oxygen. BROMAN has mentioned the particular resistance of the blood-brain barrier to hypoxia. In addition, some essential skin mechanisms are based on the pentose pathway, including those that produce horn formation. That is why hair and finger nails continue to grow after clinical death, and in the same manner skin can develop in a nutritive culture medium. Finally, the shunt between fat metabolism and carbohydrate metabolism and vice versa, through which undesired fatty depots have to proceed for their consumption, belongs evidently to the pentose pathway system. It is quite possible that an overdose of orotic acid would lead to a shift-back self-inhibition of this mechanism which could then explain the formation of the already mentioned fatty liver.

The unusual effect of Mg-orotate on arteriosclerosis and on cholesterol metabolism can only be explained by the hypothesis that orotic acid is metabolised in the pentose pathway of vessel walls (ribose coupling) (ARDVISON, 1949) and that the thereby locally liberated magnesium activates cholesterol esterases. Comparative tests with other salts of orotic acid, for instance, Ca-orotate, seem to confirm this since, in general, orotic acid salts fill the usual requirements for an electrolyte carrier system that we have developed and described.

Since we have now been conducting for several years with success tests on calcium carriers as a protective measure for numerous tissues against auto-aggression and foreign aggressions (NIEPER 1966,1968) among which calcium-l, dl-aspatate and calcium -2-aminoethanol phosphate have played a particular role, we have now tried to define the

clinical action of calcium orotate. This salt - as all other electrolytic carriers that we have used so far with the exception of Mg-orotate - was synthetized by KÖHLER.

Ca-orotate was used in tablets containing 300 mg. Suppositories have been used only lately. Ambulatory and clinical testing was started in October 1967. In view of the observations made after the use of about 55,000 daily doses of Ca-orotate, results appear to be so remarkable that they warrant the writing up of a preliminary report.

(1) Effect on healthy subjects: No subjective or objective effects were observed, nor any side-effects except à slight loss of appetite. Contrary to what is observed with calcium-2-aminoethanol phosphate and calcium-1, dl-aspartate, no gall bladder dyskinesia or stenocardia sensations are noted, even with such high daily doses as 660 mg. This may indicate that the action of Ca-orotate, contrary to that of the above Ca-carriers, is not to be situated on the cell membrane, and that Ca-orotate does note induce any Mg exchange. Transaminases and phosphatases (5/5) remain unchanged, and total serum cholesterol is not significantly decreased, in contradiction to Mg orotate.

(2) The initial effect of Ca-orotate treatment is that about half the patients show spontaneously less appetite. About 1/3rd of the subjects lose 50-70 % of their overweight. But these are principally patients who are used to eat too much, especially carbohydrates.

Overweight based on endocrine disturbances seem to be less influenced by Ca-orotate, but even so, some loss of weight has been observed in these cases too. Mg-orotate does not have this effect. No answer can yet be given to the question as to whether the consumption of the fatty depot caused by Ca-orotate is related to the Ca^{++} activation of lipases in the pentose pathway, which was discovered by C.E. ELVEHJEM and his group. However, this hypothesis is the most likely, and it may be important for the treatment of arteriosclerosis.

(3) *Psoriasis :* Patients who had been given Mg-orotate treatment for arteriosclerosis, reported simultaneous improvement of their psoriasis. Thereafter three patients suffering from psoriasis were treated with Ca-orotate. All three had extremely severe forms of the disease covering completely body and limbs. In all cases the disease was over 10 years old; results previously obtained with vitamin F, Chrysarubin, and other drugs had been unsatisfactory, and above all, this type of therapy cannot be continued over long periods of time. Ca-EAP had a positive effect only when applied intravenously.

The daily intake of 300-500 mg of Ca-orotate in capsules during meals produced stable improvement of psoriasis, a result never obtained with any of the drugs previously applied. The patients were able to remuse fully all their social activities. Observation time : 12, 13 and 14 months. Recently, MALINA and BIELICKY (1968) pointed out that the pentose cycle of carbohydrate metabolism is stimulated by chloroquine and that this mechanism explains the detrimental effect of chloroquine on psoriatic skin lesions.

(4) *Arteritis and Arteriosclerosis :* A building promotor, aged 65, presented circulation defects in both legs, with dry and damp necroses of the toes of both feet. No diagnosed diabetes, smoker. Previously he had received very expensive treatment in several hospitals and university clinics comprising the most effective hemoregulating medication including oxygen insufflation. In addition, treatment with Decortilen. A slight primary chronic articulation rheumatism developed also with coxarthrosis. The patient could not walk and he complained of cerebral blackout episodes. Arterial pressure 185/125.

A single tablet of 330 mg of Ca-orotate caused a strong heat reaction in tighs, legs and feet lasting for 4 hours. This very intensive reaction was probably not due to any improvement in circulation or to an increase in tissue temperature, but rather to a direct reaction in vessel walls which would seem to be related to local liberation of Ca^{++}. Mg-orotate does not produce this reaction, neither does Ca-EAP or Ca-aspartate which have proven to be very effective as calcium carriers in other indications (NIEPER 1968). No such heat reaction is observed either in patients with healthy vessel system, even when Ca-orotate is applied in very high doses. After two months of treatment with 1 tablet of 330 mg daily of Ca-orotate, the patient was able to run; necroses had disappeared but for a single spot, skin temperature on the back of the foot had risen by 2°, cerebral symptoms had disappeared and arterial pressure had dropped to about 155/8-. No simultaneous therapy with other drugs had been prescribed. The patient was able to resume full-time work, and hospitalisation was no longer required.

After this observation, we applied Ca-orotate orally or by the rectal route to another 24 patients. The following orientation was then discovered :

(a) The best reaction develops only when the disease of the vessel walls is due to an inflam-

matory process (toxic, rheumatic, autoimmune). This is particularly so in the case of smokers and diabetics.

(b) The intensivity and duration of the heat reaction depend on the seriousness of the inflammatory vessel disease and on the positive reaction obtained in the three clinical immunity tests described earlier (NIEPER, 1966).

(c) In the case of arteriosclerotic circulation disturbances without any evident inflammatory components, a heat reaction does not develop, but if treatment is prolonged, circulation disturbances are nevertheless greatly improved.

(d) The decrease in brachial blood pressure and above all, the relative and absolute increase in amplitude are quite the peripheral circulation for a decrease in the peripheral circulation resistance and for an increase in vessel elasticity. These assumptions were confirmed by an extensive control of the peripheral blood flow by an electronic capillarographic monitor.

Among this group, the observations made on two patients are particularly interesting: A 14 year old girl was suffering of hypertension with 210/135 mm Hg, peripheral pallidness, but according to the ophthalmologist, the fundus revealed a vessel picture of arterial hypotonia in spite of the high brachial pressure. The paternal lineage of the patient is burdened with nephrosclerotic diseases and the maternal, with essential hypertonia and secondary renal involvement.

Ca-orotate treatment with 330 mg per os 4 times a week produced a drop in blood pressure to 135/70, the ophtalmologist discovered normalisation of vessel tone in the fundus and also "gestose-type" vessel modifications. Six months later, no change had been noted in the improvement of the patient.

A 37 year old man had been suffering for the past three years from most severe attacks of angina pectoris, with prolonged pain and "destructive pain", projecting to the left shoulder muscles with muscle induration. He had been treated in Germany and in the British Commonwealth in several hospitals for various infarct-like conditions. In earlier clinical treatment, certain fast resorbable nitro preparations, Norflex, Ca-EAP iv, Ozone iv and Mercumar had shown some activity against the pain. This was a case of highly immune-positive coronaritis. Incidentally, the condition of this patient brought very severe criticism against the theory concerning the action of cumarin (Mercumar), for in this case, Mercumar produced certainly a direct effect on vessels. The intake of two tablets daily of Ca-orotate containing 330 mg each, led progressively to almost complete disappearance of the condition with no pain during the intervals, and the angina pectoris attacks became weaker and the intervals between them grew longer. Simultaneous treatment with K, Mg-aspartate for 10 months brought about a progressive decrease in complaints.

Another man aged 63, suffering for several years of severe angina pectoris and cardiac insufficiency with evident coronary sclerosis, saw his condition improved after a treatment lasting for several months with Mg-orotate (Hippokras), but subsequently Ca-orotate was applied and decisive improvement was then obtained.

Our past work, our findings and observations indicate that Mg-orotate and Ca-orotate possess a strong action on vessel walls which is definitely much stronger than that of Mg- and Ca-aspartate or Mg- and Ca-EAP. It is clear that Mg-orotate activates cholesterol esterases which, in view of their function, depend on Mg^{++}. Ca-orotate activates probably lipases which depend on Ca^{++}, but in particular, it liberates specifically in the vessel walls Ca^{++} as the anti-inflammatory principle.

We do not know of any other drug whose action on vessels could be compared with that of Ca-orotate as far as effectiveness and prolonged tolerance are concerned and which, in addition, would not rise any clinical or financial problems. But only the future will be able to tell whether this is also the case in the treatment of nephrosclerosis where Ca-EAP has shown such very good results. So far, our observations seem to confirm such a hypothesis.

The results which we came about by the clinical assay of calcium orotate and by the application of a capillarographic monitor parallel entirely the findings and statements of MAC MAHON. There MAC MAHON differenciates a primary (immune) arteriolitis with successive involvement of the kidneys from a primary nephro-sclerosis followed by a participation of the general arteriolic system. According to our observations the primary arteriolitis is more frequent, develops in younger people and shows strong relations to inherit conditions.

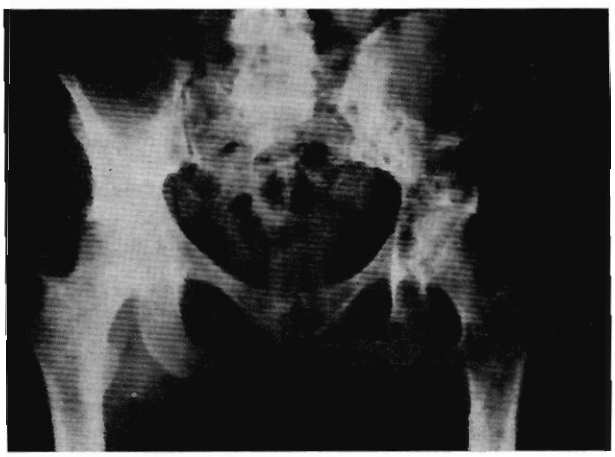
(5) The inflammatory reaction of veins respond also remarkably well to Ca-orotate ointment (for instance, a 2 % Ca-orotate ointment).

We had already mentioned in earlier publications (NIEPER, 1967) that Ca-l, dl-aspartate and especially Ca-EAP have a very favorable effect

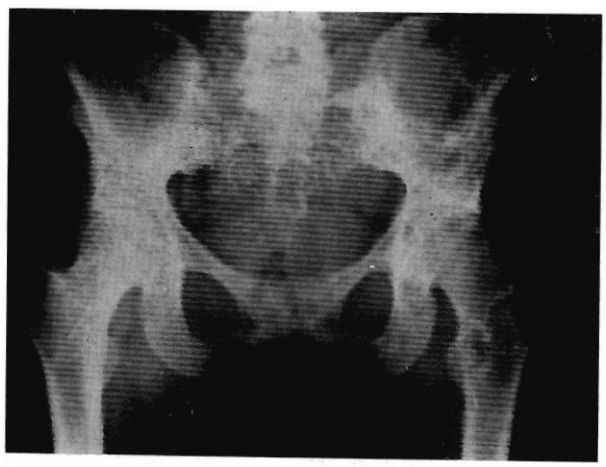
ment of senile osteoporosis. In any event, the effect of Ca-orotate on the pain of the spine is as good as that of Ca-aspartate and Ca-2-amino-ethanol phosphate. But since the problem of senile osteoporosis has been solved satisfactorily with the administration of Ca-1-dl-aspartate and Ca-EAP, we did not pay any further attention to this indication.

But the case is quite different in the treatment of decalcifications of the osseous system originating quite frequently from inflammatory or immunological processes that are often seen in young people. Whenever the decalcification originates from an autoimmune reaction against the osseous matrice, the action of Ca-EAP is encouraging, as described earlier. There are, however, decalcification processes which, according to the most important up-to-date diagnostic criteria, are caused by arteriitis (increased peripheric resistance, angiospasma or hypotonia of the ocular fundus in the presence of brachial hypertonia, peripheral pallor, positive immune reactions and nephropathy) which results eventually in very severe decalcifications of the spine, or in a greatly delayed healing of bone injury after accidents. In such patients the action of Ca-1-dl-aspartate is only very slight, and an infusion of Ca-EAP does not yield any satisfactory results. But the oral administration of Ca-orotate leads to marked improvement of such decalcifications. A patient who for the past three years had been treated in several hospitals for arteriitic decalcification, stated that the effect of Ca-orotate was "definite and dramatic". This patient was also controlled by the electronic capillarographic monitor.

Very severe metabolic decalcification of the skeletal system is often observed in cancer diseases. The case of a 49 year old patient with abdominal metastatic thyroid gland carcinoma is worth mentioning. An extremely painful metabolic but not metastatic decalcification, ressembling the SCHLATTER disease, developed in the cap of the frontal tibia. Various calcium preparations and anti-rheumatic drugs did not produce any effect, but Ca-orotate removed the very strong pain completely within two days.



a) before Ca-orotate



b) after Ca-orotate treatment 660 mgs/day, 10 weeks.

Radiography of a woman (34). Three years after mastectomy-X-ray and ^{60}Co - treatment of chest, left pelvis, and dorsal spine had already been exhausted. Roentgen castration 2 years before. Improvement of metastatic pain and general condition after treatment with 300 mg Chloroquine-diphosphate and 150 mg Atabrine/day. K, Mg-Aspartate, Fe-Aspartate, substitution of chloride and phosphate. However, the metastatic destruction proceeded, and furthermore there was evidence of maybe non-metastatic decalcification at the sites of former radiation. Calcium gluconate, calcium-1, dl-aspartate (Calciretard), orally and by drip infusions, had no effect on the destructions. By early Feruary, 1969, patient was unable to walk, severe pain. Almost unable to sit. Admitted to our clinic for potential danger of spontaneous fracture of left femur neck. After 10 weeks of daily intake of 660 mgs of Ca-orotate together with cream or egg yolk the patient was free from major complaints, went off for holidays by car. Chloroquine-Atabrine therapy, however, had been continued. By mid-1969 condition is still continuously improving. As for the radiographs compare improved calcification of left pelvis, roof of joint, os publis and symphysis. « encaging » and recalcification of the destruction in left femur neck. Please consider unwanted inhomogeneity of exposure. 5/5 patients treated this way showed comparatively the same positive results.

FIGURE 1

on various forms of evolution of multiples sclerosis and disseminated encephalitis. This is particularly so during the early stages of the disease and also on cerebral and cerebellar symptoms. DURAK (1968) had also observed this effect during experimentation on a very large number of patients. Now, after 4 years of experimentation, it has become fairly clear that there is no other medication that can compare with these Ca carriers in *the prolonged treatment* of multiple sclerosis.

In addition to the specific effect of Ca-orotate as a Ca carrier, other aspects have also been observed in the treatment of multiple sclerosis and disseminated encephalitis which we believe are very promising. The papers presented by T. BROMAN and T. FOG at the International Symposium on Multiple Sclerosis held in Montana, in July 1968, have largely contributed to the understanding of these new possibilities in the treatment of multiple sclerosis.

According to the studies carried by BROMAN and STEINWALL (1967), it appears to be fairly clear now that the initial site of damage in disseminated encephalitis is the venola area of the blood brain barrier (BBB). Thus disseminated encephalitis would primarily not be a neurological disease but rather a circulatory disorder. In fact, some specific investigations in patients with disseminated encephalitis have revealed both ophtalmologically and immunologically, and also as far as blood circulation is concerned, that there is a probability of moderate aggression against the whole vessel system. For instance, it may be assumed that appropriate viruses produce specifically infectious damage in the filter system of the blood brain barrier, which then acts as a start-off mechanism for the autoimmunisation that follows, and which affects the structure of the blood brain barrier. Studies conducted by FOG have now revealed that the demyelinising process and the formation of glial scars in multiple sclerosis are secondary processes that follow quite different time constants to those of "encephalitic" inflammation in the blood brain barrier. Since specific antimyeline autoantibodies have often been observed in multiple sclerosis, demyelinisation can be regarded as a secondary autoimmune damage, the degree of activity of which differenciates also the symptoms of disseminated encephalitis from those of multiple sclerosis. It is however also possible that the damage caused to the blood brain barrier has a direct unfavorable effect on myeline metabolism and its structural turnover. The time constants discovered by FOG support also this assumption. Since the tissue of the blood brain barrier, as also the myeline and the glia, is based on the metabolic principle of the pentose pathway, orotic acid carriers may be able to interfere here directly. Ca-orotate could block immune reactions against the blood brain barrier, the myeline and the glia. Mg-orotate, however, could probably activate the synthetic metabolism of myeline.

The results obtarined so far in disseminated encephalitis and in multiple sclerosis with long-duration therapy lasting for one year are more favorable than those obtained with any other known substance; even better than with Ca-EAP. But of course, no definite judgment can be made before 2-3 years. The following observation, however, is of particular interest: the intake of 330 mg of Ca-orotate causes a rather intense reaction of pain and heat in the brain area or the site of the head which is known to have been specially damaged; this reaction decreases nevertheless within 2-5 days even if Ca-orotate treatment is not interrupted. And from then on, there is continuous improvement of pain and of symptoms. Occasionally MS-patients increased on their own the daily intake of Ca-orotate to some 800 mg since they felt a striking improvement of the symptoms by increasing the daily doses.

As in the case of the heat reaction caused by Ca-orotate in arteritic circulation disturbances, Mg-orotate, Ca-EAP and Ca-aspartate do not have such an effect and, moreover, Ca-orotate does not cause any type of cephalalgia in healthy subjects.

(6) *Retinitis :* We have already mentioned the improvement obtained with Ca-orotate in arteritic, spastic, "gestotic" and sclerotic changes of the ocular fundus. These observations are that much clearer as to date no medication has even been able to produce such an effect.

The history of two other patients (aged 46 and 42) is quite remarkable. They had been diagnosed as having a retinitis of rheumatic origin. But Prednison treatment did not produce any obective improvement of the symptoms which had been discovered by the ophtalmologist, or of the subjective disorders, and any improvement noted was so slow that even from the point of view of length of treatment the effect of Prednison remained doubtful. Then the patients received 330 mg of Co-orotate daily in capsules and the retinitis disappeared completely within two weeks but for some slight residual damage.

(7) *Inflammatory and osteoporotic decalcifications:* It would appear that Ca-orotate is as effective as Ca-EAP and Ca-aspartate in the treat-

The observation that out of all calcium transport substances tested only Ca-orotate proved to be able to improve the very painful « SCHLATTER-LIKE " decalcification of the tibial head in patients suffering from metastazising thyroid carcinoma encouraged us to try calcium orotate in patients suffering from bone metastases of breast cancer.

(8) *Chronic Hepatitis* : Four patients who had received Ca-orotate treatment for another disease, suffered independently from chronic hepatitis with sporadic cholangic pain and an increase in SGOT values to 50-85 WE. Marked improvement was obtained in all patients; in three of them, several controls revealed a significant decrease in SGOT values; this however was not observed in the 4th patient. This observation is important since such results had never been obtained with other Ca carriers. On the contrary, they had even produced an increase in cholestatic disturbances since these were not compensated by an adequate amount of K and Mg carriers. We are, therefore, almost convinced that the essential impact area of Ca-orotate - in opposition to that of Ca-1-aspartate and Ca-EAP - is *not* located on the outer cell membrane.

(9) In the case of *Colitis Mucosa,* the intravenous injection of Ca-EAP is the choice treatment; even suitable cortisones do not produce the same resuls, and above all, they cannot be applied for such long periods of time. The oral application of Ca-EAP and of Ca-1-dl-aspartate has only very little effect on colitis. On the contrary, the oral administration of 330-990 mg of Ca-orotate daily has a very positive effect after a latent period of about 15 days (12 patients, from 5 to 12 months of follow-up). Contrary to Ca-EAP, Ca-orotate has a relatively poor, but also interesting, effect on gastritis. Moreover, when Ca-orotate is administered in the form of an open powder, it is less effective than when capsuled substance is applied. In contrast to the effects observed with capsules, open powder does not cause the heat reaction in arteritis. Probably this is the result of inactivation in an acid medium by means of hydrolysis.

(10) We are not yet in a position to confirm that Ca-orotate has a protective action on cartilage, for instance, in arthritis and arthrosis. But since for the past 5 years, Ca-EAP has offered almost complete protection against any development of rheumatic joint deformation (NIEPER, 1968), we did not pay any further attention to this indication for Ca carrier substances.

(11) Patients who are treated with Ca-orotate present an exceptionnally good trophic of skin, hair and finger nails. This is especially so in the case of sebhorric disorders and skin inflammations.

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SUMMARY

THE ANTI-INFLAMMATORY AND IMMUNE-INHIBITING EFFECTS OF CALCIUM OROTATE ON BRADYTROPHIC TISSUES

H.A. NIEPER.

A clinical study has been made on the Ca carrier, Ca-orotate. Orotic acid behaves as an activator of direct oxidation (pentose pathway) through the coupling of ribose. This is the reason why Ca-orotate effects in particular, those tissues whose metabolism is based on the pentose pathway: glia, myeline, vessel walls, blood brain barrier, connective tissue, joints and also the skin- and horn-forming organs. The anti-inflammatory effect of Ca-orotate includes therefore arteriitis, allergic and inflammatory complicated arteriosclerosis with circulation disorders, nephropathies, retinitis, disseminated encephaliitis, coronariitis, arteriitic decalcification and phlebitis. In addition, the action of Ca-orotate is very effective against psoriasis. Its action against demyelinising diseases and against general aging is also discussed. The long-term clinical tolerance, and, in many respects, the clinical value of the calcium transporters is superior to both classical calcium substances and immune depressors acting on the lymphocytic system. In spite of a relatively limited effect at the beginning of therapy, the calcium transporters seem to slow down progressively the vicious circle: antibody aggression - liberation of antigen-boostering of a new antibodies, as observed in chronic autoimmune disease.

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RÉSUMÉ

EFFETS ANTIINFLAMMATOIRES ET INHIBITEURS D'IMMUNITÉ, SUR DES TISSUS HYPOTROPHIQUES, DE L'OROTATE DE CALCIUM

H.A. NIEPER.

Etude clinique d'un transporteur de calcium, l'orotate de calcium. L'acide orotique se comporte comme un activateur de l'oxydation directe (voie des pentoses) par l'activation de la formation de ribose. Ce qui expliquerait les effets prépondérants de l'orotate de calcium sur les tissus à voie des pentoses prédominante : glia, myeline, parois vasculaires, barrière hémoencéphalique, tissu conjonctif, articulations, mais aussi peau et phanères. L'effet anti-inflammatoire de l'orotate de calcium concerne les artérites, l'artériosclérose compliquée allergique et inflammatoire avec désordres circulatoires. En outre l'orotate de calcium agit très efficacement contre le psoriasis. Son activité contre les affections démyélinisantes et contre le vieillissement généralisé est aussi discutée. La tolérance clinique à long terme et, à de nombreux égards, la valeur clinique des transporteurs de calcium est supérieure à la fois aux sels de calcium habituels et aux dépresseurs immunitaires du système lymphocytaire. En dépit d'un effet relativement limité en début de traitement, les transporteurs de calcium rompent progressivement le cercle vicieux : agression par anticorps - libération d'antigènes créateurs de nouveaux anticorps, comme on l'observe dans les maladies auto-immunes.

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ZUSAMMENFASSUNG

ENTZÜNDUNGSHEMMENDER UND IMMUNHEMMENDER EFFEKT VON CALCIUM OROTAT AUF BRADYTROPHE GEWEBEE

H.A. NIEPER

Eine klinische Untersuchung wurde über den Calcium-Schlepper Ca-orotat durchgeführt. Orotsäure wirkt als Aktivator der direkten Oxydation (pentose pathway) durch Ribose - Koppelung. Dies ist der Grund warum Ca-orotat in besonderem auf solche Gewebe wirkt, deren Metabolismus auf dem pentose pathway beruht : Glia, Myelin, Gefässwände, Blut-Liquor-Schranke, Bindegewebe, Gelenkknorpel und Haut- und Horn-bildende Organe. Der anti-inflammatorische Effekt von Ca-orotat bezieht sich daher auf Arteriitis, allergisch und enzündlich komplizierte Arteriosklerose mit Durchblutungsstörungen, Nephropathie, Retinitis, Encephalitis disseminata, Coronariitis, arteriolitische Entkalkung der Wirbelsäule und Phlebitis. Ferner ist die Wirkung von Ca-orotat sehr stark gegen Psoriasis. Seine Wirkung gegen demyelinisierende Erkrankungen und gegen allgemeines Altern wird ebenfalls diskutiert. Die klinische Langzeitverträglichkeit, und in vieler Hinsicht der klinische Wert des Calcium Transporters ist ist sowobl klassischen Calcium Substanzen als auch Immundepressoren, die auf das lymphozytäre System wirken, überlegen. Trotz eines relativ begrenzten Effektes bei Beginn der Behandlung scheinen die Calcium Transporter progressiv den circulus vitiosus abzubremsen : Antikörper Agression — Freisetzung von Antigen — Boostern von neuen Antikörpern, wie es bei chronischen Autoimmunkrankheiten beobachtet wird. Calcium orotat ist ferner hochwirksam bei der Behandlung der Osteoporose, bei sonst therapieresistenten Entkalkungen nach Knochentrauma und Fraktur und im Gegensatz zu bisher untersuchten Calcium-Transport-Substanzen bei der provozierten Verkalkung maligner Knochendestruktionen, auch wenn aktive Metastasen in diesen vorliegen.

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RESUMEN

LOS EFECTOS ANTI-INFLAMATORIO Y DE INHIBICION INMUNOLOGICA DEL OROTATO DE CALCIO EN LOS TEJIDOS HIPOTROFICOS

H.A. NIEPER

Estudio clínico sobre un portador de calcio, el orotato de calcio. El ácido orótico se comporta como activador de la oxidación directa (vía de las pentosas) por activación de la formación de ribosa. Ello justificaría los efectos preponderantes del orotato de calcio sobre aquellos tejidos en los que predomina el metabolismo de vía de las pentosas : glia, mielina, paredes vasculares, barrera hemoencefálica, tejido conjuntivo, articulaciones, así como piel y faneras. El efecto anti-inflamatorio del orotato de calcio se ejerce pues sobre las arteritis, la arterioesclerosis complicada alérgica e inflamatoria, con trastornos circulatorios. Por otra parte el orotado de calcio actúa de modo muy eficaz contra la psoriasis. Su actividad contra las afecciones desmielinizantes y contra el envejecimiento generalizado es tambien discutida. La tolerancia clínica a largo plazo y el valor clínico que en muchos aspectos presentan los portadores de calcio son superiores a las sales de calcio habituales y a los inhibidores inmunitarios del sistema linfocitario. A pesar del efecto relativamente limitado que se logra al comienzo del tratamiento, los portadores de calcio van venciendo progresivamente el círculo vicioso : agresión por anticuerpos, liberación de antigenes creadores de nuevos anticuerpos, como suele observarse en las enfermedades autoinmunes.

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A clinical study of the calcium transport substances Ca 1-dl aspartate and Ca 2-aminoethanol phosphate as potent agents against autoimmunity and other anticytological aggressions.

2nd communication

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Since the publication of our first observations (NIEPER 1966) of clinical results with Calciretard* and Ca-EAP**, numerous additional observations have been made which have enabled to reach conclusions that will be described here. In many instances, however, these results can only serve as an orientation. The multiple activities of Calciretard and particularly of Ca-EAP that had not been disclosed in previous preliminary investigations will certainly require further numerous and detailed studies (fig. 1).

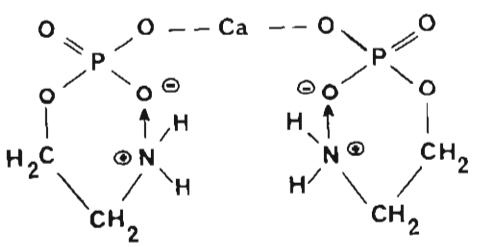
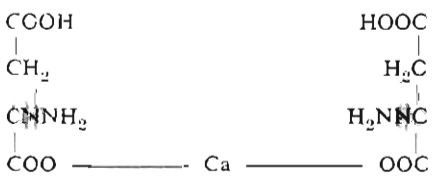


FIGURE 1.
Structural formula of Calcium-EAP (Ca-2-aminoethanol phosphate) and calcium aspartate.



The introduction of the principle of directed active transport (LABORIT 1958, NIEPER and BLUMBERGER 1962) in therapy based on inorganic agents covers progressively all branches of medicine and almost all diseases. SELYE's concept (1962), according to which the symptoms of a disease find their explanation and description in a small number of fundamental pathological disturbances of the cell, finds here its practical therapeutic correlation. If the explanation of a disease can be based on a few fundamental cell disturbances such as membrane permeability, thesaurosis, structural alterations, cancerization processes and disturbances of some important metabolic pathways, there should consequently exist agents, each of which could improve or cure a large number of diseases.

The properties of original Ca transport agents, synthetized after our discovery in the field of electrolyte carriers (NIEPER 1962, NIEPER and BLUMBERGER 1966), to decrease membrane permeability as does cortisone, for instance, and to transport calcium actively, would make them belong to this new group of substances. Since Ca-EAP and most calcium salts are not readily absorbable, the tablets have to be administered with a bile flow

(*) Calciretard : Ca 1-dl-aspartate.
(**) Ca-EAP : Ca 2-aminoethanol phosphate.

stimulating diet (bouillon with egg, cream, bread and butter), for if not, the treatment may fail. The absorption of small tablets appears to be somewhat better.

Animal experimentation with Ca-transporters, using the classical inflammation tests, produces only partial results which bear, however, no relation to their clinical activity. Ca-transporters have less effect on existing inflammatory reactions than when these reactions are only in their development stage.

BUCHI's study (BUCHI and PERLIA 1962) of the chemical and functional structure of cell membranes has yielded valuable information on the possible mechanism of action of Ca-EAP, in particular, from the view point of mechanism of action and extent of application.

According to these studies, 2-aminoethanol phosphoric acid (EAP) plays an important part in binding fatty acid chains to preceding and following peptide chains.

The specific incorporation of molecules of carrier compounds that have to transport actively inorganic electrolytes through the cell membrane depends on the peptic layer of the cell membrane (fig. 2).

If the calcium chelate of EAP is introduced into the blood stream, it produces probably a specific calcium hydrolysis of the lipid EAP peptide complex since EAP exists only at the intracellular level, and is directed from the blood stream toward the membrane and intracellular space, especially when inflammation has produced organ alterations (NIEPER 1966). This decreases water solubility and the permeability of the membrane to foreign substances such as toxins and antibodies. It is interesting to note that the mechanism of active transport through the cell membrane does not appear to be antagonized by Ca hydrolysis. This would correspond entirely to the function of the membrane model conceived by BUCHI, according to which the filtration through the cell wall of substances necessary for life is an active metabolic process that starts with the acceptance by the outer peptide layer. Indeed, even after 2 *years of daily* administration of high doses of Ca-EAP (300-500 mg) no disturbances or side-effects habe been observed, nor has the cell secretion ability been affected. In view of this, doubt arises as to the actual structure of the cell membrane in general, whether this is an economic and efficient structure, or whether its properties are rather those of a cheap, ready-made structure containing between the individual structural elements large empty holes that must be filled. If this is the case, the maintenance of the youth and good functioning of the cell, and

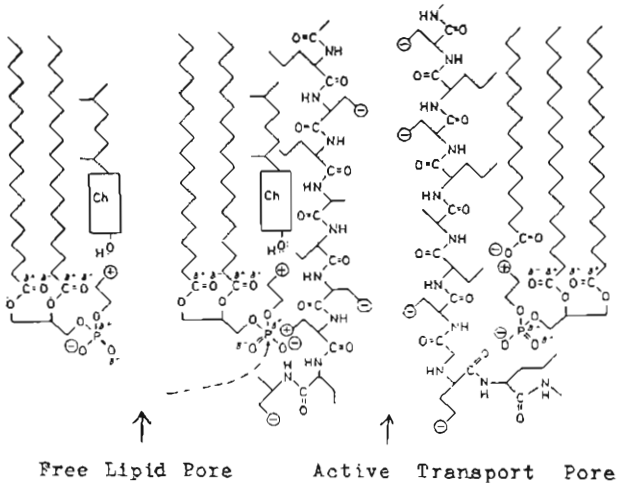


FIGURE 2.

Model of cell membrane : The pores (on the right), lined with a peptide, serve in part for the control and exchange of inorganic electrolytes, and in part for the absorption of nutritive substances such as fatty acids, amino-acids and carbohydrates, and also vitamins, hormones, steroids and in the cardiac muscle cell membrane, digitalis. According to BÜCHI and PERLIA, it is obvious that since the pores (on the left) are lipidic, they permit the agressive penetration into the cell of undesirable substances such as toxins, antibodies, possibly also infectious viral particles. EAP can exert its reaction only at the entrance of the free lipid pore, but not at the entrance of the peptide-lined transport pore. This may well be the reason why Ca-EAP protects the cell only against aggressive substances penetrating through the free lipid pore, but permits the penetration of nutritive substances. This hypothesis stipulates that the Ca-EAP administered must be immediately fixed at the entrance of the free lipid pore.

Indeed, the effect of Ca-EAP decreases progressively in the course of continuous treatment, but an interval of a few weeks permits to restore its previous effectiveness.

there by of the whole organism is a problem that must be considered most carefully. We have already discussed this hypothesis on the basis of WALFORD's experiments (1962)*.

In our earlier work, we described a large number of clinical observations made with Ca-EAP and Calciretard. We would like now to add precision to the work since we have now been using Ca-EAP for more than two years and Calciretard for more than 2 1/2 years. Our experience with Ca-EAP activity is based on the administration of about

(*) Recent investigation with labelled ^{14}C l-aspartic salts demonstrated the specific fixation of the substance within the cell membranes of different tissues. See : T. MIZUKAWA, M. SAKUMA, and Y. SATO (1966). *Autoradiographic Studies on Uptake of Ophthalmic Agents Instilled into the Conjunctival Cul-de-sac*. Fol. Ophthal. Japonica **17**, 11 : 1047-1058.

50,000 daily doses. At times, we were obliged to interrupt some treatments because of produce shortage.

As previously indicated, the most effective clinical action of Ca-EAP has been again obtained in gastritis and duodenitis, with or without ulceration. The iv injection is most effective when followed by the administration of drinkable ampoules and powder. Stomach trouble, even when acute, disappears in about 1 to 2 minutes after the injection. This is an immediate effect that can be otherwise seen only with Ca-EAP in the treatment of toxic tissue inflammation (NIEPER 1966). The pain, therefore, cannot be caused by the gastric autoimmunity process (ANDERSEN, GRAY et al., 1964) in itself, but rather by an effective aggression of stomach juice constituants. This is also confirmed by the fact that gastric pain caused by methotrexate treatment disappears after Ca-EAP injection. Four hours after injection, a second action takes place within a typical lapse of time in some instances expressed by a second disappearance of pain, but above all, by an intense feeling of hunger. To this day, we have not observed any treatment failure even in alcoholic gastrites, stump gastrites and ulcer pain. Even perforating ulcers heal without any additional therapy. Ca-EAP eliminates practically all other therapeutic problems connected with gastritis, duodenitis and ulcer pain, with the exception, in some cases, of additional enzymes and acid substitution therapy, as well as azulene therapy. Prescriptions, high cost stomach treatment, diets, ulcer treatment and a large part of X-ray controls are not longer required. What this would mean for the health and productivity especially of the industrialized nations of Europe, Asia and America does not have to be explained. Other consequences of this therapy are described below.

Gastric patients are treated as a rule twice daily for unlimited periods but for not less than one year. It is remarkable to note that with Ca-EAP treatment, gastric Fetor Oris and coated tongue disappear quite regularly. Calciretard has no effect on the stomach.

After 4 monts of treatment, Ca-EAP appears to lose some of its effectiveness in the treatment of any gastric disturbance that may still persist, but after an interval of 4 to 6 weeks, effectiveness is restored at its previous level. This phenomenon is possibly due to the exhaustion of membrane capacity to fix EAP. Also the decrease noted in the sensation of warmth produced by the iv injection, and which is strongest at the time of the first injection, may have an identical explanation.

As already stated, continuous treatment with Ca-EAP (2/2) of juvenile diabetes produces also satisfactory results. The required insulin doses decrease and continue to decrease even after more than 8 months of daily Ca-EAP treatment. This would again indicate that the active autoimmunological organ process reaches exhaustion only after several months to 1 1/2 year of continuous Ca-EAP treatment.

Diabetic patients with suspected etiological autoimmunity can be classified into two groups, according to the criterium of Ca-EAP activity: juvenile diabetics with light to moderate retinopathy, requiring large doses of insulin, or with high blood glycogenesis and high glucose excretion. Here, Ca-EAP treatment can produce a drop in blood glycogenesis and sugar excretion; insulin requirements decrease, growth and development disturbances disappear. This seems to indicate the presence of an anti-pancreatic immuno-autoaggression inhibited by Ca-EAP. The second group is characterized by severe vascular retinopathy with precipitation of shaft vision and vitrous body opacity. Blood glycogenesis is moderately increased and sugar excretion is within limits: insulin requirements are low, particularly when the antigenically low Leo or Novo insulin is administered. In contrast to the first group, Ca-EAP treatment produces in these patients an increase in blood glycogenesis. Our explanation of this phenomenon is a theory according to which there exists in these patients an insulin autoantibody complex with cytotoxic action, for instance, on the vessels of the retina, although it still possesses some insulin properties. Ca-EAP treatment would then block the passage of these insulin antibody complexes through the membrane and thus cause an increase in blood glycogenesis due to intracellular insulin depletion. These are only observations and very detailed additional investigations will have to be conducted.

Above all, it appears that the forms of diabetes that produce retinopathy are the most receptive to appropriate Ca-EAP treatment. In the case of the juvenile diabetic patient, the success of treatment is that much greater the sooner Ca-EAP is applied after diagnosis. It is recommended to administer iv injection (300 mg) three times a week and oral therapy on the other days.

The effect of Ca-EAP appears also to be excellent in the case of chronic painful adnexitis, especially when it is administered iv. The acute pain disappears almost completely and a cure can be achieved in a few days (4/4), but fort bacteriological reasons this requires the simultaneous admi-

nistration of antibiotics and sulfonamides. The effect of Calciretard is not yet quite clear.

The semiology of chronic autoimmune diseases of the mucous membrane of the stomach, of the colon, breast and thyroid gland that have the form of gastritis with or without ulceration, duodenitis, colitis, fibrotic breast induration, and hyperthyroiditis and hyperthyreotic thyroiditis, raises a hypothesis that has already been extensively discussed in the literature (HORNECKE and BERNDT, 1966) and that we believe is very important: i.e., much seems to indicate that any organ lesions of autoimmune origin that develops over several years opens the road to future cancerisation. If this is true, a large number of carcinomas that appear in later years find here their origin, or at least their timely determination. In such cases an effective, uncomplicated anti-autoimmune therapy over many years would be the cost effective prophylactic measure against potential cancerization. Latest investigations seem to indicate that this would also apply to bronchial carcinoma. Indeed, DEAN (1966) considers that cigarette smokers are only then preferential victims of bronchial carcinoma when the present symptoms of several years old bronchitis with morning cough. Smokers who do not suffer of bronchitis are statistically in much less danger. It would, therefore, appear that bronchitis is a very important intermediary phenomenon in the causal relationship: cigarette smoke - bronchial cancer... Such a treatment of bronchitis could then also be a prophylactic measure against potential malignancy. We ourselves have observed a polytopic malignancy process in a HEILMEYER lund dystrophia; in another instance, carcinoma on a tissue presenting several years old sclerodermic changes; both are autoimmune diseases. Lately, SERAFINI (1966) has shown that years old autoimmune thyroiditis is a precursor of cancerization of the thyroid gland. In the meantime, SERAFINI (Proc. I. Congr. Europ. Soc. Pathol., 1966) has stated that he had discovered autoantibody processes in 24.26 p. cent of 1430 apparently healthy individuals. SERAFINI is also of the opinion that this latent autoimmunisation - mostly appearing in older subjects - could be a pathfinder for future lesions. We had already discussed this on the bases of WALFORD's work (1962) on aging, and also in cancerisation of immunologically damaged organs.

The application of Ca-EAP seems to place also in a new light the problem of allergic inflammatory changes of the myocardium, which, in view of the therapeutic effect of Ca-EAP, are undoubtedly evenly distributed among the allergic (NIEPER 1966) and rheumatic processes, and the focal-toxically induced myocarditis. About 20 p. cent of the patients who had come to the consultation for cardiac pain of varying intensity, state that the application of K-Mg aspartate, beta-receptor inhibitors, or coronary dilators produced unsatisfactory results, while in another 30 p. cent of these patients, some pain continued to persist. This persisting pain after treatment can be alleviated — but for a few exceptions — with Ca-EAP, often with only a single injection.

This observation raises the question as to whether the focal chronic disease, usually latent or rheumatic auto-allergic, of toxic origin, of the cardiac muscle does not occur much more frequently than expected and whether it does not contribute largely to premature degeneration.

In this event, the lesions of the capillaries assuring cardiac supply would be the result of the above process, according to LINZBACH's concept (NIEPER and BLUMBERGER, 1966). Should this be the case, an anti-inflammatory or anti-autoallergic treatment that can be continued for a long period could assure the lasting and satisfactory function of the cardiac muscle. The therapeutic possibilities of Ca-EAP have incited us, in the meantime, to try and gain a better understanding of the diagnosis of latent myocarditis. Results will be published elsewhere (NIEPER and ROYSTON 1968).

Here it should, namely, be stressed that in the case of advanced autoimmune myocarditis, multiple sclerosis, severe colitis and advanced HODGKIN's disease, it is difficult or may even become impossible to bring proof of the existence of specific antibodies. This is simply because in such cases all free antibodies are immediately fixed in the blood stream so that they are no longer typically detectable. The omission of this fundamental principle is at the origin of the erroneous conclusions often reached in numerous investigations of autoimmune diseases. It is also not exceptional that the demonstration of the presence of antibodies in mild autoimmune processes is found to be difficult.

In this perspective, it would appear that the therapeutic effect of Ca-EAP is also interesting from the diagnostical standpoint *.

(*) JAFFÉ (Arzneim.-Forsch., 9 : 657- - 1959), states in his classical work on the autoimmune process of the heart, that it was possible to prove the presence of such processes in 20-43 p.. cent of all mortality cases in Venezuela. In patients with myocardial infarct. rheumatic or chronic myocarditis, such processes were present in 30/47 cases. On the basis of the diagnostic value of Ca-EAP, we must presume that not less than 60/175 of all cardiac patients present a chronic inflammatory process of the myocardium since only inflammatory or rheumatic pain of the myocardium reacts to Ca-EAP therapy, others do not.

The treatment of chronic nephritis, malignant nephrosclerosis and chronic kidney tuberculosis with Ca-EAP transport substances is found to be at least as effective after 2 years of uninterrupted administration as described earlier **. During this period of time, we have not lost a single patient out of 78: 6 patients with severe chronic nephritis or malignant nephrosclerosis, considered as incurable and unable to work, have returned to permanent jobs without a single break during the past year. Headache and uremia have generally disappeared. This is, however, conditioned by a permanent and precise correction of electrolyte and water intake. Moreover, it is remarkable that in the case of malignant nephrosclerosis, the treatment with Ca-EAP restores the response to Rauwolfia preparations, or at least potentiates such response manifold. For instance, with Ca-AEP, one Modenol tablet has more effect than 4-5 Modenol tablets without Ca-EAP treatment. This would indicate — as could be foreseen — that the inhibition of the hypertensive effects of nephrosclerosis liberates again the original mechanism of essential hypertonia. As is known, the latter responds well to Rauwolfia.

It is surprising that under Ca-EAP treatment, the concentration index of the kidneys increases significantly, in some cases from 1008 to more than 1022 specific gravity. In the average, urine is more colored. Obviously, the neophrotic immunity processes condition a gradual functional inhibition of renal filtration capacity.

Remarkable observations were made in four patients with cystic kidneys among whom, a mother and her daughter. All these patients had shown a total gamma-globulin deficit on the ANTWEILER electrophoresis and also a positive HEITAN sludge test (NIEPER 1965, 1966). Arterial pressure of all these patients was of about 175/125 mm Hg; headache and angiopastic ocular fundus. After Ca-EAP, every third day 350 mg, iv., and 750 mg orally on the other days, arterial pressure dropped to 130/85 mm Hg, and headache disappeared. This indicates that a *specific local hereditary autoimmune process* was present in their tubules, which led only secondarily to cyst formation owing to alteration of efflux. It is perhaps possbile to decrease or even stop the cyst-forming tendancy by inhibiting the mechanism of autoimmunity. Chronic allergic and also tuberculous prostatitis respond about as favorably to Calciretard as to Ca-EAP. The results are just as convincing as those obtained with Ca-EAP in the treatment of gastritis. As a rule, a single injection is sufficient to do away almost completely with severe pain. The same is observed in cases that had not responded for many months to treatment with antibiotics and cortisone. In the case of prostatitis and gastritis, an unusual phenomenon is observed that is particularly marked with Ca-EAP: the progression of the effect. In relative and absolute value, Ca-EAP is that much more effective the more intense the inflammation. This may be related to the specific accumulation of EAP in inflamed tissues in the regeneration stage (FERRARI and HARKNESS, 1951). The inflammation in itself, therefore, conditions the activity of the therapeutic agent.

The study of the treatment of tuberculosis and leprosy with autoimmune calcium transporters will be — as already mentioned — the subject of investigations conducted elsewhere. But the results, as expected, seem to open new perspectives in the control of these diseases. In this respect, it is interesting to note the work that is being performed by the Firm Minophagen of Tokyo. These laboratories are preparing a practically pure glycyrrhizin named Glycerone which corresponds to the anti-immune principle of licorice. Glycerone is not only active in gastritis, but shows also interesting results in exsudative pulmonary tuberculosis (YAMAMOTO). Calcium transporters appear to be superior to Glycerone not only as far as their effectiveness is concerned, but they are also more economical.

The results of treatment of hyperthyreosis with calcium transporters, particularly with Ca-EAP, are as a rule good, but there are some exceptions. Ca-EAP is more active than Calciretard. A single injection of Ca-EAP can decrease the size of goiter to such an extent that all vocal interference is abolished. The internal causes of hyperthyreosis decrease. Ca-tyrosinate does not appear to equal the effect of Ca-EAP in the treatment of hyperthyreosis. Nodular changes of the thyroid gland are not visibly or measurably influenced. Numerous, more detailed investigations will have to be made, mainly in the treatment of hyperthyreosis with

(**) It has been observed that Ca-EAP treatment must be often continued for 12 to 18 months to obtain good or the best possible results. This is particularly true in the treatment of nephritis and hypertensive nephrosclerosis or nephrogenic hypertension, but it is also true in some cases of cystic kidneys, early arteriosclerosis and allergic myocardial processes. The specific reason for this long-term effect is at present only based on theoretical assumptions. Moreover, it seems clear that long-term treatment with Ca-EAP prevents decalcificaiton in the vicinity of rheumatic inflammation areas and thus prevents bone and joint deformities.

Ca-transport substances. The effect of Ca-EAP is also excellent in the treatment of combined thyreoditis and gastritis, an autoimmune syndrome confirmed by ANDERSEN, GRAY and al. (1964).

Some aspects in the treatment of multiple sclerosis with Calciretard and Ca-EAP — already described in detail earlier — are very interesting, and following careful observations made in 35 patients, can be described as follows : the effect, particularly of Ca-EAP, is that much better, the shorter the complete history of the disease and the clearer the syndrome of the earlier attack. We had already mentioned this. Multiple sclerosis in its initial but clearly evolutive stage appears to recede with consequent treatment — as far as this may be confirmed after two years of follow-up. No progress of the disease can be detected even under very careful investigation. When the general conditions are worse, especially when the disease lasts for many years, the activity of Ca-EAP decreases and at the end, it does not have any effect at all on the aggravation. Thus, in such a case, the above described « progressive effect » is missing and the opposite can be observed. As an illustration, to explain this phenomenon, we believe that in progressive multiple sclerosis, the membranes of the SCHWANN sheaths are destroyed and the myelin is directly subjected to immunity aggression. With the loss of the membranes, the basis of Ca-transporter activity disappears, and its effect vanishes.

In such cases it will be necessary, therefore, to seek for other methods to change the direction of immunity mechanism according to SELZER's suggestion who is using influenza vaccin to achieve this aim.

Results obtained with Ca-EAP in chronic autoallergic encephalitis after measles are also very encouraging (3/3). An 11 years old girl had been placed in a psychiatric school as a result of this disease. Six months after treatment had been started with Ca-EAP combined with K-Mg-aspartate, it was high time to send the child to a convalescence school. An again six months later, the child skipped a class. Her social behavior became normal. Fortunately, the Education Department appreciated the importance of this original treatment.

The diagnosis of acute and dangerous encephalitis was established in a 41-year old women a fews days after her 4-year old daughter had developed measles. Hypokenesis of mimic and limbs, almost complete aphasia, ventilation obstruction, RR 80/50 mm Hg, temperature 39.5° C... No improvement during the first four days of treatment with Reverin, Novadral and Proscillaridine A, except for a decrease in temperature. From the 4th day, the patient received daily 9 tablets containing a total of 530 mg of Ca-EAP.

Ten hours later, the symptoms of acute encephalitis disappeared, but returned when tablets were discontinued ; once treatment was resumed the symptoms disappeared again for about 3 hours after each tablet, and did not reappear after continuous treatment for one week.

In this connection, an important discovery must be mentioned which was only lately published (KOUPERNIK 1966, HEATH and KRUPP 1967). Antibodies against gangliosides are discovered with remarkable regularity in the serum of schizophrenics. This is another reason to draw attention to XALABARDER's work (1957, 1959) which had raised hardly any interest although this author had found characteristic surface changes in the thrombocytes during electron micoscope investigations — an absolutely typical condition in schizophenics. The most plausible explanation of such changes in thrombocytes is an immune aggression. If an autoaggression process is the cause of shizophrenia this would mean that the metabolic and enzymatic deficiencies discovered or suspected earlier are only secondary results of autoaggression.

We have not yet studied the effect of calcium transporters with immunity inhibiting properties in schizophrenics.

The treatment of HODGKIN's lymphogranulomatosis opens very interesting prospects. As already described in the case of histologically established lymphogranulomatosis, pruritus and swelling of lymph nodulae disappear if Ca-EAP is injected or administered orally in sufficient quantity. In the meantime, we have treated two patients whose condition had not improved with exhaustive X-ray treatment, cytostatics and cortisone therapy prescribed elsewhere. They were considered as incurable. Based on vital indications, we applied simultaneously Natulan in relatively low doses of 150-200 mg daily and Ca-EAP (daily 350 mg, i.v.). Five to six months later, both patients were again fully active in their profession (fig. 3 a and b).

Judging from the behavior of the blood picture and its unquestionable criterion it would appear that no problems could arise with the doses that produce such remission even when administered for very long periods of time. The safety margin thus obtained is certainly remarkable.

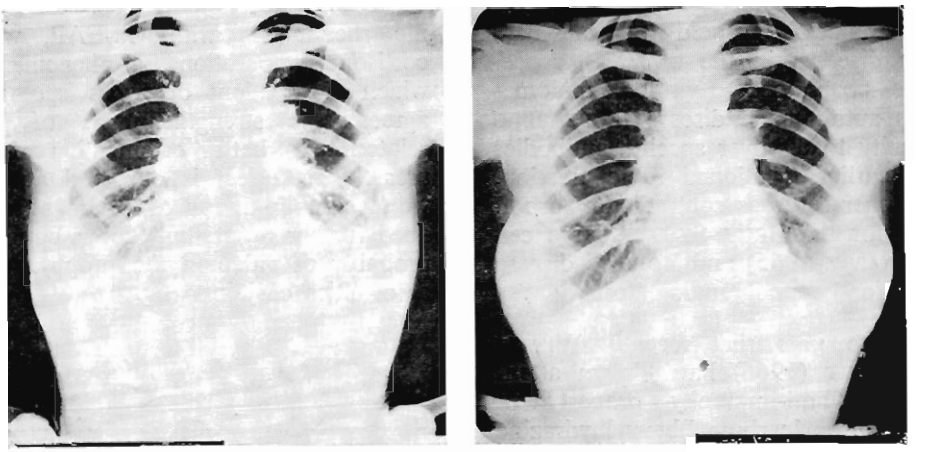


FIGURE 3 *a*.

HODGKIN'S disease in a 28-year old woman.

Daily treatment for 3 weeks with 150 mg of Natulan and 300 mg of Ca-EAP, i v. Not only did the tumor in the mediastinum decrease, but breathing difficulty and a tumor on the left anterior breast wall disappeared. Initially, very severe condition. When released from hospital she was able to resume complete work activity. A daily dose of 200 mg of Natulan, but without Ca-EAP did not produce earlier any satisfactory results. X-ray therapy had already been exhausted.

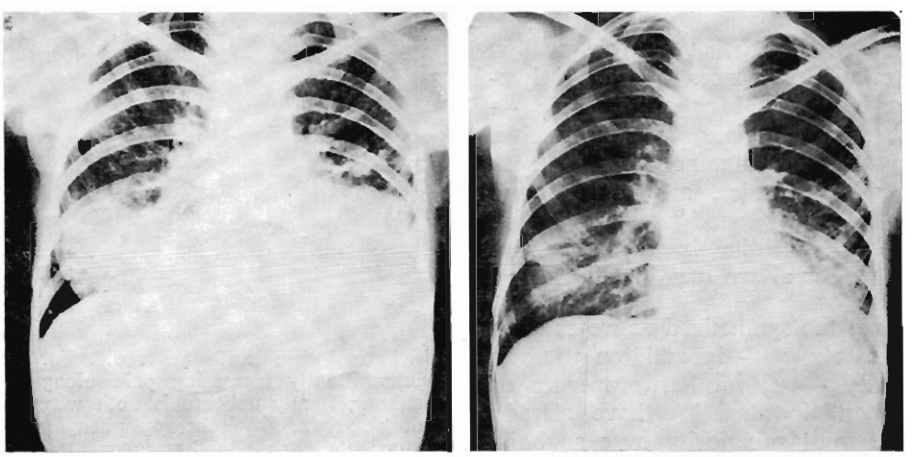


FIGURE 3 *b*.

HODGKIN'S disease in a 16-year old girl.

Most severe condition, the tumor compressed also the esophagus. Results of an 8-week treatment with daily doses of 150 mg of Natulan and 300 mg of Ca-EAP, i.v.: the obstruction of the esophagus was largely releaved. Earlier-long and disappointing cytostatic therapy in other hospitals.

In view of these therapeutic results, the concept that lymphogranulomatosis should be classified among malignant diseases in the sense of cancerization must be abandoned. Lymphogranulomatosis is rather an autoimmune disease (AISENBERG 1964). The difficulty to discover specific antibodies results from the earlier mentioned rapid fixation, and can in no manner serve as contradictory proof. The same is true for the BRILL-SYMMER large cell lymphoblast (GERHARTZ 1965) and BOECK's disease (NIEPER 1954) as for lymphogranulomatosis.

It is important to note that recently WITTE, MARTIN and SCHUBERT (1966) have drawn attention to the strong anti-immunity property of 1 - methyl - 2 - p(isopropylcarbomyl)benzylhydrazine hydrochloride (NATULAN), which proved to be effective not only in HODGKIN's disease, but also in other steroid-resistant autoaggression diseases. The methylhydrazine component undergoes auto-oxidation and forms thus peroxyde and free OH· radicals. In addition, it should be remembered that ozone, when administered in single doses of 400-600 gamma, i. v., produces a form of depression of the immune mechanism clinically comparable in many respects to that of Ca-EAP. Ca-EAP — as also this dose of ozone — is contra-indicated in cancer, as we have learned from our own experience. The immuno-depressive effect weakens probably the defense of the host against tumors and cancer. We shall describe just one exception to this rule which can only be appreciated by the experienced scientific research worker.

These observations indicate that any observation of activity of cytostatic substances — should lymphogranulomatosis be adopted as an exemple — may well lead to error and is not representative. In this case cytostatic and immunodepressive activities, proper to all cytostatics, are coupled and produce thus the relatively good results. But in the treatment of cancer, the immunodepressive effect is not desirable for above mentioned reasons.

On the other hand, the synthetized active calcium transport compounds show — in addition to their anti-immunity activity — also other properties of great actual or potential value. We have already mentioned their apparent superiority over anabolic hormones and conventional calcium preparations in the treatment of osteoporosis and fractures (NIEPER 1966). It is also interesting to note that they protect against osteoporosis without causing any hypercalciuria during the long period of treatment required for cortisone therapy. This cannot be obtained with calcium-gluconate or with other conventional calcium compounds (SCHWARZ). Moreover, in longterm treatment of primary chronic rheumatism with Ca-EAP, with or without cortisone preparations, a phenomenon is observed which the patient describes spontaneously as an agreeable « strengthening » of joints, probably related to a better calcification of the bony joint areas. This effect is observed at the earliest 6-8 weeks after initiation of treatment. It will, however, need further proof, but if it is confirmed, it will be probably of value in the prophylaxis of rheumatic deformities of joints (fig. 4).

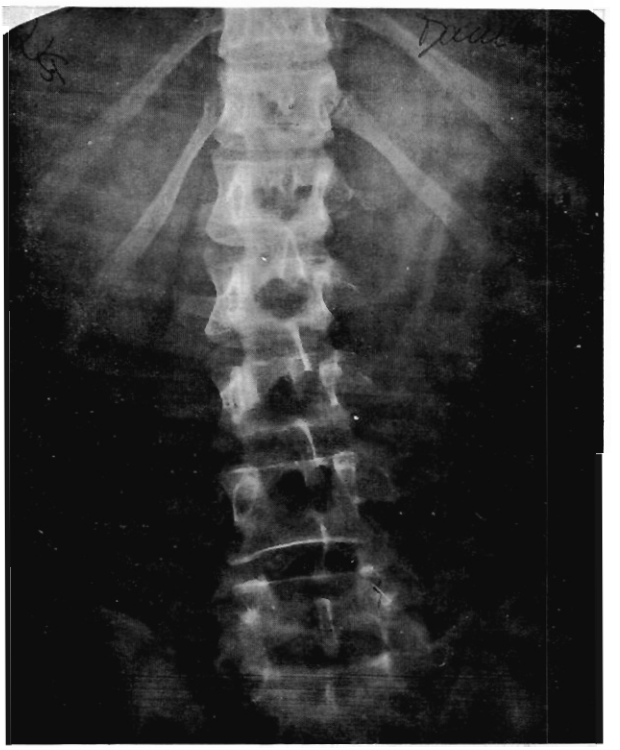
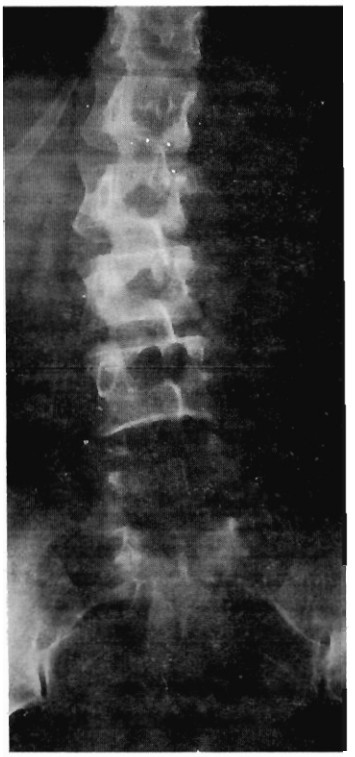


FIGURE 4 a

Patient, female, 29 years old. For the past six months, intermittantly increasing pain along the whole vertebral colum ; finally unbearable both when lying down or standing upright. Physiotherapy, phenylbutazone, cortisone, Ca-gluconate, anabolic hormones, but without any effect. Condition worsened after chiropractor treatment. Monthly, up to 100 tablets of Dolviran, a powerful analgetic.

In February 1966, initiation of treatment with infusions containing 2.0 gm of K-Mg aspartate, 1-2 gm of calcium 1-d1-aspartate and 400 mg of Ca-EAP, 10 resp. 25 mg of hydrocortison ; followed by the usual treatment with a single tablet daily of Ca-EAP, 500 mg p o. Since August-September 1966, all spinal pain has practically disappeared. 2-3 tablets of Dolviran per month. Disappearance of calcium phosphate excretion in the urin.



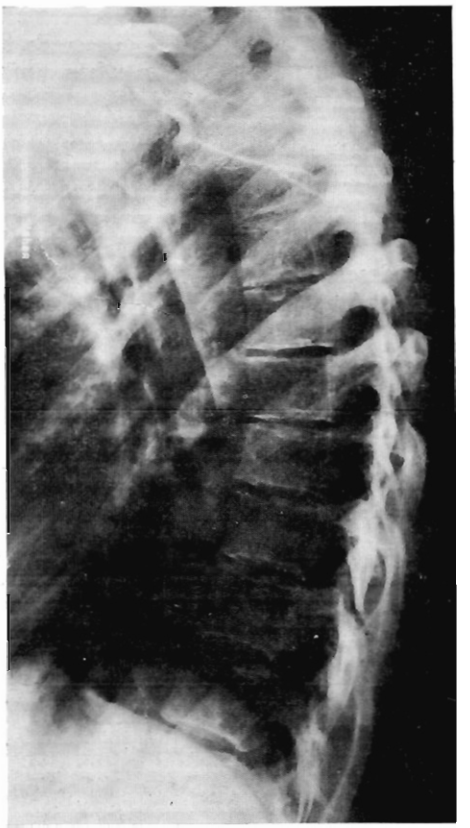


FIGURE 4 b

Comparison of X-ray pictures of October 1965 (*a*) and October 1966 (*b*) show that the excellent improvement of the vertebral column syndrome obtained with Ca-EAP is not due to a definite increase of the calcium accumulation, but that the blocking of chronic inflammation or of immunity processes of the bone matrix is probably responsible for the effect. This would also explain why X-ray irradiation of a painful vertebral column syndrome can produce a lasting therapeutic effect. Here too, there does not seem to exist any other interpretation than that of the irradiation therapy blocking of inflammatory or immunity processes of the bone matrix.

Till now, we have treated 18 younger patients (below 40 years of age) with inflammatory painful vertebral column syndromes. In all cases, Ca-EAP had a very favorable action. Calciretard less so. This also confirms that the therapeutic success is due to immunity inhibition. There are other clinical indications that there exists a hereditary immunological phase in this syndrome that plays an etiological role which would also be responsible for the decrease in the ATP supply.

But in the case of osteoporosis of old age, Calciretard seems, as a rule, to have the same therapeutical value as Ca-EAP: both preparations are decisively superior in the case of osteoporosis to any therapy applied so far.

We had described already in detail in our earlier communication why sufficient K and Mg aspartate (Trophicard) compensation is required in the treatment with Ca transport preparations to avoid late stenocardiac complications and/or gall bladder dyskinesia. However, even with such compensation, larger doses of Calciretard (3-4 mg daily) may produce disturbances especially with perfusion therapy, which appear then in the form of true calcium depletion tetany. This appears at first sight paradoxical, but the phenomenon may be explained by the strong cellular affinity of Ca transporters, *to which should be added the calcium fixation activity of Trophicard when administered primarily for compensation needs.* This causes a relative calcium imbalance between the extra- and intracellular calcium, and thus produces tetany. Experience has shown, however, that such paradoxical tetanies observed during Ca transport therapy can be inhibited by a supply of conventional calcium prepa-

rations such as calcium gluconate. The same phenomenon as described here is also observed, for instance, in potassium metabolism when influenced by K-Mg aspartate.

The synthetic selective active calcium transporter reveals, however, some additional prospects described by SELYE, TUCHWEBER and GABBIANI (1964) in the course of their investigations of the calciphylaxis as described by SELYE (1962) : the calcification of malignant tumors or of their periphery. It has been proven that calcified connective tissues are barriers that the tumor cannot cross, in contrast to spongeous calcareous bone structures. At présent, attempts to calcify malignant tumors are still in the experimental stage. But there is no reason why it should not be possible some day to calcify tumors with the aim of producing an advanced original cancer therapy. This concept of anticancer therapy, first developed by SELYE, is certainly very tempting and presents numerous very important advantages that we cannot describe here, and which are in contrast with all anticancer therapy concepts so far developed. Moreover, progress achieved in infracellular cancer therapy (NIEPER and XALABARDER 1962, NIEPER and KOHLER 1963) offers additional support to the concept of tumor calcification, and reciprocally, tumor calcification gives support to the infracellular cancer therapy.

Both SELYE's concept of calciphylaxis, which is a calcium *fixation* phenomenon, and our selective calcium transport compounds which represent a calcium *missive* principle could progress here independently or in association. At present, the above mentioned calcium transport substances have been used with significant success by various hospitals in the treatment of bone metastases after breast carcinoma, and prostate carcinoma. In these cases, therapeutic values appears to surpass the disadvantages of the above-mentioned blocking of anti-immunity against cancer caused by calcium transport substances.

As already stated in our first communication on calcium transport substances, we are only able to indicate here a fragmentary orientation of the clinical activity of these substances and of their mechanism of action. The areas of investigation opened by calcium transport substances are very large. Both LABORIT and myself and our collaborators, have noted that more than 1 000 publications have appeared till mid-1966 on K and Mg aspartate alone (Aspartat, Trophicard, Spartase). Quite a while ago, we had already to admit that we, the initiators of these studies, are unable to keep track of all observations that have been reported. But when compared to the potential area of application of calcium transport substances, that of K-Mg aspartate can only be considered as small.

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RESUMES

The author describes the probable mechanism of action of the anti-immune calcium transport substances Ca-l-dl-aspartate and Ca 2-aminoethanol phosphate (Ca-EAP) and their clinical activity in a number of autoaggression diseases. Special emphasis is given to the treatment of gastritis, colitis, juvenile and retinotoxic diabetes, indurative mastitis, thyreoiditis, spondylitis, BECHTEREW'S *disease, renal hypertension, chronic nephritis, myocarditis, degenerative diseases of the lung, encephalitis following measles, multiple sclerosis, schizophrenia, chronic rheumatoid arthritis and* HODGKIN'S *disease.*

Observations were collected in the course of administration of about 55 000 daily doses of Ca-EAP. The findings described in an earlier communication are confirmed and in part more detailed explanations or interpretations are presented.

An explanation for the selective membrane permeability decreasing effect of Ca-EAP is offered, based on BÜCHI'S *cell membrane model. The cell membrane becomes impermeable to aggressive substances and antibodies but permits the active passage of nutritive substances of steroids.*

L'auteur décrit le mécanisme vraisemblable d'action anti-immunitaire de composés transporteurs de calcium, le d-l-aspartate de calcium et le 2-aminoéthanol-phospbate de calcium (Ca-EAP) et leur activité clinique dans un certain nombre d'affections par auto-agression. Il insiste surtout sur le traitement des gastite, colite, diabète juvénile et avec rétinopathie, mastite scléreuse, thyroïdite, spondylite, maladie de BECHTEREW, hypertension d'origine rénale, néphrite chronique, myocardite, affection dégénérative du poumon, encéphalite post-rougeoleuse, sclérose en plaques, schizophrénie, arthrite rhumatismale, et maladie d'HODGKIN.

Les observations portent actuellement sur l'administration d'environ 55 000 doses journalières de Ca-EAP. Les résultats décrits dans un article précédent sont confirmés et détaillés ; des explications ou des interprétations sont proposées.

En particulier le modèle de membrane cellulaire de BUCHI, permet d'expliquer la diminution élective de la perméabilité membranaire : la membrane cellulaire deviendrait imperméable aux substances agressives et aux anticorps mais permettrait encore le passage de substances nutritives ou de stéroïdes.

Der Autor beschreibt den wahrscheinlichen Wirkungsmechanismus der anti-immun wirksamen Calzium-Transport-Verbindungen. Ca-l-dl-Aspartat und Ca-2-aminoaethanol Phosphat (Ca-EAP) und deren klinische Wirksamkeit in einer Anzahl von Autoaggressionskrankheiten. Besondere Berücksichtigung wird der Behandlung von folgenden Leiden gegeben : Gastritis. Colitis; jugendlicher und retinotoxischer Diabetes, indurative Mastitis, Thyreoiditis, Spondylitis, Bechterew's Krankheit, renaler Hochdruck, chronische Nephritis, Myocarditis, degenerative Erkrankungen der Lunge, Encephalitis nach Masern, Multiple Sklerose, Schizophrenie, chronische rheumatische Arthritis und Hodgkin's Erkrankung.

Beobachtungen wurden im Verlauf der Anwendung von etwa 55 000 täglichen Dosen von Ca-EAP gesammelt. Die Befunde, die in einer früheren Publikation beschrieben worden sind, werden bestätigt, und es werden teilweise speziellere Erklärungen oder Interpretationen präsentiert.

Eine Erklärung für die Verminderung der selektiven Membranpermeabilität durch Ca-EAP wird unterbreitet, basierend auf Büchi's Zellmembranmodell. Die Zellmembran wird impermeabel durch aggressive Substanzen und Antikörper, erlaubt jedoch die aktive Passage von Nährstoffen oder Steroiden.

El autor describe el mecanismo verosimil de la acción anti-imunitaria de compuestos transportadores del calcio, el ld-l aspartato de calcio y el 2-aminoéthanol-fosfato de calcio (Ca-EAP) y su actividad clínica en cierto número de afecciones por auto-agresión. Insiste sobre todo sobre el tratamiento de las gastritis, colitis, diabetes juvenil y con renopatia, mastitis esclerosa, tiroiditis, spondilitis, enfermedad de Bechterew, hipertensión de origén renal, nefritis crónica, miocarditis, afección degenerativa del pulmón, encefalitis post-sarampión, esclerosis en placas, esquisofrenia, artritis reumática y enfermedad de HODGKIN.

Las observaciones tratan actualmente de la administración de 55.000 dosis por dia aproximadamente de Ca EAP. Los resultados descritos en un articulo precedente están confirmados y detallados ; explicaciones o interpretaciones estan propuestas.

En particular el modelo de membrana celular de Buchi, permite explicar la diminución electiva de la permeabilidad membranaria : la membrana celular llegaria a ser impermeable a las substancias agresivas y a los anticuerpos pero permitiría todavía el pasaje de substancias nutritivas o de esteroides.

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A comparative study of the clinical effect of Ca-1-d l-aspartate (Calciretard), of Ca-2-aminœthanol phosphate (Ca - E A P) and of the cortisones

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The clinical action of the calcium transport substances Ca-l-dl-aspartate and Ca-2-aminoethanol phosphate (Ca-EAP) have been described in earlier communications (NIEPER, 1966, 1967). These substances act essentially as inhibitors of autoimmune processes, but they are just as effective in the treatment of decalcification processes of the skeletal system (NIEPER 1966, 1967).

The clinical activity of both these transport substances is so diversified and of such therapeutic magnitude that in spite of many detailed publications, only part of the effects observed have been described. It has now been confirmed that calcium transporters act at the level of cell membranes subjected either to immunological, or to toxic or viral aggressions. In the past three years a great number of observations have been collected (mostly ambulatory) on the clinical use of about 80,000 day/dose of Ca-EAP and 40,000 day/doses of Calciretard.

As already mentioned previously (NIEPER 1962, 1966, 1967) both these substances produce different clinical effects depending on the differential affinity of their carrier molecules toward the various cellular systems. Lately, we have been repeatedly asked to evaluate the differential clinical effects of these substances. In the Table I, a comparison is made between the effects observed and those produced by cortisone, and in a few single cases also by the immunity inhibiting action of Natulan (R), intravenous ozone (*), of glycerone (**), and of artificial intermitting direct electrical fields (1,1 Hz/8 000 Vm). Under « Cortisone » is indicated also the cortisone derivatives that produce the best results in each respective indication. In the case of nephrosclerosis, nephritis and nephrosis, observations cover periods of more than 12 months of treatment ; in the case of multiple sclerosis, or encephalitis following measles and disseminated encephalitis, observations cover periods of more than 24 months of treatment.

In the discussion of this table which reflects to some extent our observations and those made by our collaborators, the following points are of particular interest :

1) In the case of tissue inflammation, the activity of the calcium transporters is at its highest where cortisone remains completely ineffective and vice versa***. As a rule, cortisone is to be preferred

(*) Average single dose of ozone, i v (about 600 gamma).

(**) Glycerone is pure glycyrrhizin, the active principle of licorice; (manufacturer : Minophagen Pharmaceuticals, Co., Tokyo. YAMAMOTO and TERAMATSU 1965).

(***) Whereas the cortisones, and also the phenylbutazones, indomethazine, and fluphenazine act primarily on mesodermal tissue Ca-EAP directs itself more to entodermal organs.

TABLE I

C = contraindicated
(—) = effect doubtful
— = no effect

(+) = poor effect
\+ = effect
++ = good effect

+++ = very good effect
? = not yet clearly observed

	Calciretard		Ca-EAP		Cortisone	Various
	i v	orally	i v	orally		
Gastritis	—	—	+++	+/++	— (C)	elect. field + glycerone ++
Colitis muc. and ulc.	+	(+)	++	+	+/++	Ozone ++
Prostatitis (chronic)	++	+	+++	+	(+)	
Hypertensive nephritis and nephrosclerosis.	+	(+)	++	+	(—)	
Normotensive nephrosis	?	?	+/++	+	(—)	
Allerg. lymphadenosis	(+)/+	(—)	++	+	+	Ozone ++
Hodgkin	?	?	++	+	++	Ozone ++ (itching) Natulan ++
Erythema nodosum	++	+	++/+++	+	++	
Erythema exs. multiform.	++	+	+++	+	++	Ozone +
M. Boeck	+	?	++	+	++	
TB of kidney, prostat, gld	+	+	++	+	(—)	
Pulm. TB (study underway elsewhere)	+/++	(+)	++	+	(+)/+	Glycerone +/++
Endarteritis, endangitis	(—)	—	+	+/++	—	Ozone ++
Myocarditis (rheum. all. focal-tox.).	+	+	++	++	(+)/+	(Ledercort)
All. thyreoditis Hashimoto	(+)	—	+/++	+	(—)/(+)	
Sciatic neurit.	—	—	—	--	(—)	
Musc. lumbago	+	(+)	++	+	+/++	
Myogen progr. musc. dystrophy.	(+)	(—)	+	+	(—)	
Neurogen. progr. musc. dystrophy	—	—	—	—	—	
Aller. hay fever	(+)	(—)	+	(+)	++/+++	
Aller. bronch. asthma	+	—	+	(+)/+	++/+++	
Aller. lung. dystrophy	—	—	+	+	+	
Chron. hepatitis	(+)/+	(+)	C	C	(+)/+	elect. field + Natulan ++/+++
Prim. chron. rheumat. arthr. (PCP) (pain)	(+)	(—)	(—)/+++	+	+/+++	elect. field ++ Ozone ++
PCP, joint decalcification	+/++	+	++	+	—	
Mammit. indurat. fibrosis of breast	++	+++	++	(+)	(—)	Ozone +/++
Juven spondylitis	++	+	++	+/++	+ (C ?)	
Osteoporosis	++	++/+++	+/++	+/++	C ?	Calc. glucon. (+)
Decalcific. by cortisone treat.	++	++	+	+	...	
			(Hepatitis : C.)			
Bechterew.	+	(+)	++	+/++	+/++	
Persistent bone lesions by osteomyelitis	+	(+)	++	++	C	
Bone fractures	++	++/+++	?	+/++	—/C	
Aller. skin lesions	?	(+)	+/++	+	++/+++	
Skin aging hair growth	?	+	++	++	+ ?	
Aller. encephal.	?	?	++	+	—	Phosetamin ++ (Mg-K-Ca-EAP)
Encephalitis disseminata	(—)	(—)	+	+	—	
Early multiple sclerosis	(+)	(—)	(—)/++	(—)/+	(—) (+)	
Malignant tumor	—	—	C	C	C/+	Ozone : C
(Exceptions : Hodgkin, Brill-Symmers, osteoclast.			++	+	++	
Metast. of prostat cancer	+/++	+			(+)/C	
General decalcification in cancer disease.	++	++	C	C	C	Calc glucon. (—)
Late manifest. of syphilis (neural and vascular)	?	?	++/+++	+/++	(—)/(+)	
(Juvenile diabètes)	+	?	++	+/++	(—)	30 mths. observ.

in primary chronic polyarthritis — as far as pain is concerned — as well as in asthma and hay fever (Triamcinolon), and in diseases of the connective tissues and of the epidermis. But it should be noted that in long-duration treatment, the action of Ca-EAP and that of Calciretard on the epidermis are both interesting (see aging) and particularly so when applied locally. Since in contrast to cortisone, calcium transporters do not cause any side-effects when used in dermatology, their importance is infinitely greater than that of the cortisones for the free market of cosmetics.

2) It has been noted that calcium transporters are exceptionally active in chronic prostatitis, gastritis, nephritis and nephrosclerosis, and also in myocarditis, juvenile diabetes and in some auto-immune diseases of the nervous system, while cortisone has only a very poor effect in all these diseases.

Since neither cortisone nor Ca-EAP have yielded satisfactory results in chronic hepatitis with confirmed auto-immune mechanism, we have used Imuran (R), chlorambucil and Natulan (R) in the treatment of auto-immune chronic hepatitis. According to our observations, Natulan proved to be markedly more effective. Although the number of our observations is very limited (4/4), Natulan should probably be considered at present as a treatment of choice for chronic hepatitis*, concomitant antibiotic therapy seems to be advisable. As had been mentioned earlier (WITTE, MARTIN and SCHUBERT, 1966), the immunity-inhibiting action of Natulan results probably — or at least in part — from some membrane activity. This compound can, therefore, fix itself on the organ concerned, while Imuran and chlorambucil, because of their pharmacology, can only have an inhibiting effect on the immune body production of the lymphatic and reticular systems, and conversely, cannot protect directly the organ concerned. Thus we can confirm the observations that WITTE, MARTIN and SCHUBERT (1966) have reported concerning the immunity inhibiting action of Natulan. As a rule, daily doses of 150-200 mg are sufficient to produce 8-10 days later a drastic decrease of SGOT and of alkaline phosphatase, as also a marked inhibition of the otherwise uncontrolable production of ascites and a normalisation of chlolekinesis. Present observations are still very limited in time, and we do not have yet any concerning the use of Natulan in chronic nephritis. It should also be mentioned that in investigated cases the little effective and already long-standing treatment with cortisone and Calciretard was continued.

(*) This seems also to se true for Glycerone.

In cases of severe chronic dermatitis, which respond only very slightly to Triamcinolon and only moderately to Ca-EAP, chlorambucil, iv, have proven to be superior to Imuran and also to Natulan. But the latent period before onset of action is of at least three weeks. This observation confirms also the membrane action of Natulan as does also the difference of the equally effective doses.

On the basis of the membrane model (BÜCHI), and on the theory of membrane activity of Ca-EAP (NIEPER, 1967), the following hypothesis may explain this phenomenon : the pores for active transport that at least the heart, the kidney and the gastric mucous membrane have at their disposal offer great mobility to the steroids involved in electrolyte exchange. This phenomenon may well contribute to the inactivation of the cortisones on such cell systems because of insufficient membrane fixation.

3) As is seen, a few contraindications have been listed for Ca-EAP, particularly in the case of malignant tumors since it has been observed that Ca-EAP and also ozone stimulate markedly the growth of tumors. This may well be the result of the inhibition of the immunity defenses of the organism against tumor cells. The more so, since EAP shows great affinity for tumor tissue (FERRARI and HARKNESS, 1951). But it is also possible that Ca-EAP provides the tumor cell with a structural element which it needs most urgently to develop its membranes and thus grow more rapidly. Ca-EAP is also contraindicated in the case of acute and chronic hepatitis with or without icterus for it causes in these diseases an inhibition of the cholekinesis and of the choleresis with hepatic hypertensive pain. The reason for this appears to be both an inhibition of the cholinergic stimulation caused by the exchange of Mg for Ca (NIEPER and BLUMBERGER, 1964) and also the inhibition of the bilirubin passage through the cell membrane. These disturbances can be compensated by Mg-K-EAP (Phosetamine) and by Mg-K-aspartate. This is particularly so in the case of patients who are not affected by any severe hepatic disease.

It is not advisable to use Ca-EAP in advanced myocarditis since the negative effect produced by the Mg exchange, although slight, is yet greater than the therapeutic effect obtained.

In any event it is better to recommend a combined treatment with Mg-K-EAP, or better still, with Mg-K-aspartate. Long-duration therapy of rheumatic myocarditis should last at least 12-16 months before evaluating the results. A favorable effect, however, can often be observed after a few

days or weeks, but it should be noted that it progresses still further during the following months.

4) Calciretard is ineffective on gastric pain, while here Ca-EAP is even more active than Banthine. This is especially so for the severe gastric pains which are associated with migraine and in the serum, with sodium retention.

5) In the treatment of primary chronic polyarthritis, the best treatment consists of a combination of cortisones and indomethazine with Ca-EAP, for it prevents almost in every case any possible deformity of the joints — as much as this may be stated after an observation period of three years. But in this Ca-EAP can be completely replaced by Calciretard.

6) Calciretard appears to be the best medication for the prevention of decalcification processes during long-duration cortisone therapy. This is particularly so in the case of hepatitis or of malignant processes. As a rule, we also prefer Calciretard in the case of osteoporosis of the aged for we do not know of any effective treatment, not even with Ca-EAP.

7) Calciretard appears to be much more efficient than Ca-EAP in activating the healing of bone fractures, especially in the aged. Observations of thigh fractures show that Calciretard can accelerate greatly the healing process. It is interesting to note that although these fractures show very early consolidations on the X-ray, there appears to be hardly any callous formation.

8) A remarkable property of Calciretard which never fails with doses of 300-600 mg (1-2 tablets) is its capacity to suppress fibrous induration pain of the female breast and to render the tissues much softer. The effect lasts for about 24 hours and can be renewed for years whenever necessary. The same effect is obtained with Calciretard, iv, Ca-EAP, iv and sometimes with ozone (600 gamma, iv) but not with oral Ca-EAP.

This phenomenon is being used daily to establish the differential diagnosis of breast carcinoma. Any palpable lump that does not react to Calciretard is excised for histological investigation. Palpable lumps that react to the Calciretard test by becoming painless and soft are without any possible doubt of inflammatory origin. Calciretard is therefore a choice treatment of chronic fibrous and cystic breast induration auto-immunologically conditioned. It has already been described earlier how this immunity inhibiting long-duration therapy with Calciretard of fibrous breast indurations decreases the potential danger of breast cancerisation. The explanation for the remarkable effect of Calciretard on the female breast is probably to be sought in the great affinity of the mammalian gland tissues for aspartic acid and calcium. This could eventually lead to very strong binding of aspartate (MIZUKAWA, SAKUNA and SATO, 1966) to the membrane of the mammalian gland tissues.

9) In spite of the great variety of clinical application of Ca transport substances, and in many instances of the very convincing results obtained, it is still very difficult to reproduce them in animal investigation. This is particularly so for the action of Ca-EAP on the auto-allergic inflammation of mucous membranes, glands and secretion organs, but also for the action of Calciretard on mammalian glands. As often in medicine, it is difficult in such instances to set up a protocol for animal investigation which could be representative of the clinical reality and observations collected in more than 1,000 patients of different out-patient clinics and hospitals in various countries.

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RESUMES

A COMPARATIVE STUDY OF THE CLINICAL EFFECT OF CA 1- dl-ASPARTATE (CALCIRETARD), OF CA-2 - AMINOETHANOL PHOSPHATE (CA-EAP) AND OF THE CORTISONES

In a series of autoaggression and decalcification diseases the average clinical effects of the calcium transport substances Ca- l-dl-aspartate (Calziretard) and Ca- 2- aminoéthanol phosphate (Ca-EAP) are compared with the effects achieved with cortisones, and different immunodepressive substances. The results are briefly discussed.

Für eine Serie von Autoaggressions- und Entkalkungs-Erkrankungen werden die durchschnittlichen klinischen Wirkungen der Calzium- Transport- Substanzen Ca- l- dl-Aspartat (Calziretard) und Ca-2 Aminoaethanolphosphat (Ca-EAP) mit denjenigen Wirkungen verglichen, die durch Cortisone und verschiedene immunodepressive Substanzen erzielt werden. Die Ergebnisse werden kurz diskutiert.

ETUDE COMPARATIVE DES EFFETS CLINIQUES DU DL-ASPARTATE DE CALCIUM (CALCIRETARD), DU 2-AMINOETHANOL PHOSPHATE DE CALCIUM (Ca EAP) ET DE CORTISONIQUES

L'auteur établit un bilan clinique des effets thérapeutiques de corps transporteurs de calcium (l-dl aspartate de Ca : Calci-retard et phosphate de Ca-2-aminoethanol : Ca-EAP) dans une série de maladies par autoagression et de décalcifications en le comparant à ceux obtenus avec des cortisoniques et des substances immuno-dépressives. Ces résultats sont brièvement discutés.

El autor establece un balance clínico de los efectos terapeúticos cuerpos transportadores de calcio (L-dL aspartato de Ca : calci-retraso y fosfato de Ca-2-aminoethanol : Ca-EAP) en una serie de enfermedades por autoagresión y de decalcificación, comparándolo a los obtenidos con corióónicos y substancias inmuno-depresivas. Estos resultados están rápidamente discutidos.

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THE CLINICAL EFFECT OF CALCIUM OROTATE[1] ON CARTILAGE TISSUE

A Specific function in relation to pentose metabolism of bradytrophic tissue?
We are presenting here an orientation into the clinical effect of calcium orotate. Calcium orotate is absolutely free of any side effects and in this respect, it is far superior to all the conventional calcium salts now being used. Because calcium orotate can penetrate the complex cell membranes, it can compensate for a disturbed calcium transport through these cell membranes. In addition, calcium orotate has a special affinity for bradytrophic tissue—cartilage, for example—where it is metabolized. Parallel studies have shown that a defective calcium transport through the cell membrane is of great pathogenetical significance.

Previous experience, up to now:
We have employed calcium orotate extensively since 1968, hospitalized and ambulatory, to treat decalcification conditions and even in many cases, immunological diseases. The results accomplished here are in complete accord with what we discovered in 1959 concerning the transmembrane transport complex. Calcium is first released as an ion, on the cytoplasma membrane level, because orotic acid is chiefly metabolized there, not in the outer cell membrane. The clinical results that we have seen up to now are very encouraging, with a minimum of side effects completely unparalleled with anything that we have seen in the entire field of calcium supplementation.

And what is more, in suitable cases, this substance is a very satisfactory agent in the recalcification of metastatic defects in the skeletal system (1), (2). I reported this at the 1970 cancer congress in Houston.

The results of calcium orotate therapy with juvenile decalcification and with osteoporosis of the aged, are completely satisfactory for the first time, especially in view of the absence of side effects. This finding was contrary to all my previous experience with recalcification therapy.

The very remarkable results which we have achieved in hip joint plastic surgery, (3) are due to a hardening of the bone by preliminary treatment with calcium orotate. Previously, in this periodical, I reported the recalcification of bone metastases. Illustration 1. show another patient (f), in which a severe defect of the acetabular roof was so improved (recalcified), that hopeless

[1] also known as calcium diorotate

immobilization was replaced by fully normal, pain-free locomotive ability. This was accomplished after about 2.5g calcium orotate tgl[2] for 10 weeks. A long period of therapy with a conventinal calcium seltzer, had been carried out previously, with no effect.

Calcium orotate and Liver:
A several year search through many long term treatments with calcium orotate for side effects was absolutely negative. On the contrary, a whole series of positive observations came to light, which may be connected with the unique transmembrane calcium transport, we should mention here, that there is still quite a bit of clinical interest here. I will discuss this before I dwell on the main theme of the skeletal effect of calcium orotate.

One noteworthy observation is that patients with chronic cholangitis and light cases of chronic hepatitis—and also in severe aggressive cases—show a considerable improvement in their ailments, their state of health, their gall function, and to some extent, their biochemical and biological findings. This is especially true under long term therapy. It appears to be associated with an anti-inflammatory effect on the mesenchymal stroma system in the liver.

The carrier molecule—orotic acid—has an especially high affinity for mesenchymal tissue (4). Free orotic acid, magnesium orotate, or other calcium salts do not show this effect on the liver. We should refer here to the research of DEBORAH DONIACH (10) on all immulogical liver disease—with and without cirrhosis—concerning antimitochondrial (not anticellular) antibodies, as sickness motivation. Calcium orotate liberates its calcium ion—this is the classic anti-inflammatory principle—at the level of the mitochondrial membrane. This explains the anti-inflammatory effect in the liver.

Four patients who had taken, on the average, 3g of calcium orotate in stomach acid resistant capsules per day, for more than a year, submitted to a liver puncture. (For reasons which had nothing to do with the application of calcium orotate.) In all cases there was no sign of fatty liver development. Quite the contrary, three of the patients with stage 3 fatty liver showed a remarkable improvement under long term calcium orotate therapy.

The first patient was a teamster—very heavy consumption of alcohol. His condition had been a constant stage III for six years. After one year of therapy—tgl 2g calcium orotate—not only were the complaints lessened, but a liver biopsy showed nothing but a normal amount of fat accumulation.

Another patient—U.S. American (f)—came to us for treatment for a severe case of fatty liver. In just ten days, after tgl 6g calcium orotate therapy, the

[2] tgl=daily (from the German "taglich")

complaint was improved and also a mild case of jaundice was cleared up, which had been with her for three years, following an influenza attack. After three weeks, a biopsy showed a dramatic improvement. Every possible liver therapy had been tried earlier, both in the United States, and here in Germany, with no success whatsoever. A third case of fatty liver III, showed a similar improvement after hyperalimentation.

It is absolutely necessary that we conduct a very thorough investigation on this effect of calcium orotate on fatty liver. We must remember that the lipase enzymes which are necessary for the mobilization of stored fat, are activated by Ca^{++}. I might assume, in this connection, that the primary source of fatty liver is a defective calcium transit in the liver cell. A magnesium washout caused by chronic alcoholism, in the liver cell membrane, could explain this. Mg^{++} is necessary in the cell membrane for Ca-transit into the cell. (6a) Anything which disturbs or injures the cell membrane function can affect calcium transit through the cell membrane. So there are possibly some other significant considerations, such as essential hypertonia or the ingestion of detergents which stick to kitchen utensils after washing. Also a fare too rich in carbohydrates puts a strain on the P-pools and likewise interrupts the Ca-transport through the membranes. Free orotic acid has no effect on the fatty liver condition. Likewise the same is true for magnesium orotate.

Effect on heart and circulation:
Another interesting observation is of a moderate, to often marked, dropping of the blood pressure with fixed hypertonia. This treatment will elevate the lowered blood pressure both in the chronic, as well as the light form of renal hypertonia. Normal blood pressure is not affected. What is especially convincing is the disappearance of angina pains, especially with a hypertrophied heart. In addition, the improvement is remarkably good with infarct anamnesis with hypertonia and a distinct sclerosis of the heart. Digitalis or Strophanthin tolerance appears to be better. With a dosage of 10g calcium orotate tgl., no incompatability of Digitalis can be observed, in the EKG, subjectively, or otherwise. Probably because no membraneous calcium ions are created. In this connection, I must point out that some time ago, KAUFMANN and coworkers (KAUFMANN and MITARBEIT) (11), researched the problem of defective or insufficient calcium transit in hypertrophia of the heart muscles. They conclude, that this is the reason for contractile insufficiency, in hypertrophy and other metabolic problems of the hypertrophic heart. Special reference must be made to the papers of the KAUFMANN group. We have made a series of tests with 14 year old dogs on a 14 percent incline. Our results were a very good confirmation of the pathogenetic mechanism that KAUFMANN portrayed. We will give you the details in a later article.

RILLING (12) has verified the research of ZONDEK (13) and KYLIN (14) with his comprehensive spectrographic studies. These authors maintain that essential

hypertonia is a cellular calcium-deficient pathognomonic condition. This interpretation is much the same as KAUFMANN'S explanation of heart muscle hypertrophy and would explain the blood pressure-lowering effect of calcium orotate. At the time that NIEPER and LABORIT were doing clinical research on potassium magnesium aspartate, we hoped to be able to correct disturbances of the heart action regulation system. Except for a suppression of ventricular and supraventricular extrastole, this hope was not realized. (15) As you know, the heart action regulation system is musculature in nature, which consists of a different type of metabolism, the direct oxygen or "pentose pathway". The stimulatory regulation and ganglion tissue provide especially good protection against oxygen deficiency intrafetally and later. Orotic acid plays an essential role in the pentose pathway, and so appears to be the electrolyte transporter needed for that tissue. In view of that, it should not be surprising to learn that we were able to normalize apparently therapy-resistant tachyarrhythmia with auricle flutter, in three cases, with a dosage of 5g calicum tgl.

After this excursus, I would like to mention the immune-inhibiting effect (as already reported) (4), of calcium orotate on a succession of bradytrophic tissues.

Specific effect on cartilage:
It was first reported by WHITE towards the end of 1969, that calcium orotate showed an astounding curative effect on the Tietze syndrome. These reports were repeated over and over during 1970 and 1971, so that we were induced to try calcium orotate in three cases of stubborn Tietze syndrome. The effect of the calium orotate was indeed surprising—all the details of the WHITE article were fully verified. Tietze syndrome, according to our information, is much more common in the US than here in Germany. According to WHITE, the syndrome is suppressed by very low doses—down to 1g/week, which we could verify. A dosage of 500mg/day is fully effective. It is highly significant that there is no effect whatsoever from calcium EAP, calcium-L dl aspartate (calciretard), calcium gluconate, calcium citrate, magnesium orotate, and K-Mg-aspartate, upon the Tietze syndrome.

On the basis of our knowledge of the effect of calcium orotate on the Tietze syndrome, we must conclude, that a favorable trophic effect on the cartilaginous intervertebral substance is the reason for the not infrequently spectacular improvement of the patient.

This fully specific effect of calcium orotate on cartilage, as evidenced by the Tietze syndrome experience, appears now to be of tremendous clinical significance. Unfortunately, we only learned this after the repeated reports of WHITE. While we were treating patients with spinal coumn syndrome and calcification damage, it had been apparent, for a long time, that the reported and verified improvement of their condition, must be attributed to more

than simply an influence on the bone tissue. For example, we had five patients (f) and one patient (m) from 26 to 76 years, with symptoms of weakness and painful sensitivity in the wrists. In three cases, it could be observed only with an sphygmomanometer, and in three cases observation was not possible at all. In every case, the complaints disappeared with calcium orotate therapy. Upon the removal of the therapy, or when the dosage was insufficient (less than about 1.6g/week) the complaints returned.

Especially puzzling are the findings for 18 patients from our files, in which there were severe dislocating alterations of the spinal column. Treated with calcium orotate, these patients became exceptionally free of complaints. Other medications—Butazonderivate, cortisone, indomethacin, physical therapy, gold medication—had failed. Even intensive treatment with calcium EAP, and calciretard along with calcim-sandoz and K-Mg-aspartate were ineffectual.

CASE HISTORY:
NOTE: The illustrations which are x-ray images cannot be reproduced by our copy machine, so they are omitted here. They are in the German manuscript however.

Illustration 1, Frau K, 35 years old, before and after therapy with calcium orotate. Metast. Mamma-carcinoma

Illustration 2a, patient (f) H. Sch. 64 years
Severe complaint complex with LWS syndrome. Every imaginable therapeutic preventive measure taken to no avail. Infusion treatment with calcium-L-dl aspartate (calciretard) plus calcium EAP for more than six months. Complete stationary immobilization for three months 1970/71 to no avail. The pain associated with the LWS syndrome had forced her almost to the point of complete immobility. About three to five weeks after starting calcium orotate therapy—an average of 3g/daily—the patient was complaint free and remained so for 16 months—practically normal movement and walking ability. In contrast to calcium orotate, other calcium transporters such as calcium EAP and calciretard were fully ineffective. Is the improvement to be sought in a structurally favorable influence of the intervertebral tissue?

Illustration 2b,

Almost complaint free after six weeks intensive treatment with calcium orotate. Reconstruction mainly in the gap between 3 and 4. LWK Both developments are stabilized. These findings are not the only ones which gave rise to our questions about the effectiveness of calcium orotate on cartilage.

In 1968, we started using calcium orotate to treat patients with definite Bechterewschen disease. There were, in all, five such patients and in all the cases the very intense pain in the spinal column disappeared for the most part. All previous treatments—phenylbutazone, cortisone, gold therapy and healing baths—had been ineffective.

Illustration 3, patient (f) N. N. 56 years.

In 1963, the disease has progressed so far in this 56 year old patient, that she was almost completely immobilized. In spite of standard therapies and seltzer water cure, the progression continued. By 1968, the face was almost in a fixed position, movement and sitting were almost impossible. 1.5g calcium orotate was prescribed daily for 54 months continuously. No more complaints. The face could be moved normally and the patient resumed her household duties. The second picture is the patient (f) with Morbus Bechterew after 54 months continuous treatment with calcium orotate.

Illustration 4, patient (f) M.B. 71 years,

Most severe complaits for three years as a result of spondylitic arthrosis deformation. Treatment with phenylbutazone and also in combination with cortisone and with pyrazolone showed only slight palliative effect. Calcium-sandoz forte tgl. 3 tabl. for over four months without any effect. After 10 days tgl. 5g calcium orotate, the patient was almost complaint free, and has remained that way.

Illustration 5, patient (f) N.B. 81 years,

A sister of Frau M.B. above. 10 years older. Xrays and symptom complex indicate a very severe case. After being treated with calcium orotate tgl. 5g, she became complaint free, that she again took up vigorous employment after previous inactivity.

Illustration 6, patient R. 79 years (f)

Frau R., mentally and bodily vigorous. Had an acute attack of a long time existing osteochondrosis. Quite comfortable lying down, but experienced immediate unbearable pain in the spinal column upon standing up. After treatment with 5g calcium orotate daily, the patient became complaint free within three weeks. The pain had previously worsened under cortisone therapy. Calcium-gluconate-citrate, phenylbutazone and indomethazine had no effect whatsoever. The curative effect of calcium orotate was permanent (now over 14 months).

Illustration 7, patient (m) St. 55 years

Acute monarthritis of the right tibiotarsal joint, forcing him almost to the point of immobilization. Three tablets realin daily were of very little effect. Soludecortin H 50mg likewise. Volon 80 brought limited relief for 36 hours. Calcium orotate 8 tabl. each .5g daily brought improvement after 2 days and corrected the condition in 6. There are four similar cases.

Latest findings

By the end of 1972, we had experience with 21 cases of deforming spondylarthosis—five men, sixteen women, from 58 years up. Clinical and objective findings were consistent with the cases mentioned previously.

14 out of 16 women and 4 out of 5 men were helped by calcium orotate alone. They were observed for over a year. The remarkable effect of calcium orotate (called Ca orotate for short) with Tietze syndrome in the intervertebral disk (and possibly in the ligamentous apparatus) causes us to again evaluate the metabolic specificity of cartilage and other bradytrophic tissue. Here the pentose pathway (so-called direct oxidation) plays a very crucial role—an extremely old phylogenetic-metabolic pathway, which is not dependent upon the erythrocyte oxygen donation. In the pentose pathway, the ribose is activated through orotate coupling. For this reason, orotic acid plays a very essential role in the pentose pathway.

Here we are concerned with a large variety of tissues. Besides cartilage and ligamentous tissue, there is the connective tissue, the skin, the walls of the blood vessels, a specific section of the venules in the blood-brain-barrier, the heart stimulation-regulation tissue and keratin building tissue (hair, nails, etc.). Also the pentose pathway plays a very important role in the bone matrix, in the heart muscle and in the liver (both in the liver cells and in the stroma). The aromatic structure of the orotic acid is responsible for the high complex stability of the salts, and the already mentioned highly complex passage though the cell membrane typical of orotic acid, plainly make the orotate an ideal mineral transporter. (4)

We are indebted to the tireless effort of LABORIT (8) and his scholars (7) who made public the results of their year-long research program which disclosed the vital effect of the pentose pathway in the function and structure of bradytrophic tissue. Life would not be possible without it. Previously, cartilage and connective tissue had been considered uninfluencable, for the most part.

If calcium orotate can bring about a change here, as was demonstrated, then there is not much value in the geriatric therapeutic concept.

Summary
An orientation is given concerning the clinical effects of calcium orotate (called Ca orotate for short). Because calcium orotate is free from side effects,

it is superior to conventional calcium salts, which have certain problems when applied in osteoporosis with concomitant arteriosclerosis of the abdominal aorta. Calcium orotate, on the other hand, protects the body from arteriosclerosis.

Calcium, for this reason, is of value as a food supplement when used in the form of calcium orotate, which can penetrate the cell membranes as a complex form, compensating for defective calcium transit into the cells. In addition, calcium orotate has a special affinity for cartilage and other bradytrophic tissue, where it is metabolized.

Not only is the basic principle of action quite simple, but the long time therapeutic effects are of considerable interest. A new dimension of therapy now appears with the improvements in osteochondrosis and disk degeneration treatment. Far better than the present therapeutic possibilities. Much the same observations seem to apply to osteoporosis.

Parallel investigations point to the important pathogenetic significance of a defective calcium transport through the cell membrane. This is the case, for example, in hypertensions—especially essential hypertension—in fatty liver, in disturbances of the ductile of the heart, and in contractile and metabolic insufficiency of the hypertrophic myocardium. In respect to all of these indications, calcium seems to bring about the most promising therapeutic results, when combined with the carrier orotic acid for better transmembrane transport, in the form of calcium orotate.

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