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Recalcification of bone metastases by calcium diorotate*

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RECALCIFICATION OF BONE METASTASES BY CALCIUM DIOROTATE
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The calcium-transporting substances Ca-l, dl-aspartate, Ca-2- amino-ethanolphosphate (Ca-EAP), and Ca-diorotate seem to be the most active substances in the treatment of all kinds decalcification processes of the bone system. They are superior to conventional calcium salts and anabolic hormones, however, the show clinically less side effects than the latter. In contrast to Ca-aspartate and to Ca-EAP, Ca-Diorotate is capable to recalcify malignant metastatic lesions of the bone tissue and decalcifications followings extensive X-ray treatment. This phenomenon is interpreted by the specific mechanism by which the orotic salts get into the cell. Whereas Ca-EAP and Ca-aspartate are already bound and maybe metabolized within the cell membrane Ca-diorotate penetrates it as an undissociated complex by mans of active transport mechanisms. Metabolization and thus dissociation only occurs on the level of plasmatic structures. No clinical side effects of the treatment with Ca-diorotate were observed even after the application of more than 200 000 *day/doses within three years.*

A number of compounds which we defined as « Electrolyte Carriers » were synthetized and introduced by NIEPER and KÖHLER since 1957 (NIEPER, 1961 ; NIEPER and BLUMBERGER, 1966 ; NIEPER, 1967). The compounds transport actively cations in undissociated form into the cell membrane or cell. All electrolyte carriers must possess three properties : 1). They must have a low dissociation constant, or be a chelate, 2) they must show great affinity for specific cell systems or organs, and 3) they must be metabolized there and thus liberate the cation in the organ of affinity.

Suitable carrier molecules are e.g. aspartic acid, serine, orotic acid, 2-amino-ethanolphosphoric acid, nicotinyl-aspartic acid and certain peptides. As cationic components were studied : Potassium, magnesium, calcium, iron, cobalt, zinc, copper and manganese.

To this date about 1 500 paper have been published on electrolyte carriers. Today, the best known is K-, Mg-aspartate which is used as a protector against myocardial necroses (WEBER, LABORIT *et al,* 1958), and also to improve renal and hepatic functions. It speeds up the formation of ATP by activating phosphorylations (NAKAHARA, YAMADA *et al.,* 1964) and thus improves the condition of the host in cancer patients (NIEPER, 1961). K-, Mg-aspartate is, therefore, marketed in combination with the cytostatic trioxymethylmelamine.

We have been studying since 1964 the various calcium preparations of the above listed electrolyte carriers, which are all — but at different sites — inhibitors of immune reactions and autoaggressive diseases and, therefore, extremely interesting from the clinical viewpoint. Moreover, they are more efficient than any drug we know in the treatment of osteoporosis, juvenile decalcifications, inflammatory decalcification, as a preventive of rheumatic joint deformations, and for the enhancement of the healing of bone fractures. According to investigations made by NAKAMURA (1966) the calcium carrier Ca-l-aspartate appears to be significantly more potent in the experimental treatment of artificial bone decalcification in rodents than the conventional calcium salts and anabolic steroids.

Three calcium transport preparations appeared to be particularly efficient against decalcification of bone tissue (NIEPER, 1968, 1969) :

(*) Presented at the Xth. International Cancer Congress, Houston, Texas, 1970.

— Ca-l-aspartate and Ca-dl-aspartate in a 50:50 proportion (Calciretard)
— Ca-2-aminoethanol phosphate (Ca-EAP), and
— Ca-diorotate.

Initially we had thought to use calcium carriers for the treatment of malignant bone destructions in man because of the results obtained by SELYE (1962) in his work on calciphylaxis. However, the phenomenon of calciphylaxis cannot be compared to the effect of the calcium carriers since the activity of the latter is related to a missive calcium transport principle, while calciphylaxis is based on acceptive calcium fixation following a specific artificial conditioning of an organ.

It appeared, therefore, interesting to try and see whether by both means, calciphylaxis and synthetic calcium carriers, a specific calcification of tumors could be obtained.

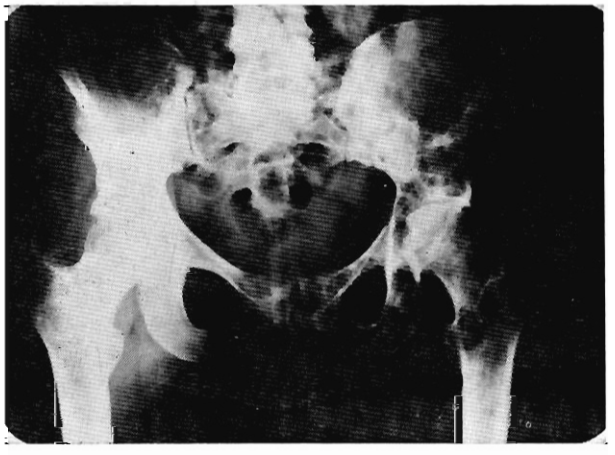
SELYE, TUCHWEBER and GABBIANI (1964) demonstrated in the rat that tumors are unable to break through tissue calcified after KMn04 - induced calciphylaxis. This wound mean that also an artificial calcification of the tumor bed could be of therapeutic value.

A slowing down of the bone invasion by the tumor and a hardening of the bone tissue surrounding malignant lesions were found by BIERMAN, WINER *et al.* (1969) after daily application of sodium fluoride in 14/50 patients. This again points in the direction that the therapy of active calcification can be useful in such cases.

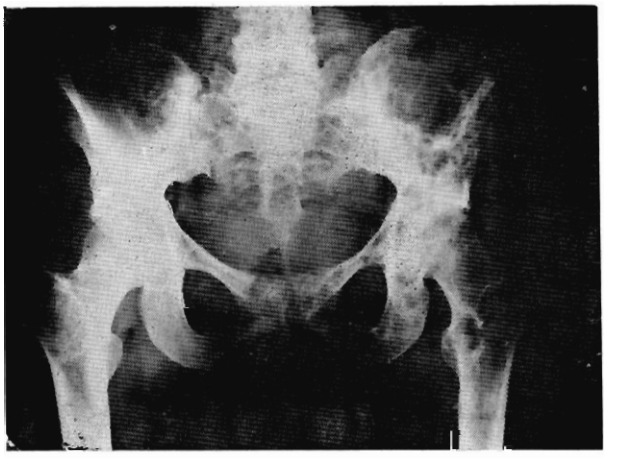
In the course of widespread clinical trial of calcium carriers we have also used them in cancer patients, especially in those with X-ray controllable bone metastases.

Our observations indicate that oral Ca-EAP as well as calcium-l, dl-aspartate have a certain positive action in the treatment of cancer patients since they prevent the general systemic decalcification in malignant disease (MYERS, 1960). The condition of 14/14 patients with spinal pain due to the calcification was much improved although in 10 of these cases the administration of conventional calcium glutonate, even when combined with anabolic hormones, had not produced any improvement. This parallels BIERMAN's observation who found anabolic hormones less active than sodium fluoride. Ca-aspartate and Ca-EAP, however, do not seem to have any effect on the development of bone metastases.

Following these observations, the results which we obtained with Ca-diorotate in the treatment of bone metastases appear quite surprising. Under good conditions, i.e. good renal function and good appetite, Ca-diorotate can immure bone metastases and lead to their recalcification. Moreover, decalcified areas produced by- X-ray treatment can also be recalcified. Such treatment consists in daily doses of 2 capsules containing 300 mg each, together

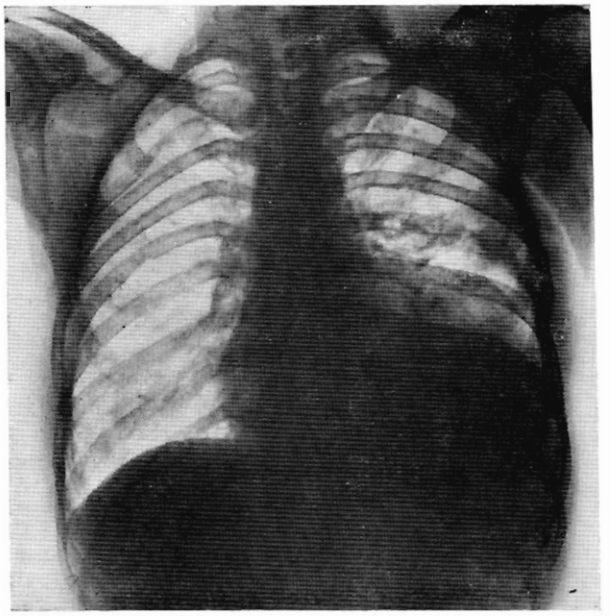


a) before treatment

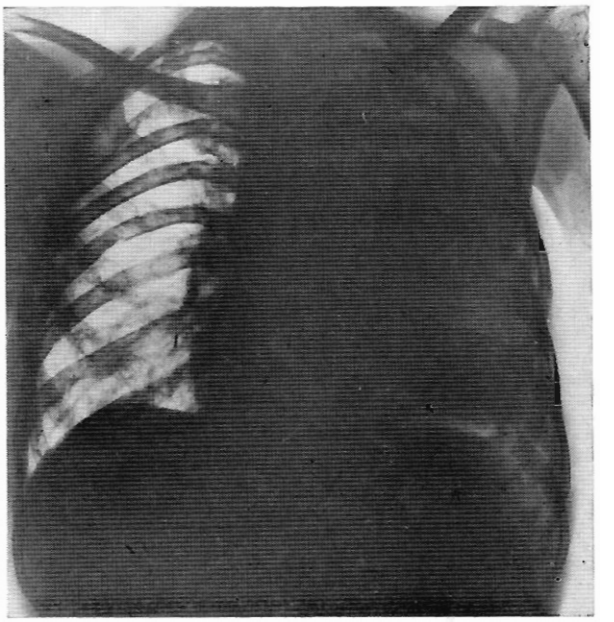


b) after treatment

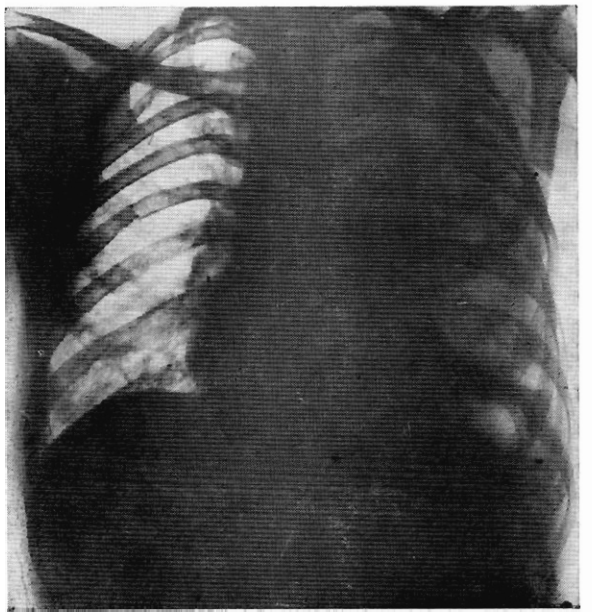
FIGURE 1. — Metastatic breast carcinoma, at age of 35 years. Surgery 6 years earlier. X-ray, telecobalt exhausted. X-ray castration 3 years earlier. No beneficial effect from a course of Cyclophosphamide, no effect from high doses of calcium gluconate plus anabolic hormones. Obvious relief for pain and tumor progression by atabrine and chloroquine (Rhetis Winthrop) and Allicine.
By Febr. 1969 pt. is bedridden, even unable to sit for severe pain. Admission to our hospital for imminent spontaneous fracture. Intake of 800 mgs of calcium diorotate per day together with egg yolk or cheese for better intestinal resorption, plus a total of XII suppositories of 800 mgs ca-diorotate each. 10 weeks after the onset of the Ca-diorotate thera py the pt. could walk almost normamly, was free from pain, went in car for holidays.



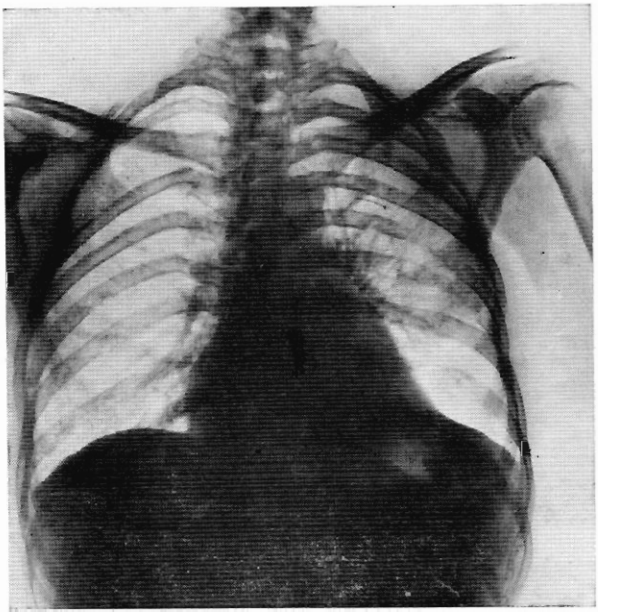
a) may 20, 1969.



b) oct. 6, 1969.

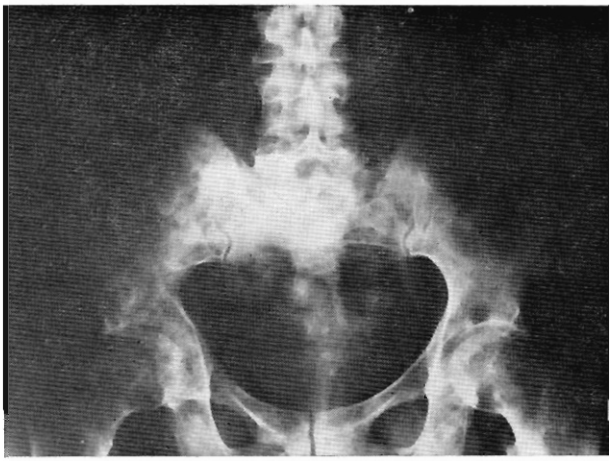


c) oct. 20, 1969 - after punct. of effusion, remaining solid pleura carcinosis.

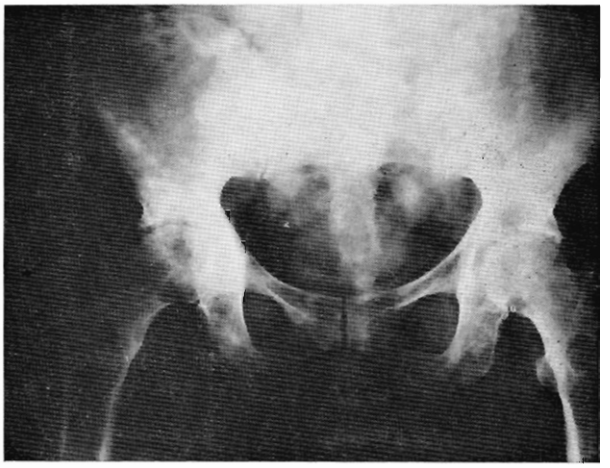


d) March 29, 1970 - same pt. after 5 mo. of oral Laetrile plus Ca-diorotate, 700 mg each.

FIGURE 2. — Same pt. as in figure 1. By Oct., 1969 she developed a pleura carcinosis with effusion. A part of the pleura carcinosis proved to be solid. After five months of continuous intake of 800 - 1 000 mgs. of amygdalin per day the pleura carcinosis had disappeared. Therapy with Ca-diorotate had been carried on all the time, no complaints from bone lesions. In March 1970 the pt. came again into hospital for obvious malignant lymphadenosis of mediastinum and lungs. High rates of pulse and respiration. One blood transfusion, three courses of 3 g of amygdalin intravenously, plus 200 mgs. of oral thiosulfate, Ca-diorotate still going on. Returns to home two weeks later in much improved condition and still is this way by July, 1970. After the i.v. injection of amygdalin the pt. excreted a marked amount of thiocyanate in the urine.



a) before treatment.



b) after 8 weeks of Ca-diorotate plus Ca-EAP i.v., plus oral Leatrile.

FIGURE 3. — Metastatic breast carcinoma, at age of 47. Mammectomy 5 1/2 years earlier. X-ray treatment exhausted, Cyclophosphamide, calcium gluconate and anabolic hormones without measurable benefit. Pt. almost unable to walk, need two sticks. Severe pain. After 600 mgs. of Ca-diorotate per day orally and 600 mgs. per day in suppositories sight improvement, but more pronounced improvement and relief for pain when 400 mgs. of Ca-EAP (Ca-2-amino-ethanol-phosphate) were given i.v. 3 times a week, and 150 mgs of Ca-EAP were incorporated into the suppositories in addition to Na-thiosulfate were given every day. Bay July, 1970, almost no complaints, walking almost normally without sticks, resuming work as administration official after 14 months of inability.

with egg yolk, or in suppositories containing 800 mg (Fig. 1, 2, 3).

While Ca-EAP and Ca-aspartate are initially fixed on the cell membrane, Ca-diorotate seems to pass through it and to become active only when it reaches the cytoplasmic structures. Whether this is the reason for the powerful recalcifying activity of Ca-diorotate on the bone matrix in e.g. osteoporosis has not yet been clarified. The recalcification process is limited to bone metastases, Ca-diorotate appears not to have any effect on soft tissue tumors. The immuring of bone metastases by Ca-diorotate seems to correspond to the above described experimental model presented by SELYE (1962), and parallels the findings of BIERMAN *et al.* In 10/13 cases with bone metastases we had a positive response.

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RÉSUMÉ

CALCIFICATION DE MÉTASTASES OSSEUSES PAR LE DIOROTATE DE CALCIUM

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Les transporteurs de calcium que sont le dl-asparaginate de calcium, l'aminoéthanol phosphate de calcium (CaEAP) et le diorotate de calcium semblent être les substances les plus actives dans tous les types de décalcification du système osseux. Ils sont supérieurs aux sels habituels de calcium et aux hormones anabolisantes bien que provoquant cliniquement moins d'effets secondaires. A la différence de l'aspartate de calcium et du CaEAP, le diorotate de Ca est capable de recalcifier les lésions osseuses malignes métastatiques et les décalcifications consécutives aux traitements par rayons X. Ce phénomène est interprété comme dépendant du mécanisme spécifique de pénétration cellulaire des sels de l'acide orotique. Alors que l'aspartate de calcium et le CaEAP sont toujours liés à, et peut-être métabolisés sur la membrane cellulaire, le diorotate de calcium la traverse par un mécanisme de transport actif sous forme non dissociée. Son métabolisme et donc sa dissociation seraient cytoplasmiques. Aucun effet secondaire n'a été observé avec le diorotate de calcium après utilisation de plus de 200 000 doses journalières en trois ans.

ZUSAMMENFASSUNG

REKALZIFIZIERUNG VON ENTKALKUNGSLEIDEN BEI CALCIUM-DIOROTAT

H.A. NIEPER

Agressologie 1970, **11**, 6 : 495-502

Die Calzium-Transporter Ca-l. dl-Asparaginat, Ca-2-amino-Aethanolphosphat (Ca-EAP) und Calcium- diorotat gehören zu den wirksamsten Substanzen bei der Behandlung aller Arten von Entkalkungsleiden des Knochensystemes. Sie sind konventionellen Calcium-Verbindungen und anabolen Hormonen in der Wirkung erheblich überlegen, jedoch an Nebenwirkungen geringer. Im Gegensatz zu Ca-Asparaginat und Ca-EAP ist Ca-diorotat in der Lage, maligne metastatische Destruktionen des Knochensystemes und Schadensfolgen von Röntgenbestrahlung am Knochen zu rekalzifizieren. Dieses Phänomen wird mit der besonderen komplexen transmembranären Transportfunktion der Orotate erklärt. Diese scheinen die Zellmembran als undissoziierter Komplex aktiv zu durchwandern, während Ca-Asparaginat und Ca-EAP breits innerhalb der Zellmembran bindende Reaktionen eingehen.

RESUMEN

DECALCIFICACION DE METASTASIS OSLAS POR EL DIOROTATO DE CALCIO.

NIEPER H.A.

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Los transportadores de calcio, que son el dl-asparaginato de calcio, el aminoétanol fosfato de calcio (CaEAP) y el diorotato de calcio, parecen ser las substancias más activas en todo tipo de decalcificación ósea. Son superiores a las sales comunes calcio y a las hormona enabolizantes y en cambio provocan menos efectos secundarios en la práctica clínica. A diferencia del asparto de calcio y de CaEAP, el diorotato de calcio tiene la capacidad de recalcificar las lesiones óseas malignas metastáticas y las decalcificaciones provocadas por irradiaciones X. Dicha acción se interpreta como propia del mecanismo específico de acción celular de las sales del ácido orótico. Mientras que el aspartato de calcio y el CaEAP se ligan y quizás metabolizan sobre la membrana celular, el diorotato de calcio la atraviesa en forma integra mediante un mecanismo de transporte activo. De modo que su metabolismo y su disociación se harian en el citoplasma. El diorotato de calcio ha sido utilizado durante tres años con más de 200.000 dosis diarias sin que haya ocasionado efecto secundario alguno.

КАЛЬЦИФИКАЦИЯ КОСТНЫХ МЕТАСТАЗ ДИОРОТАТОМ КАЛЬЦИЯ

Аспарагинат и диоротат кальция являются , по-видимому , наиболее активным средством лечения при декальцификации костной ткани . Они более активны чем анаболизирующие гормоны и обычно применяемые соли кальция . При этом не наблюдается побочных эффектов . В отличие от аспартата кальция и от CaEAP диоротат кальция вызывает рекальцификацию костных поражений , наступающих в результате злокачественных метастаз и рентгеновского облучения . Это действие связано со способностью солей оротиновой кислоты проходить через клеточные мембраны в недиссоциированной форме , в то время как аспартат кальция и CaEAP метаболизированы , по-видимому , клеточной мембраной . При применении этого вещества в течении 3 лет (200000 доз) авторы не отметили никакого побочного действия .