Professional Cardiovascular Articles

by

Dr. Hans A. Nieper

*Coronary Heart Disease and Symposium on Magnesium

*Electrolyte Transport Therapy of Cardiovascular Diseases

CM9

International Society for Infarct Control
Excecutive Offices: 7060 Schorndorf-Haubersbronn
Kastellstrasse 11

October 10, 1977

Circular letter 28

Coronary heart disease: Coronary super sufficiency ?
and not like assumed hitherto: Coronary insufficiency ?

Since now and then voices of caution have been heard against the use of Glucoside medication for coronary heart diseases and new infarcts, we are taking this occasion to once more present our scientific point of view in this connection.

Generally, it is assumed (as per the short course in the book "Internal Medicine", issued by G. Schettler, 4th edition 1976) that

> "the question in connection with severe coronary sufficiency according to theologic significance of the vascular lumen (4th potence) in most cases is about direct organic restriction of the coronary reserve down to the reduction of passive perfusion". "Further, it says: Through increased 0_2-extraction, only insignificant compensation can be attained."

However, what was measured by Cohen, Holmberg and Carlsten in reality ? (American Journal of Cardiology 1966, page 153 ff; 1976, page 486 and 492 and the pages following.)

1. During rest, instead of a lowered coronary blood flow (which does not rise through movement), a NORMAL coronary blood flow was measured (which increased through movement NORMALLY).

2. During rest and movement, instead of an intensified and increased oxygen extraction, a clearly REDUCED oxygen extraction was measured (in the blood of coronary veins there were increased values of – evidently unused – oxygen).

3. Instead of an anticipated evenly remaining LOW lactate extraction during rest and movement, there is a subsiding lactate extraction with higher production of lactate, i.e. a lactate softening.

Both facts,

1. the normal coronary blood flow during rest , which rises linearly during stress, and

2. a reduced oxygen extraction during rest and movement indicate, that instead of an anticipated coronary insufficiency there possibly may be a coronary super sufficiency.*

*Due to a regrettable printing error in Circular Letter 27, the words "Coronary super inefficienc printed instead of correctly: "Coronary Super Suffciency."

Further allegations, that a slow-down of the extramural coronaries would clearly follow after the 4^{th} potency of the stenosis radius, it would mean, that only 21.0% of remaining blood flow is attainable already at the remaining diamater of 70% - which is at a stenosis of 30%. In reality, however, it shows, that it takes a stenosis of 80% to really effectively reduce the flow and some Authors even claim it to be 90% .

Rau, Heberer and Loehr already did state in their book "Aorta and large arteries", why it has to be so. Relation to the 4^{th} potency of the stenosis radius exists only for those tubes, allowing free and unhampered drainage behind the constriction. However, since an artery and capillary bed with significant peripheral pressure resistance follows same, it is not the 4^{th} radius potency which becomes effective also accordingly to the law of Poiseuille, but it is the pressure gradient of the drainage tube! In addition, since according to Thoma (before 1923), Doerr (1975), U. Kreinsen (1971), Kern (1968) the extra mural coronaries, just like the remaining artery system, - as far as they athero-arteriosclerotically changed – are DILATATED but not stenosized (In most cases they become stenosized not until postmortal stiffness takes place with about $1/5^{th}$ of the diameter present during life!) (Doerr 1975: "Here in Heidelberg we are aware of dilatative athero-artisclerosis in aged people, but, indeed, outside of Heidelberg, it is not known!"), because, in other words, the coronaries are dilatated with Athero-Arteriosclerosis and therefore, the organic coronary insufficiency in general would belong to rarities.

In this direction, a re-orientation should be taken into consideration to the effect, that

1. the relative coronary insufficiency as hitherto assumed in coronary heart disease, is in reality a coronary super sufficency, and

2. that the hitherto assumed organic, or "atheromatheuse", coronary insufficiency is in reality a dilatative arteriosclerosis signifying consequently also an ORGANIC CORONARY SUPERSUFFICIENCY.

However, both of this means, that nothing shall be feared of g-Strophanthin in new infarcts or in coronary heart sickness. To the contrary, since we evidently have to do here with an 0_2 - utiliztion disturbance of the Myocard cell being favorably affected by Strophanthin (as it is attested to by measuring of ph-values by von Ardenne 1970/71, which quickly normalize), the use of Strophantin for coronary heart ailments as well as for new infarcts is, the same as ever, clearly indicated

SYMPOSIUM OF MAGNESIUM, Stuttgart-Hohenhein, Sept. 29-30, 1977.

During two days of meetings and 46 brief lectures presentations were made and discussions held regarding the Present stage of research in magnesium and its application. The scope of subjects included agricultural science of soil, plant physiology, animal physiology, animal medicine, human nutrition, human nephrology, sport medicine, human biology and pathology, with cardiological therapy being the highlight of the Conference.

The very small circle of participants and listeners amounting to not more than 65 people stood in no relationship with the significance of the material presented, in any way; however, we are convinced that the subject shall be presented before larger audiences in only a few months.

GENERAL BIOLOGY

From general biological viewpoints, magnesium is considered to be a catalyzer, due to the fact that there is a constant inclination for it to be joined with Adenosintriphosphate and form a complex of three teeth by which the ATP-molecule stabilizes and is stiffened and only by the fact that the molecule has been stiffened, one or two of Enzymes to be split (like: Muscel-ATPase at contraction, membrane-ATPase [Ion pump] by virtue of which finally the transfer of energy takes place.) (H. Rieder, Tutzing)

Syndromes of lack of Magnesium

Chronic lack of magnesium caused by nutrition, on one hand, has been characterized by a number of speakers as a widespread phenomenon among the population in general and on the other, as clear biological danger. This lack of Magnesium not only produces a large palette of generally vegetative symptoms (Matusczyk-Prien), which could then be well affected by magnesium therapy. The chronic lack of magnesium generally leads to increased cell membrane permeability and as a consequence hereof is followed by Ca- and Na-Influx, and, on the other hand, to K- and Mg-Efflux. Besides, due to lack of magnesium, proportionately increased catecholamine reaction is attained, and the cycle Adenosinemonophosphate is being activated, by which, again, membrane permeability is secondarily increased. This increased Katecholamine activity may be measured in urinary output. By affection of catecholamines (because they also agree with local Fibrocytes) there follows local stimulation of the collagen synthesis and Mucopolysaccharide synthesis. Impressive electronoptical pictures proved the propagation of collagen content (T. Guenther, Ising and Gelderblom, Berlin).

HEART GLUCOSIDES AND MAGNESIUM

Having taken g-Strophantine as an example, Krawietz and Erdmann (Giessen) showed that the affinity of the heart glucosides toward the heart glucoside receiver is increased through Magnesium. The Authors underlined that this had clinical relevance!

Magnesium, a necrosis prophylaxis?

Classen and Jacob (Hohenheim) showed us, that Magnesium-Aspartate-HCl during animal experimentation (female rats) with adrenic cardiopathy intensified by Ephedrin may considerably lower (up to 40%) the frequency of necrosis. Kahles (Goettingen) reported about interesting findings at the heart lymph during experimental myocardium ischemia (hearts of dogs). A lymph acts like a biological "amplification" system. It immediately indicates when and what Iones exit from the cardiac cell. Furthermore, we succeeded, shortly after Pharmacodynamic stress on the heart was effected by a cardial lymphsystem acting like a biological amplifier to establish significant Calcium losses of the myocardial cell.

Magnesium aspartate better than Magnesium salts.

Mr. Von Jagow (Munich) reiterated the statement which had been made known to us at the Baden-Baden meeting of the IGI (1973) by Ring (Frankfurt), that Magnesium Aspartate penetrates the cell membrane better than Magnesium salts and that therefore, Aspartates (supplementary by Nieper: especially also Orotates) find better therapeutical application than salts.

Coronary sclerosis does not cause lack of magnesium.

Interesting points of the report by G. Brandt (Erlangen) (post mortal Magnesium concentrations in myocardial And skeleton muscles, liver and the brain occurring in various basic human ailments) were that critical Magnesium loss in the tissue is typical for neurosis, but that coronary sclerosis does not cause any changes in the Magnesium value of the myocard!

Magnesium in cardiological general praxis.

Without any doubt, both of the therapeutic reports were highlights of the meeting. G. Schreiber, General Practitioner from Gluecksburg, reported about his first attendance of coronary and myocardiac Cardiopathy by Magnesium-Sulphate injections. (Schreiber attributed his choice of therapy, by the way, to a suggestion by Catel. Here are some excerpts from his own report: "More than 1000 injections of Magnesium salts during ambulant treatment as well as office visits for the purpose of controlling cadio-vascular ailments as a prophlaxis and first attendance of heart infarcts proved that Magnesium is a multi-applicable, unequaled specific matter without causing any side effects or interactions. In all of the 30 cases of infarcts treated in such a manner, an infarct death was prevented and infarct repetitions were blocked out. Of all the compounds, Magnesium Sulfate, 10 ml 10% within the substance and compounded, has proven itself to be the best and it is superior to other medicines." Already earlier, G. Schreiber had reported about his Magnesium experiences in heart therapy (1959 and 1972), and lately, he wrote in "The Practician," 12 (1976), page 2513-2520, with an adjoining fact: "Researchers in matters of coronary blood vessels were able to win most valuable scientific comprehension as to how infarcts occur, however, today the efficiency of therapeutic consequences could only little be estimated."

During the discussion about Schreiber, before all, Nieper agreed, who added, in support, that the findings of Schreiber only confirm such earlier ones by B. Mackie Shapiro 1956, Parsons, Butler and Selars, Agranat and S.E. Browne (Literary statements in circular letter 24!).

Lowering of infarct incidence through Magnesium.

The highlights of the Symposium was undoubtedly, Nieper's contribution: Lowering of infarct incidence through Magnesium-Orotate and K-Orotate in combination with Bromelain. The entire report is available, upon request, from : Brewer Science Library, 325 N. Central Ave., Richland Center, WI 53581. We also have a web page which is www.mwt.net/~drbrewer. Here, we may present to you only the following: Above mentioned authors, Parsons, Browne and others harmoniously agreed that daily injection (of substance) of 20-50ml of a 5-10% solution of Magnesium-Sulphate in groups of patients who could be called cases of severe instable Angina or post infarct angina and which is charged with an infarct mortality rate of over 22% in two years, has lead to a mortality rate of less than 2%. By this therapy, lowering of infarct mortality is of a dimension which exemplifies by biostatistic observation the limit of the absolute possible. These results, having been well remembered, were reported by different authors on different occasions, the largest collective emanating from Parsons and Hobart. The misinterpretation at that time was: Magnesium impeded inclination to thrombosis by which in turn coronary thrombosis were prevented, and therefore, the reports had been filed away for that episode, at that time.

We know today, based upon the myocadial "thinking example" about infarct – and inasmuch as the entire magnesium symposium at Hohenheim was built upon such mycardial example,- that the interpretations of that time were erroneous. Not until the new thinking process example came about could the empiricism of that time be understood! Nieper said literally: "We have to add that lysosomalic chain reaction (Kern and von Ardenne) must undoubtedly be regarded as being the main cause for myocardial necrosis and heart infarcts."

Comparing Nieper's own mortality rates with other collectives:

Cleveland Clinic (on first place, Nitratherapy and anti-coagulants)
2 years: 21%, 4 years: 36%

Rotterdam-study (Erkelens) (1550 patients with and without anti-coagulants without important statistical differences)
2 years: 19%, 4 years: 32%

Magnesium-Orotate & Potassium-Orotate plus Bromelain
2 years: below 2%, 4 years: below 2 %
N>135 N>75

Controlling testing is ethically not allowed here (in Germany).

During the discussion, Floerkemeier-Vallendar objected to the fact that Nieper's collective had not been compared with own collectives. Exclamations from the audience and Niepers' statement that this could not be done ethically brought the discussion to an end.

Infarct research by pathologists has been stimulated.

Interesting as background information was the remark made by Brandt (Erlangen), that the new thinking concept had lead pathologist to a feverish scientific activity, and that until now, infarcts had been regarded as a scientifically closed chapter. (we vividly remember the statement made by Doerr (Heidelberg) during 1975: "...my colleagues are not interested in infarcts".)

The new myocardial thinking process example of heart once more has passed an examination in the field of practical application.

ATHEROSCLEROSIS PROBLEMS

Recently, Professor Mohler of Zurich called our attention to some sections of a lecture by Prof. H. Luginbuehl of Bern (The Institute for Animal Pathlogy) which would be suitable to support "some of the Kern-vonArdenne thesis." We contacted Professor Luginbuehl and he was so kind to let us have a preprint of his lecture, which shall be published in the Fall 1977 under "Advances of Veterinary Medicine and Comparative Medicine." (Academic Press, New York)

Under the heading of "Comparative Atherosclerosis," H. Luginbuel (together with G.L. Rossi, H.L. Ratcliffe and R. Mueller) is presenting a comparative summary about the occurrence of Atherosclerosis as well as Atherosclerosssis in connection with Heart Ischemia and Heart Necrosis in dogs, pigs, rabbits, rats, house birds, as well as animals of the zoo. Today, Atherosclerisos is observed by customary criteria without taking into

consideration the facts stressed by R. Thoma and W. Doerr (i.e.: Firstly, Atherosclerosis is, intially, a Media-process not primarily but secondarily an Intima-process; and secondly Atherosclerosis eventually does not cause a constriction of the clear capacity of the vessels, but their dilatation!).

The only section conforming with our views (as far as emanating from B. Kern), is Cholesterine. Here is what the section says: "Cholesterine, with regards to its participation in the creation of Atherosclerosis is in a bad press. Stressing its initial role during this ailment process is of an opportunistic character, at least to some extent. Cholesterine is an easily manipulated parameter. If we compare the abundant literature available about Cholesterine-induced Atherosclerosis with factual knowledge about the cause contributed by this substance in Atherosclerosis, it becomes clear in our minds, that its dignity has greatly been exaggerated. Undoubtedly, the blood cholesterine speculum is an important parameter, however, it may be held, that low blood cholesterine does not protect against Atherosclerosis and that high blood cholesterine does not effect Atherosclerosis."

Professor Luginbuehl's test did not include horses. However, he surely is aware of the findings by Max Buerger, a veteran of Gerontology and Lipoid research, who had pointed out with fine irony, that HORSES do develop Atheromes to an excessive extent and that they are not fed with butter, bacon and eggs, however, with exactly such vegetarian lean food as generally recommended as an antidote against Atheromes...Most interesting, however, in Luginbuel's work there is the quotation of a statement by Barnes and Barnes (1972), that availability of Coronary Atherosclerosis and myocardial infarct usually appear together with low temperature causing hypothyroidism.

Luginbuel's findings pertaining to Cholsterine confirm with those of H. Schafer and M. Blohmke ("Heart disease through psychosocial stress," please compare our book discussion Circular Letter 26), who, based upon their own epidemiological field studies, had stated the following:

"The frequency of the classical risk factors CHOLESTERINE and REDUCED VITAL CAPACITY in the group of symptom carriers of coronary heart diseases is only very little increased. At the present, Cholesterine is being allotted too much significance still, to which fact Pincheerle (1971), Frank among others (1973), Weiss (1973) and Cochrane (1975) besides others are also calling our attention." (Page 165)

Experience and Practice

As a result of the Magnesium conference in Hohenheim we wish to again make reference to Dr. Nieper's recommendations pertaining to Magnesium doses (please also refer to Circular Letter 17).

It is interesting to note, that during the Magnesium conference at Hohenheim, Professor Leder of the Freiburg Institute Fleckenstein expressedly labeled Magnesium Therapy as a calcium-antagonisstic Therapy and further that Prof. Leder-still having been a student of Buechner – especially pointed out that lysosome were able to produce necrosis.

In advance it should be stressed, that Magnesium Therapy orally is recommended only for a current long-term treatment, however, not in case of an acute attack for which clearly the injection therapy by Schreiber-Parson-Brown with Magnesium sulphate (please read the Report about the Magnesium Conference at Hohenheim) is recommended. Besides, Nieper himself reports, that he perlingually combines his Magnesium Therapy often with Strophanthine. In our opinion, never should Strophanthine perlingually be forgone prior to and during an acute attack! (Strodival or Strodival Special, please read Circular Letter 27.)

Once more, here are Nieper's recommendations:

Doses of K-Mg-Aspartate as prophylaxis for myocardial recrosis, to reduce intrapulminal (Asthma and Hypercapnia), relieving the r. heart, and activation of the Cancer-Henseleit-Cycle (Decontamination of Ammonia and the reducing of CO2 through activation of carbamide urea synthesis):
as a rule 2 g daily, especially recommended as supplement or as an infusion. Otherwise orally. Doses of Mg-Orotate, as a rule 2.5-3 g daily, orally (5-6 tablets). It takes about 6-18 months to reach maximum improvement of vascular elasticity. This is the most effective substance for the treatment of Arthritis and Arteriosclerosis, and also very effective for Angina pectoris.

Small doses of Li-Orotate (for instance 60 mg daily) work synonymous by displacing cellular sodium.

Potassium-Orotate is experimentally for the idiopathic necrosis of the heart of a BIO-Hamster the most effective Monosubstance with regards to prophylaxis AND cure of necrosis.

Clinically, it is, before all, surpassingly effective, after a latent period of about 10-18 days. Doses, as a rule, 300 mg daily, only after an appropriate test, 600 mg daily. Mg-and K (Li-) orotates are the means of choice for the prevention and treatment of damages to the rhythmic center and impulse conducting system, because Orotates do have an affinity to the Pentose metabolism of this tissue.

Hans A. Nieper, M.D.

Additional Remarks:

In the accordance with the principles of our Society which cannot and may not tie itself down to a single remedy, any remedy is welcome that performs better with the myocardial thinking process of heart infarct than all the other therapies hitherto existing which base themselves upon the coronary principle of thinking. This is why we have, this time, reported in detail about Magnesium. As stressed in earlier Circular Letters, we recommend in accordance with the Fleckenstein requirement:

"No Glucoside without Calcium-Antagonists" to be administered, the best is Strophantine with Magnesium combined.

Electrolytes and Cardiovascular Diseases, ed. by E. Bajusz, Vol. 2, pp. 141–173
(S. Karger, Basel/New York 1966)

Department of Medicine, The Silbersee Clinic, Hannover and
Department of Medicine, Municipal Hospital, Aschaffenburg

Electrolyte Transport Therapy of Cardiovascular Diseases

Experimental and Clinical Basis

H. A. Nieper and K. Blumberger

Infarction of the myocardium is usually attributed to stenotic changes in the coronary circulation, but this assumption has been questioned. Direct and indirect pathological and clinical evidence now exist to indicate that myocardial infarct does not always presuppose an intense constriction of the coronary arteries. Coronary thrombosis is seen clinically in only one of every two infarcts (1). Even complete blocking may not induce infarction (necrosis) (2); however, in some cases, especially in relatively young individuals, the smallest clot in the intima may be associated with an infarct.

Statistical proof is also available that the danger and frequency of infarct do not depend solely on the changes consequent to aging. Although myocardial infarction has increased alarmingly in the general population in the past 10 years (2), and there has been a continuous rise in the number of infarct observed among our own patients (3), coronary scleroses have remained static. Hochrein (4) noted a more rapid increase in myocardial infarction in the male than in the female for the period from 1925 to 1954. These observations were confirmed by Gundersen (5) for 1925–1927 and 1954.

In individuals less than 50 years of age, the sex ratio for infarction was 7 males to 1 female (4). Only in patients more than 70 years old did the sex ratio become 1:1. In 1954 the sex ratio was still 2.1:1; but of a total of 148 infarctions in a series seen during the period from 1958 to 1961, 120 occurred in males and only 28 in females (81 and 19 per cent, respectively, or a ratio of approximately 4.3:1) (3). One statistical review (6) shows an over-all incidence of 77 per cent myocardial infarction in men and 23 per cent in women; at less than 50 years of age the incidence in men was 93 per cent. In persons less than

40 years old, myocardial infarction was observed 24 times as often in men as in women (7). The frequency of myocardial infarct in women increases only after the menopause. The relationship between the frequency of infarction and the nature of metabolic hormonal function has been the subject of comment (8, 9).

It appears, therefore, that the predominant basic etiology of a large proportion of myocardial infarcts, especially in men, may be functional rather than morphological.

On the basis of his findings in animal experiments, Selye *et al.* (10) suggested that metabolic insufficiency of the myocardium, involving myocardial injury in the presence of anoxia, and in the absence of occlusion, might of itself cause infarct, if not angina. The coronary thromboses he had observed in his studies of myocardial necroses produced by chemical means undoubtedly were side-effects, for the coagulant properties of necrotic tissue are well known. Certain conditions noted in other situations (11), in which death occurred from infarct consequent to electrically produced circulatory damage, also would point in the same direction.

Action of Electrolytes in Protection of the Myocardium

The protective action of potassium and magnesium chlorides against experimentally induced myocardial necrosis was originally demonstrated by Selye *et al.* (12). Such action appears to depend on the enduring activation, by magnesium ions, of the phosphatases and other esterases essential to cell metabolism, and on the protection, by potassium ions, of electrically disturbed cell potentials. Thus severe disturbances in oxidative cell metabolism caused by oxygen deficiency can be overcome, so that damage to structure and function of myocardial cells may be avoided.

There are, however, major contraindications to parenteral use of large quantities of potassium and magnesium chloride for patients suffering from myocardial infarction. Such treatment could lead to increased danger of depolarization of the myocardium through relative increase in concentration of extracellular potassium. On the other hand, too large doses of magnesium can lead to an undesirable decrease in blood pressure.

Only in the British literature are to be found extensive reports on the action of parenterally injected inorganic magnesium combinations

for treatment of myocardial infarction (13–17). The authors, however, did not use magnesium on the basis of the experimental results reported by SELYE *et al.*; they wished rather to derive therapeutic benefit from the somewhat minor antithrombotic activity of magnesium, and thereby obtain a degree of anticoagulant action. The results reported appear almost incredibly favorable. For instance, MALKIEL-SHAPIRO *et al.* (15a) quote PARSONS *et al.* (16) to the effect that 'over 100 patients suffering from coronary heart diseases (of which at least one third had acute myocardial infarctions) were treated with intramuscular magnesium sulphate with only one death', compared to their findings in the previous year when, of 196 cases admitted and treated with routine anticoagulants, 60 died. They conclude as follows: 'It is evident that the work of MALKIEL-SHAPIRO AND BERSOHN (15b)' 'has been confirmed'. Others have corroborated these reports (18, 19).

It is entirely unwarranted to attribute the protective effect of magnesium on the myocardium to a supposed antithrombotic action. Do statistical data not indicate that the cumarine derivatives, which are potent anticoagulants, lack such strong prophylactic value? The effects of the magnesium used in the patients described could have resulted from the action of the substance on cellular metabolism, which permitted the myocardial cells to overcome hypoxia more easily, with consequent prevention of necrosis. Such hypothesis would conform completely to SELYE's experimental findings.

It is imperative, however, to enable the potassium and magnesium ions to exert their activity intracellularly and be properly bound therein, which is a function of carbohydrate metabolism. Potassium is about 14 times and magnesium 6 to 8 times as concentrated in the cells as in the serum. This concentration is maintained by a complicated mechanism, the 'electrolyte pump'. In myocardial hypoxia, the electrolyte pump can easily fail, and the concentration of intracellularly bound potassium may be altered (20, 21). Ions can hardly cross the cell membrane without a special mechanism. KÖHLER (22) has experimented with an original method in which he employs ionotophoresis with a galvanic current through the left thorax to induce penetration of the myocardium by magnesium ions. The effect on angina pectoris, even in severe cases, is described as 'striking'.

If potassium and magnesium ions are to be readily transported to the intracellular environment in larger quantities, these cations must be bound to a molecule in a complex, or at least little dissociated form, which itself has a tendency to penetrate the cell. This led us to the

concept of active ion transport therapy (23). We have designated a series of agents that possess such a desirable property as electrolyte transport substances ('electrolyte transporters')—substrates capable of entering the cell and of freeing cations for metabolism within. Among the most important transport molecules known are the aminoacids.

One aminoacid, aspartic acid, was first selected by LABORIT to provide the anion for potassium and magnesium as potassium aspartate—$HOO\text{-}CH_2\text{-}CH(NH_2)\text{-}CH_2\text{-}COOK$—and magnesium aspartate—$HOOC - CH_2 - CH(NH_2) - COO - Mg - COO - CH(NH_2) - CH_2\text{-}COOH$*. To restore and/or maintain a physiological potassium and magnesium gradient, it is essential that cellular metabolism be adequate (24, 25) and aspartic acid was selected by LABORIT on account of its rôle in intermediary metabolism (26, 27).

Previous to the work of the French researchers, it had been difficult to apply SELYE's experimental concept to clinical use. Now, for the first time, it is feasible to administer suitable electrolyte therapy for cell hypoxia. We were the first to use clinically, and in Germany, potassium + magnesium aspartates within the framework of our concept of electrolyte transport therapy.

The potassium and magnesium aspartate had been prepared for us by KÖHLER in 1957. The combination had also been used in France experimentally, in the clinic and in private practice, to facilitate recovery from fatigue (28), to correct certain types of metabolic insufficiency, particularly hepatic (29), and for prophylaxis and therapy of angina pectoris and myocardial infarction (30, 31, 32).

Some Properties of Electrolyte Transporters Demonstrated in Pharmacological and Clinical Studies

L-aspartic acid is a normal constituent of proteins and consequently part of the normal diet. Since the preparation that we use clinically is a 50:50 mixture of the K and Mg salts of D,L-aspartic acid, in addition to pharmacological and clinical studies, it is essential

* The K and Mg salts of D,L-aspartic acid have been consistently used throughout the experimentations described in this article, except when otherwise mentioned. The preparation described as K + Mg aspartates is a 50:50 mixture of both salts.

also to demonstrate experimentally that this mixture possesses properties which cannot be duplicated by a simple mixture of L-aspartic acid with the potassium and magnesium salts of some other acids. The following is a review of the most significant pharmacological and clinical studies in our area of interest to this day.

Pharmacological Studies

1. Among the extensive pharmacological studies conducted by LABORIT *et al.*, these are the more important ones:

a) If a coronary artery of, for instance, the rabbit is ligated, a typical infarct is obtained; the electrocardiogram shows a pronounced ST depression. After injection of potassium aspartates, the tracing reverts to normal for a few minutes. On injection of a mixture of potassium+magnesium aspartates, the normalizing effect lasts an hour or more. The action of potassium aspartate is potentiated twenty-fold by combination with magnesium aspartate. Such potentiation is probably the result of more efficient binding of intracellular potassium (33). This was actually a discovery simultaneous to and independent of SELYE's (12) on this protective action of the K and Mg ions.

b) An isolated heart preparation functions for a few hours when it is perfused with an oxygenated Tyrode solution. Interruption of oxygenation leads to deterioration of cardiac activity within 90 seconds, but addition of potassium+magnesium aspartates in a 1:10 000 concentration enables heart contractions to last for 225 seconds (34). From this experiment, it appears that, under the influence of the aspartates, the myocardium can function better and longer with a minimum of oxygen. Several other experiments confirmed this hypothesis, particularly the return to normal, under the influence of the aspartates, of nitrogen metabolism in muscle and liver after toxic conditions or hypoxia (35, 36). An enduring improvement in experimental ammonia poisoning and hyperammoniemia has been confirmed (37, 38, 39).

c) A simple mixture of free aspartic acid with potassium and magnesium chloride will not produce the favorable result observed from the combined potassium and magnesium salts of aspartic acid (34, 37, 40).

2. TAPIN (41) studied also the action of potassium and magnesium aspartates on the isolated heart:

a) His study confirms the unique action of the combination of these salts in increasing resistance to anoxia.

b) Potassium+magnesium L-aspartates produce no demonstrable effect under the same experimental conditions.

3. LAMARCHE *et al.* (42) demonstrated clearly that:

a) *in vivo*, myocardium resistance to hypoxia as well as recovery time were markedly improved by potassium+magnesium aspartates.

b) Under the same experimental conditions, potassium+magnesium chlorides, and also the nicotinyl ester of diethylaminoethanol, failed to show the same effect.

4. Finally, in the United States, H. ROSEN *et al.* demonstrated:

a) An increase in resistance to anoxia of the isolated heart under the influence of potassium+magnesium aspartates (43);

b) the impossibility to duplicate this effect with sodium aspartate, sodium+magnesium aspartate or potassium+magnesium chloride.

c) The same author in another experiment aimed at showing the effect of potassium+magnesium aspartates on ammonia intoxication in the rat, showed that optical activity plays a rôle in the protection obtained. *L*-potassium aspartate was as active as the racemic form. However, in this particular experiment, it was shown that for the magnesium salt, the *D*-component accounted for the activity (44).

Biochemical Studies

We were able to demonstrate in clinical studies (23) the action of potassium+magnesium aspartates in normalizing metabolism in the presence of deficient cellular oxidation. A useful method of measuring oxidative activity is the determination of pyruvic acid/lactic acid ratio (PA/LA), since these two substrates can be considered a redox system (45). The ratio is normally 0.075 (45). In the case of hyperthyroidism, it is increased. After prolonged therapy with cardiac glycosides, the ratio may decrease markedly. Administration of potassium+magnesium aspartates causes a rise toward normal (23), as illustrated in figures 1, 2, 3 and Tables I and II. This is an indication of improvement in cell oxidative activity (46). The fact that the decrease in the PA/LA ratio caused by protracted cardiotonic glycoside therapy does not have an unfavorable dynamic effect on the heart is to be emphasized, as discussed in detail elsewhere (23). A favorable effect has been demonstrated recently in the animal by GREEFF (47), who showed that

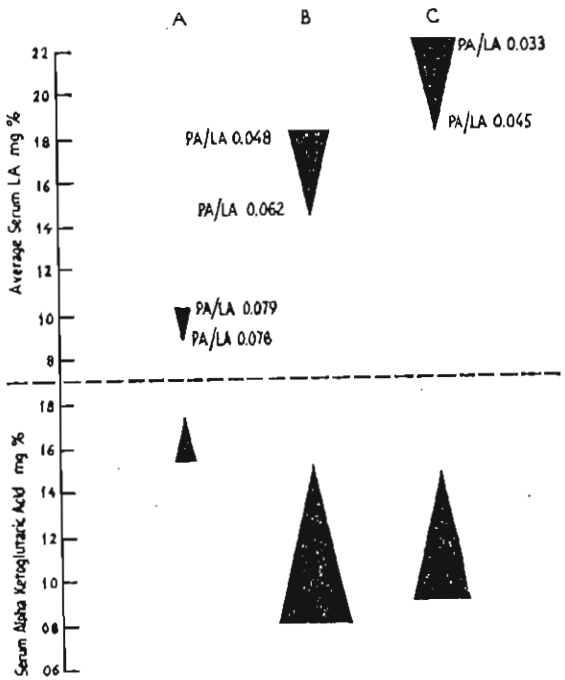

Fig. 1 Average serum pyruvic acid/lactic acid (PA/LA) ratio of patients 1 hour after intravenous injection of 1 gm potassium and magnesium aspartates under BMR conditions. A. Untreated with cardiac glycosides. B. Pretreated for 8 weeks with ouabain, 0.25 mg daily. C. Pretreated daily for 8 weeks with digitoxin, 0.5 mg orally. (Direction of arrows indicates direction of change.)

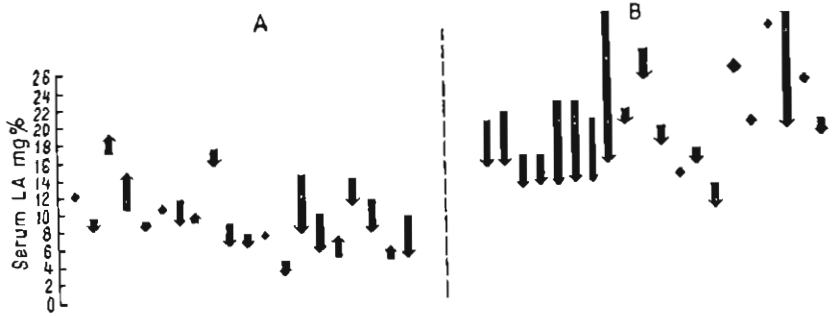

Fig. 2 Serum lactic acid (LA) levels of individual patients 1 hour after intravenous injection of 1 gm potassium and magnesium aspartates under BMR conditions. A. Untreated with cardiac glycosides. B. Treated daily with digoxin, 0.5 mg orally.

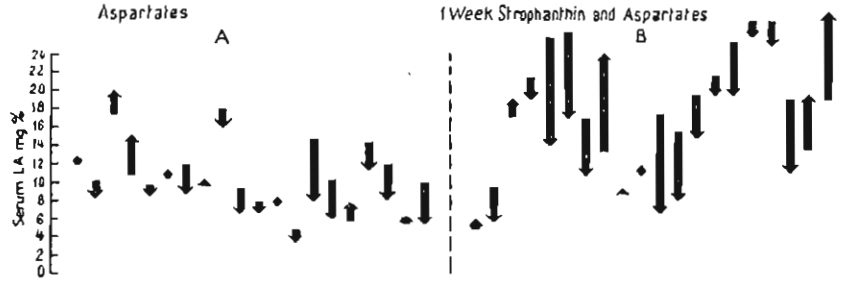

Fig. 3 Same experimental conditions as in Fig. 2, except that group B was treated with strophanthin.

the 'true' tolerance, i.e., tolerance range to ouabaine at equal efficiency level, is increased by about 50% by the administration of potassium +magnesium aspartates. This is also true for digitalis. Under the same experimental conditions, however, potassium+magnesium chlorides here again failed to show a similar effect.

Treatment with the aspartates causes an increase in the serum concentration of alpha-ketoglutaric acid, a condition that points to acti-

Table I

Summary of Changes in Average Values for Serum LA (Lactic Acid), PA (Pyruvic Acid), PA/LA Ratio and KA (α-ketoglutaric Acid) under the Experimental Procedures shown in Figs. 2 and 4

	A	B
LA initial value	10.3 mg%	22.3 mg%
K and Mg aspartates (after 1 hour)	—1.25 mg%	—4.1 mg%
PA initial value	0.82 mg%	0.75 mg%
K and Mg aspartates (after 1 hour)	—0.135 mg%	+0.06 mg%
PA/LA initial value	0.079	0.0326
K and Mg aspartates (after 1 hour)	0.076	0.045
KA initial value	0.153 mg%	0.088 mg%
K and Mg aspartates (after 1 hour)	+0.02 mg%	+0.057 mg%

A. Patients untreated with cardiac glycosides, as in Fig. 1.
B. Patients pretreated with digoxin, as in Fig. 1.

Table II

Summary of Changes in Average Values for Serum LA (Lactic Acid), PA (Pyruvic Acid), PA/LA ratio and KA (α-ketoglutaric acid) under the Experimental Procedures shown in Figs. 3 and 5

	A	B
LA initial value	10.3 mg%	18.1 mg%
K and Mg aspartates (after 1 hour)	—1.25 mg%	—3.47 mg%
PA initial value	0.82 mg%	0.875 mg%
K and Mg aspartates (after 1 hour)	—0.135 mg%	+0.033 mg%
KA initial value	0.153 mg%	0.078 mg%
K and Mg aspartates (after 1 hour)	+0.02 mg%	+0.074 mg%

A. Patients untreated with cardiac glycosides, as in Fig. 1.
B. Patients pretreated for at least 1 week with ouabain, as in Fig. 1.

vation of the tricarboxylic acid cycle (Figs. 4 and 5). On the other hand, we have also observed that free aspartic acid, and potassium and magnesium chloride show no activity in several of these metabolic tests.

Using similar tests, we have also studied recently potassium+mag-

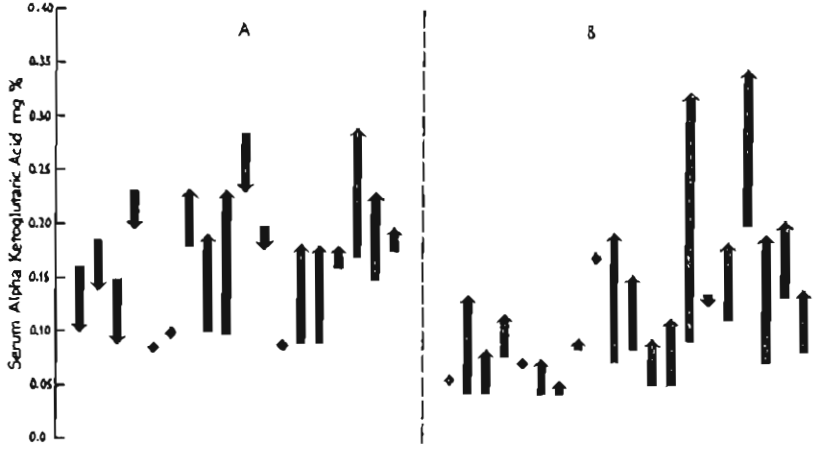

Fig. 4 Individual variations of serum alpha ketoglutaric acid (KA) under the same experimental conditions as in Fig. 2. (Arrows indicate individual observations.)

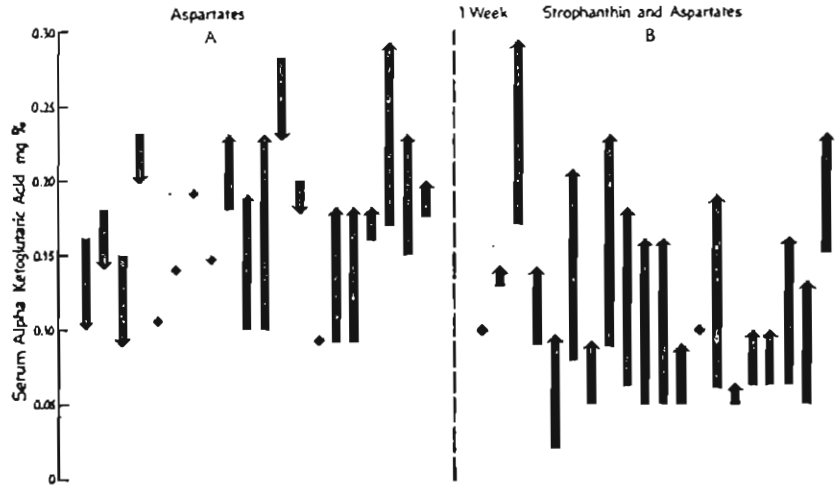

Fig. 5 Same experimental conditions as in Fig. 4, except that group B was treated with strophanthin.

nesium nicotinyl-aspartates (48). On acute administration to man, these new electrolyte transporters appear particularly active. Similar or even greater effects were obtained with a dose half that of potassium+magnesium aspartates used in our other experiments*.

Another electrolyte transporter that we have developed, potassium and magnesium 2-amino-ethyl phosphate (AEP), also modifies the PA/LA ratio toward normal, but has no influence on the alpha-ketoglutaric acid level (49).

Clinical Aspects of Determination of Serum Electrolyte Levels

Since myocardial necrosis is not solely and directly related to disturbances of coronary blood flow, and such necrosis can be avoided by furnishing the cells with potassium and magnesium, the question arises as to whether potassium and magnesium depletion of the myocardium may result in an 'infarct liability', and be the cause of more or less pronounced angina pectoris.

In living tissues, it is practically impossible to determine intracellular potassium and magnesium levels, especially in the myocardium. The electrocardiogram is often used to establish the diagnosis of cardiac potassium depletion (50), but our observations have shown that

* The same degree of greater potency is demonstrated also in muscular fatigue in the rat swim test.

this method is unreliable. It has been noted that the extreme hypokaliemia produced by sodium 4-hydroxybutyrate anesthesia causes only minor flatenning of the T wave (9, 51). In our cardiovascular laboratory, we were unable to determine any electrocardiographic changes in a large series of patients with severe hypokalemia, whereas in other patients with so-called 'normal' serum potassium levels, T wave flattening occurred that could have been regarded as the result of potassium depletion. This essentially disappeared after treatment with electrolyte transport substances. The ECG, therefore, seems little qualified for evaluation of intracellular potassium concentration in the myocardium. Possibly the ECG is rather an indicater of the 'gradient', i.e., the steepness of the difference between intra- and extracellular potassium levels. It becomes, therefore, the task of the clinical laboratory to detect intracellular potassium depletion, as far as this is possible.

The theoretical process of *chronic depletion* of intracellular potassium is perhaps reflected only in a minor decrease in serum potassium (52). The significance of such reduction in serum potassium is based on a) a well defined range of normal values, and b) efficient technical control of electrolyte determinations, which necessitates the use of good equipment (1). (We employ a Beckman DU spectrophotometer with hydrogen and oxygen flame, and an Eppendorf high precision flame photometer.)

In our investigations of the normal range of serum potassium, we have encountered reports that give rise to question. For instance, the Geigy tables, in line with the work of JEANNERET *et al.* (53), indicate the normal range for serum potassium as 16 to 22 mg per 100 ml (4.1 to 5.6 mEq), and the *average value* as 20 mg per 100 ml. But in GAUSS' view, the normal value must be 'normal' in the strictest sense of the word, i.e., have a symmetrical distribution. Accordingly, the average value must be situated in the middle of the normal range. As far as sodium and calcium are concerned, JEANNERET *et al.* indicate values that agree with this concept (314 to 326 mg, average 320 mg, per 100 ml, for sodium; and 9.5 to 10.5 mg, average 10 mg, per 100 ml, for calcium). The indicated distribution is asymmetrical only for potassium. If a symmetrical distribution is made around the average value, the lower limits of normal distribution for normal values would be about 18 mg per 100 ml. The stated range of 16 to near 18 mg per 100 ml could no longer be considered as 'normal'. We must assume that these authors unintentionally had included in

their statistics diseased as well as healthy individuals who actually suffered potassium depletion with corresponding symptoms, the genesis of which was unknown. It is, therefore, necessary to be familiar with all diseases and symptoms related to increase or decrease in serum potassium, and to eliminate these from the statistical sample before determination of the normal range. Both determinations would have to be undertaken separately in each laboratory to insure accuracy.

Increase in serum potassium can occur in: acute renal insufficiency, liver disease (sometimes), adrenocortical deficiency, after acute cellular and tissue necrosis and (rarely) after severe, usually acute overdosage with digitalis. (In the last two instances, the potassium originates from the necrotic cells, as in acute myocardial infarct or digitalis damage. In such cases, nevertheless, there is depletion of intracellular potassium.)

Decrease in serum potassium is observed most often in: patients, especially the relatively young, who already have a history of myocardial infarction; all (parasympathetic) disturbances in transmission of cholinergic stimulation (gall bladder and bile duct dyskinesia, dry mouth, disorders of the gastrointestinal tract and its glandular appendages, and symptoms often referred to as 'autonomic dystonias', or sphincter spasms seen mainly after operation); normocalcemic tetany, hyperthyroidism; after major operation and traumatic shock; in prolonged, especially diabetic, acidosis; after major fluid loss through edema or vomiting; and to a varying degree, after use of nearly all the usual diuretics.

For determination of the normal range of serum potassium, we eliminated all such cases from our statistical sample. Altogether, 600 serum potassium determinations, extending over exactly 12 months, were made for this study.

Grouping of each of the 30 'normal' determination made in our laboratories during the spring, summer and autumn of 1961 yielded the following ranges for normal values:

Spring, 1961	19.2 mg% $\pm$ 1.3 mg%,	from 17.9 to 20,5 mg% K
Summer, 1961	19.3 mg% $\pm$ 1.5 mg%,	from 17.8 to 20.8 mg% K
Autumn, 1961	19.4 mg% $\pm$ 1.6 mg%,	from 17.8 to 21 mg% K

In all cases the indicated values satisfactorily followed a symmetrical normal distribution. The indicated normal ranges correspond to the double sigma thus calculated:

$$\pm 2\sqrt{\frac{\Sigma \Delta 2}{n-1}}$$

The lower limit of 17.8 mg per 100 ml for the normal value of serum potassium also could have been approximately established from the average values quoted by JEANNERET's group (53), if they had calculated in on the basis of a symmetrical distribution.

We have an additional reason to believe that a value of 17.8 mg per 100 ml for serum potassium corresponds to the lower limit of normal. In many cases, we have observed that various conditions associated with hypokalemia, especially gall bladder dyskinesia and angina pectoris, disappear when the serum potassium is raised to about 18 mg per 100 ml during treatment with electrolyte transport substances. We believe, therefore, that a few days of electrolyte transport therapy will lead to an increase in intra- and extracellular potassium in physiological proportions. To supply ordinary potassium derivatives or highly dissociated potassium combinations would first cause an excessive one-sided loading of the extracellular environment with potassium. In view of this whole picture, an increase in serum potassium is difficult to evaluate.

Patients less than 50 years of age who have suffered angina pectoris, severe or mild, some of whom already have had myocardial infarction, and some, a tetany-like dyskinesia or other autonomic nervous system disturbances in addition, have shown the following average serum potassium levels (groups of 30 patients):

Spring, 1961	15.8 mg%
Summer, 1961	16.4 mg%
Autumn, 1961	16.3 mg%

The symptoms described, therefore, are associated on the average with a significant reduction in serum potassium. Such conditions also would indicate that with a decrease in serum potassium below 17.8 mg per 100 ml (4.5 mEq), the danger of infarction increases. This is especially important in young and middle-aged men.

Techniques

In the light of the information developed in our laboratory, and in others, some little known yet, apparently important, technical characteristics of electrolyte and especially potassium determinations have emerged. Since the erythrocytes contain considerably higher concentrations of potassium and calcium than the serum, a minor hemolysis may lead to a false rise in serum potassium. All causes of hemolysis, therefore, must be avoided. No blood foam should be present in the

collection tube; the blood-taking syringe must be carefully emptied vertically and stopped before foam is expelled. Centrifugation and separation of the serum must be performed within 30 minutes after blood-taking. We disapprove of processing whole blood received from outside. We have noted that the normal values of measurements on such blood samples made in some laboratories do not follow any normal distribution, and are probably erroneous; i.e., in many cases, too high.

Clinical Application of Electrolyte Transporters in Cardiology

Results of the Therapeutic Use of Potassium and Magnesium Aspartates

In view of the results obtained in experimental investigations, it would appear that the most important indication for use of the potassium+magnesium aspartates is the treatment and/or prophylaxis of metabolic disturbances of the myocardium, especially those associated with hypoxia, such as disorders of the coronary circulation. Reduction in intracellular concentration of potassium characterizes such cases and is reflected in a minor but, we believe, significant decrease in serum potassium.

I. Chronic Treatment of Primary Angina Pectoris or Subsequent to Myocardial Infarct

Electrolyte transport therapy was initiated between October 3, 1960, and May 10, 1961, for 84 potential victime of primary or secondary infarction (54 men, 30 women, 30 to 83 years old), who were suffering angina pain, either primary or subsequent to previous episodes of myocardial damage. Twenty-one had had infarcts more than six weeks previously. Treatment with the aspartates in total daily doses of 1 to 1.5 gm doses, that we regard now as minimal, was administered for periods up to 18 months.

In 80 per cent, the therapeutic response was more satisfactory than in our previous experience with conventional long-term therapy, and was comparable to the result achieved by KÖHLER (22) with magnesium iontophoresis. Clinical improvement (reduction of chest pain and increase in exercise tolerance) consequent to restoration of a nor-

mal intracellular medium generally occurred in 2 to 4 days. An example is the youngest patient in the series, a man of 30, who had had an anterior infarction. He was still suffering chest pain at the beginning of aspartate medication and his serum potassium level was 15 mg per 100 ml. The serum potassium concentration returned to within normal limits, according to our criteria, early in the course of treatment. At the present time, 2 years after initiation of therapy, he is symptom free.

Myocardial infarction of the posterior wall occurred in one of the patients who failed to respond more satisfactorily to this than to standard medication. The course, however, was favorable, and he is now well. Despite treatment, acute coronary pain developed in six who had a history of infarct, but in none could the presence of further infarction be proved by electrocardiogram, leukocyte count or serum glutamic oxalocetic transaminase tests. All became symptom free in a few days. According to HARTERT's extensive investigation (54), 5 to 7 infarcts or recurrendes of infarct should have been observed in a comparable group of patients under conventional medication, and within the same period of time.

Among the failures were two fatal cases: In one, the patient, a man of 83, died of cerebral hemorrhage. In the other case, that of a 48 year old hypertensive male alcoholic, the patient had had two large infarcts, and during treatment exhibited a slowly progressive myocardial failure. Although an extremely severe coronary arteriosclerosis and cardiac enlargement 40 per cent in excess of the critical dimensions were demonstrated at autopsy, no new areas of necrosis were detected, with the exception of a few isolated cells.

These therapeutic results are particularly encouraging in view of the extremely low toxicity potential of the compound and the low doses administered*.

Because of some difficulties in the follow-up of out-patients, our observations were discontinued by the fall of 1962. Meanwhile, extensive clinical trials were initiated in a number of important continental hospitals. Preliminary results appear encouraging and confirm our cardiological observations.

* In certain cases, especially of angina pectoris, rectal administration of the aspartates may be found more efficacious, perhaps because absorption from the rectum may be more efficient than from the duodenum. We have employed suppositories containing a total of 1 gm of the active substances. Daily doses of 2 suppositories have been tolerated for several weeks with practically no irritation.

An important symptom of coronary insufficiency conditioned by myocardial hypoxia is a disturbance of repolarization, with potassium depletion, after each contraction. Cellular repolarization is identifiable by a rapid accumulation of potassium after contraction. Abnormal return of excitability is indicated on the ECG by flattening of the T wave. Improvement in myocardial metabolism leads to improvement in repolarization, as indicated by increased steepness of the T wave.

Aspartate therapy is effective also when the serum potassium concentration is not lower than normal, but depletion of cellular potassium may be expected. Observations made over many months showed uniformity in the return of excitability. The pain of angina pectoris subsided almost completely after aspartate therapy.

II. Acute Treatment of Myocardial Infarct and of Severe Angina Pectoris

The pharmacological and clinical properties of K+Mg aspartates discussed above; the very good tolerance of the injectable preparation, as demonstrated by a) the study of LABORIT *et al.* (55) in normal patients receiving up to 4 gm as a slow i.v. perfusion in 10 per cent glucose; b) the work of WEBER (56) in a large number of burn patients with hypokaliemia, using doses up to 20 gm in 24 hours in slow i.v. perfusion with 15 per cent glucose (in two cases to a total of 91.5 and 93 gm respectively over 7 and 6 days); c) the routine use of high i.v. doses in hepatic coma and gall bladder surgery (6 to 12 gm daily in over 2000 cases) (57); and finally, our own extensive experience in the treatment of cancer and of certain cardiopathies in application of our concept of electrolyte transport therapy, all contributed to induce many investigators, both in Germany and in France, to study also the application of the injectable form of K+Mg aspartates more specifically in the acute and subacute treatment of myocardial infarct and of severe angina pectoris.

TAPIN (41) undertook a study on 45 recent myocardial infarcts. Treatment began upon admission. Twenty-five cases were used as controls (receiving the classical treatment with anticoagulants), and the 20 remaining cases received in addition 2 gm/day of K+Mg aspartates in their regular i.v. perfusions. When these regular perfusions were discontinued, oral therapy was installed (2 gm/day also). Follow-up was from a minimum of 6 months to a maximum of 2 years.

Although by our present standards (5 gm/day), the doses of aspartates used were quite low, the treated group, as compared to the con-

trols, showed considerable reduction of pain within the first 24 hours (in most cases without the need for analgesics and narcotics), clear reduction of anxiety and of agitation, more rapid EEG improvements and a more rapid drop in serum GOT. There were 8 deaths in the treated group against 14 in the control group, but this latter difference cannot be conclusive since the series was too small. When the absence of sequellae is considered, however, the treated group again did significantly better, showing 9 complete recoveries (45 per cent) against 2 (8 per cent) in the control group.

PILLEN (58) applied our concept of electrolyte transport therapy in the treatment of 23 myocardial infarcts. Patients received two or three daily injections of 1 gm of K+Mg aspartates, as a single dose or as a perfusion during the first 10 to 14 days following admission. Thereafter, oral treatment was applied in doses varying from 1.5 to 3 gm/day. Tolerance was excellent.

In his evaluation of results, this author used similar criteria as TAPIN (41) although his study did not include a control group. There was a total of five deaths within 6 days after the infarct (temporary improvement in three). Three had had earlier posterior wall infarct, one had hypertension, diabetis and a brain embolism, and one, a recurrent extensive posterior wall infarct.

As a whole, there were: 4 excellent results with rapid disappearance of stenocardiac pain, psychic and motor sedation, and no need for sedatives and analgesics; 12 good results, where the improvements were more progressive, and where sedative and analgesic requirements were definitely lower than with other forms of therapy; and 3 unsatisfactory results in whom the condition worsened.

The ECGs showed that the typical myocardial infarct changes usually observed were often relatively little pronounced in the course of the treatment. A very good illustration of the effects of the aspartates on the ECG is given in figure 6, using the patient as his own control.

According to the author's experience, better results were obtained with this therapy than with any other K and Mg salts, and when treatment was initiated as early as possible; the author, therefore, recommends immediate i.v. treatment by the family doctor before hospitalization, and also higher daily doses (4 to 5 gm).

In the course of the extensive clinical testing of the validity of our electrolyte transport therapy concept, we were repeatedly called to witness the efficacy of the K and Mg aspartates intravenous therapy

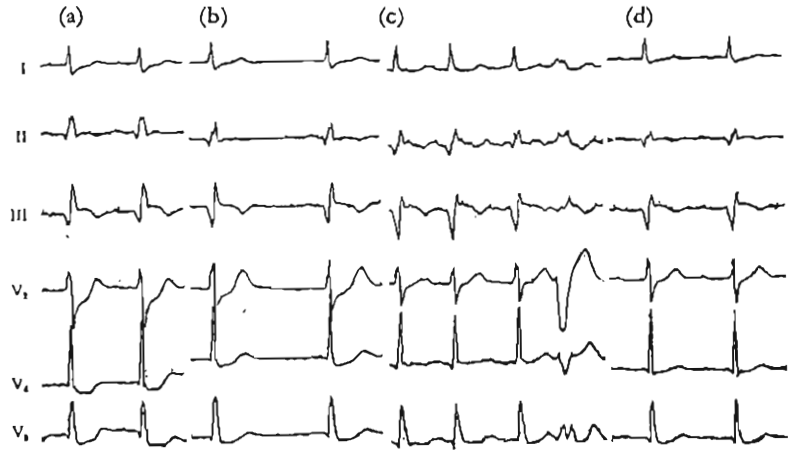

Fig. 6 Fresh posterior wall infarction (a). After immediate K+Mg aspartate therapy, 4 gm daily, the ECG shows a marked decrease of frequency on the following day (b). No cardiotonic glycosides. Therapy with 4 gm of K+Mg aspartate daily for 5 consecutive days, then supplies ran out. Two days after discontinuation of therapy, the ECG shows again a serious increase of frequency, infarct pattern and ventricular extrasystoles (c). ECG residual stage after two months (d). (ECG by courtesy of Dr. PILLEN, Mannheim).

in patients suffering from acute or subacute angina pectoris. Some of these patient, in addition, suffered from cancer or were under cardiac glycoside treatment. In a large number of cases, even a single 2 gm intravenous injection had a beneficial effect on symptoms and on

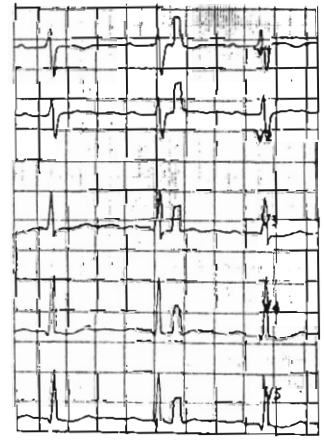

Fig. 7 Female, 55. Cancerous disease and angina pectoris. Serum K: 17.1. No glycoside treatment.

electrocardiographic signs of myocardial hypoxia. In severe cases, however, we used prolonged aspartate therapy. Figures 7, 8, 9, 10, 11 and 12 illustrate some of the results obtained.

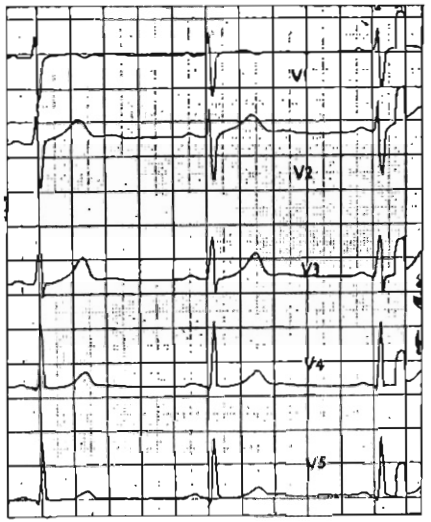

Fig. 8 Same patient as in Fig. 7, after i. v. injection of 2 gm of K and Mg aspartates. Serum K: 17.5. Still no glycoside treatment.

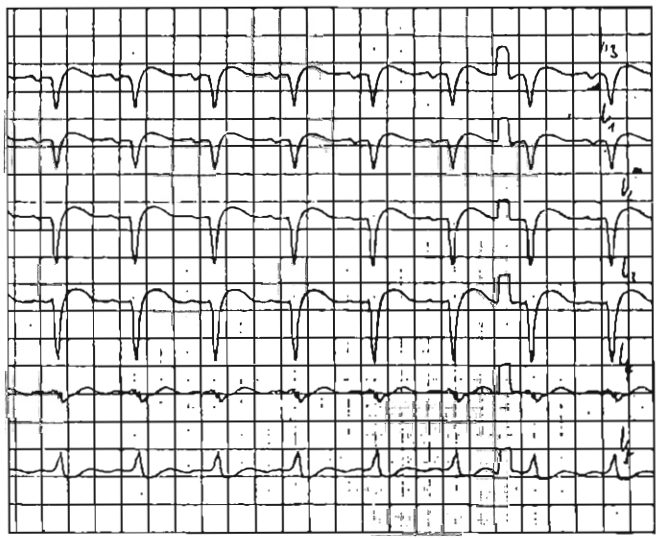

Fig. 9a (legend see p. 160).

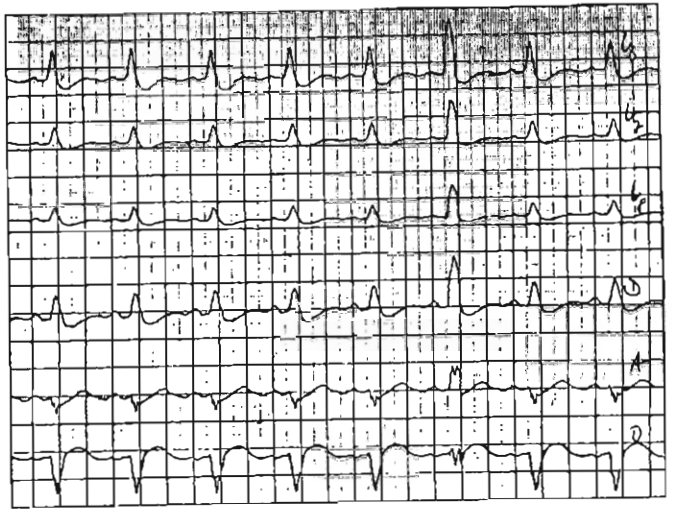

Fig. 9b

Figs. 9a and b Female, 65, diabetic. Hypokalemic ECG. Serum K: 12.3 mg%; Na: 310 mg%.

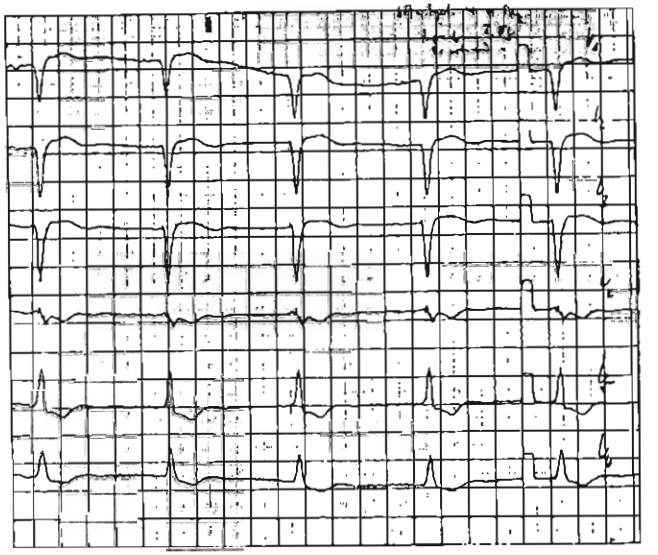

Fig. 10 Female, 65, diabetic, same as Fig. 9. After intravenous administration of 2 gm of Mg-K aspartate, complete disappearance of the hypokalemic pattern of the ECG could be observed for about 10 minutes. After 16 minutes, the ECG was almost of the same hypokalemic type as before treatment. Here 4 min after injection, typical glycoside ECG. Decrease of frequency. No signs of hypokalemic ECG. This effect has been achieved by the injection of 2 gm of M-K aspartate

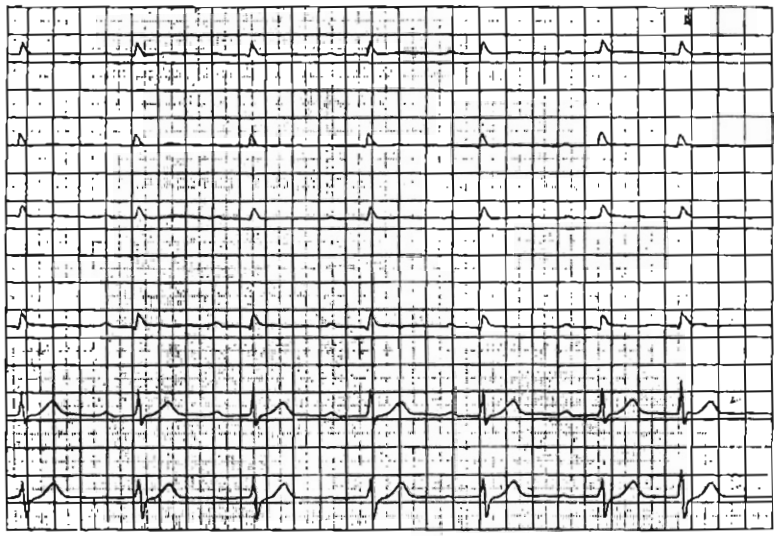

Fig. 11a

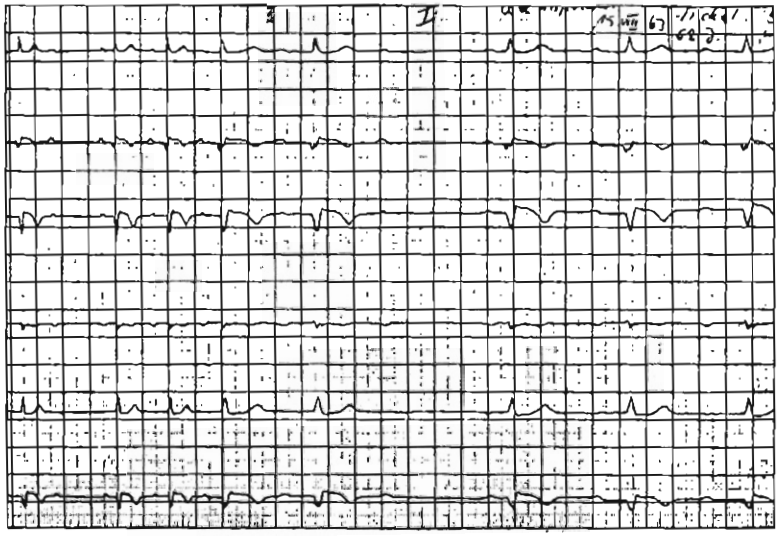

Fig. 11b

Figs. 11a and b Male, 62, EKG 8. 15. 63. Posterior infarction exactly 4 days old. A-V-dissociation of the Wenckebach type. Serum K: 21.4 mg%, Na: 332 mg%, slight serum electrolyte disturbance.

which represents only 206.6 mg of potassium. This is a very small dose compared with the potassium deficiency of this patient (12.3 mg% = 3.1 mval.). This particular activity shown on electrogenesis (perhaps at the level of the myocardial cell membrane) may be due to the specific transport mechanism involved. These cases indicate that K + Mg aspartates should be administered slowly over a long period of time. This is an important factor which leads to slow intravenous drip.

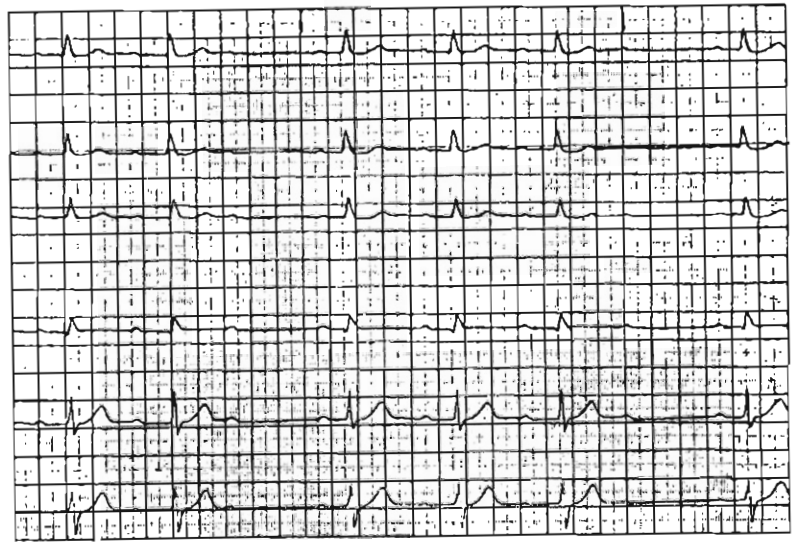

Fig. 12a

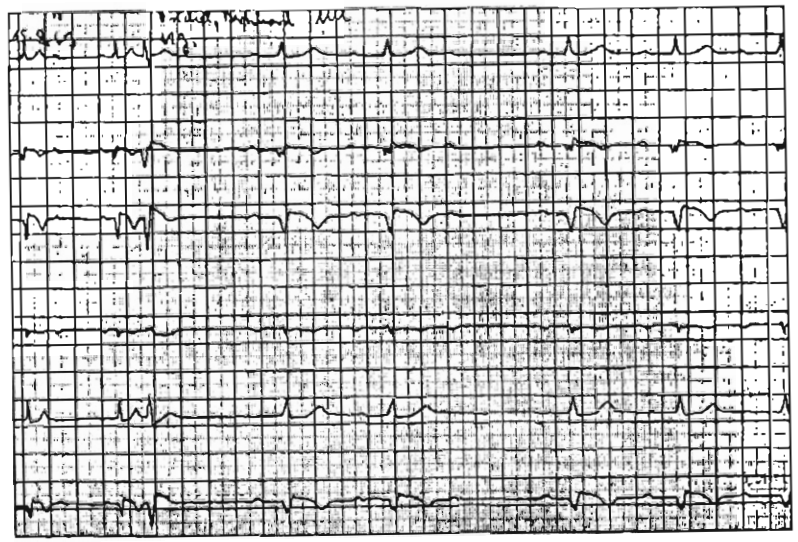

Fig. 12b

Figs. 12a and b Male, 62, EKG 8. 15. 63. Same as Fig. 11. After i.v. drip infusion of 6 gm Mg-K aspartate in 350 ml 5% glucose; no improvement of the infarct shape of the QRS-complex. Necrosis already established. No improvement of the Wenckebach, but marked improvement of the metabolically disturbed antero-lateral region (compare V_6, V_1, V_5 in Figs. 11a and 12a).

To close this particular application of K and Mg aspartates, we wish to draw the attention to figure 13 which illustrates the case of a 68 year old male with a fresh posterior wall infarct. This patient received daily 0.25 mg of strophanthin, and 6 gm of K and Mg aspartates in slow i.v. perfusion (in 10 per cent glucose). In b) a decrease in frequency with improvement in the return of excitability can be observed. In c), however, an A-V dissociation and then block appear under further identical therapy. This phenomenon is probably not a vagal effect; although Mg aspartate alone—particularly in young subjects—is a powerful sympatholytic producing lasting mydriasis, K + Mg aspartates, on the contrary, have no action on the autonomic nervous system. The cause of the frequency decrease on the development of block in the presence of a previously damaged conduction system may be found in the maintenance of a high polarization level by cellular potassium replenishment. Such an observation can be made only with K + Mg aspartates, but not with equivalent doses of $KCl + MgCl_2$. The conditioning influence of strophathin on this effect of the electrolyte transporters is still the object of investigations. The block disappeared when the combined therapy was discontinued.

III. Treatment of Extrasystoles

The favorable effect of magnesium treatment on extrasystoles has already been described (59). In our studies with our injectable prepa-

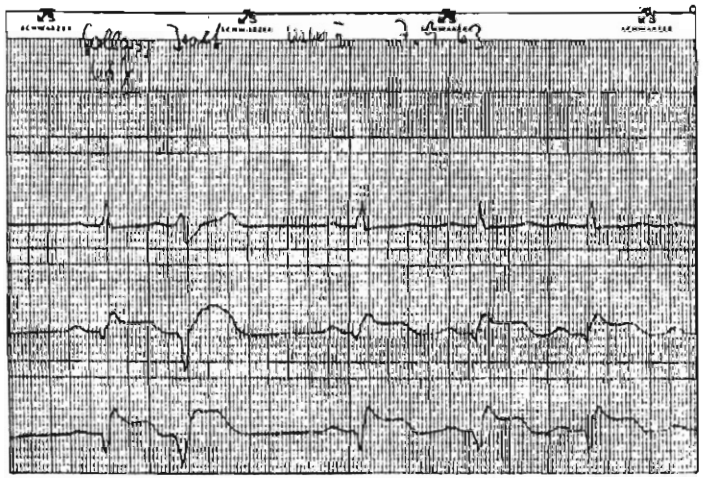

Fig. 13a (legend see p. 164).

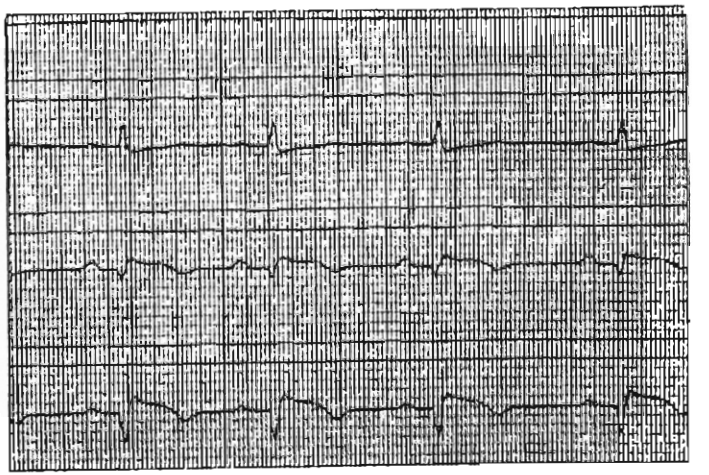

Fig. 13b

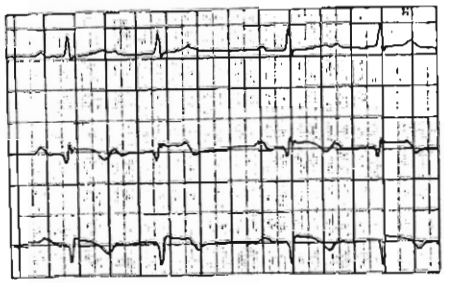

Fig. 13c

Figs. 13a, b and c Male, 68, posterior wall infarct. a) Before treatment. (See text p. 163).

ration, we have observed the disappearance or improvement of extrasystoles in about 40 per cent of cases. The best therapeutic results were obtained in ventricular extrasystoles, especially when occurring during glycoside treatment, or in the presence of hypokaliemia or infarct history (60). Atrium fibrillation, atrio-ventricular dissociation and shifting pacemaker, however, do not benefit much from this therapy. Correction of extrasystoles with electrolyte transport substances, in successful cases, permits uninterrupted glycoside therapy. Simultaneous myocardial infarct, heart block—provided any cardiac glycoside treatment is avoided—or severe bradycardias are not contraindications, in contradistinction to treatment with quinidine.

Figures 14 and 15 illustrate the efficacy of this treatment.

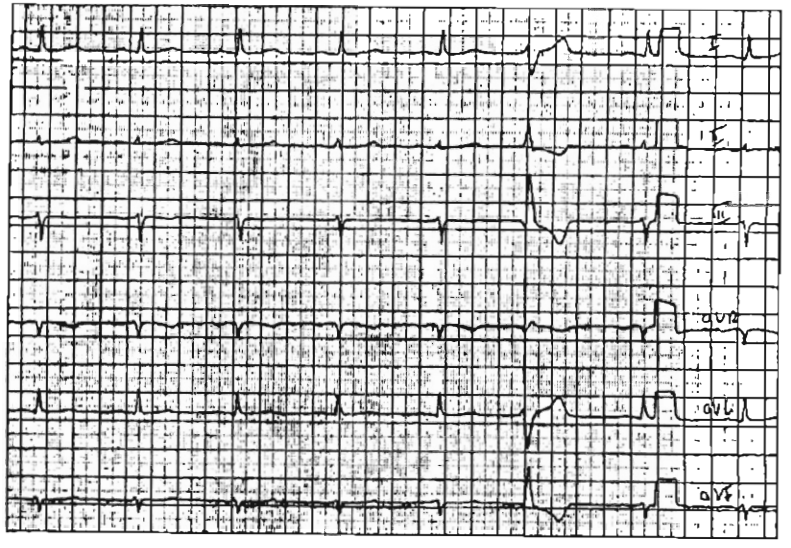

Fig. 14a

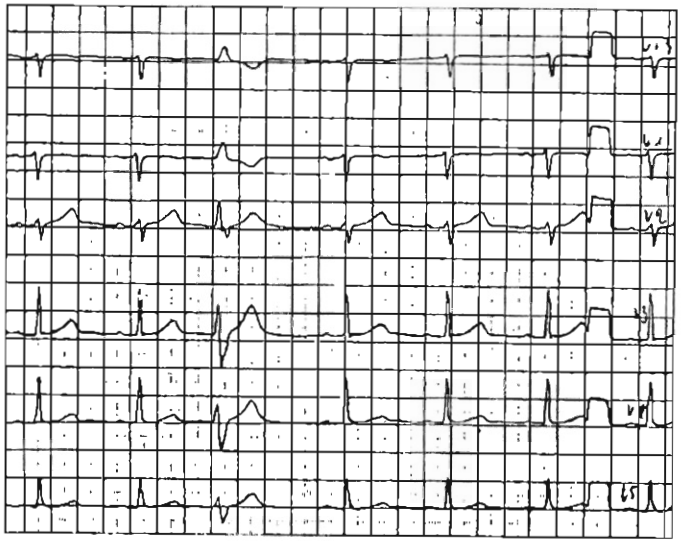

Fig. 14b

Figs. 14a and b Male, 56, EKG 6. 24. 63, angina for 4 years. Serious attacks on the five previous days, dyspneic. Serum K: 17.4 mg%, Na: 322 mg%. Ventricular extrasystoles originating from two different centers. Extrasyst./normal syst. ratio = 6:24.

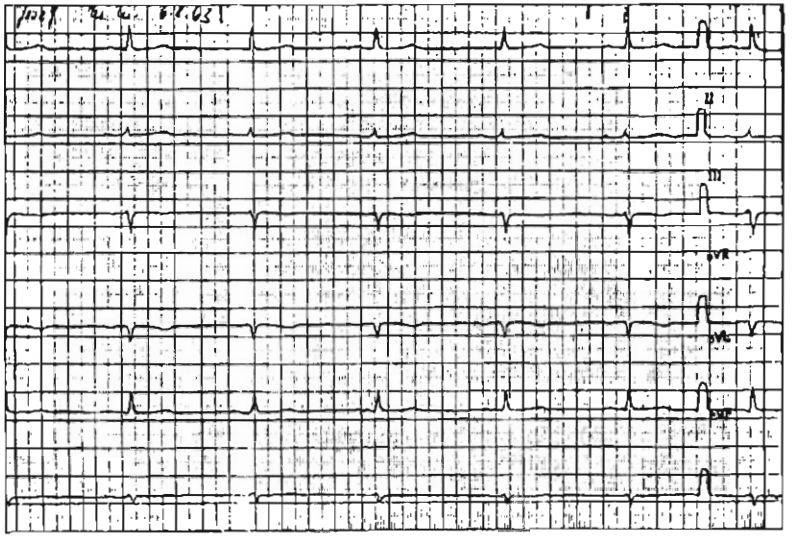

Fig. 15a

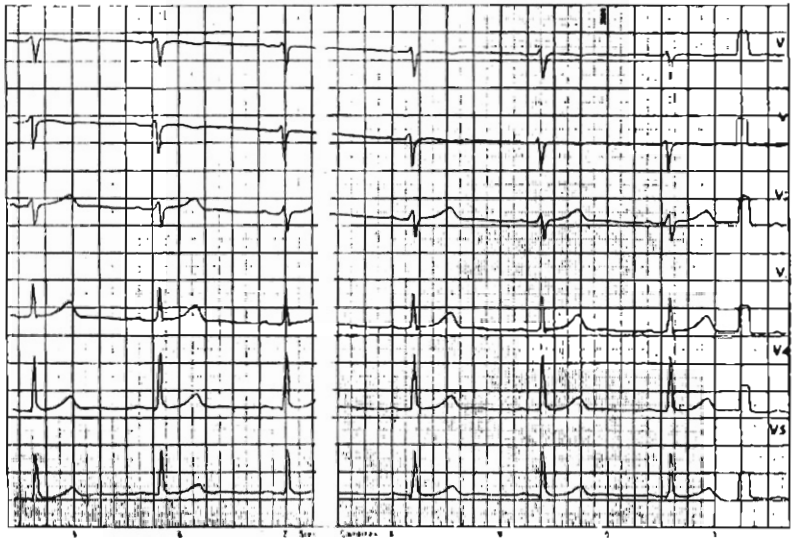

Fig. 15b

Figs. 15a and b Male, 56, EKG, 8. 6. 63. Same as in Fig. 14. After i.v. drip infusion of 6 gm of Mg-K aspartate in 250 ml of 5% glucose, 6:155 extrasystoles were recorded. The following day, without further infusion, there was complete disappearance of extrasystoles, striking relief of pain.

Conclusion

These studies seem to demonstrate clearly the importance of the original electrolyte therapy concept of SELYE. They demonstrate also that the application of our electrolyte transport theory in the form of K and Mg D,L-aspartates makes possible the clinical application of this concept, and is, therefore, a great practical improvement.

In our opinion, this improvement is mainly the result of the better intracellular penetration and retention of the K and Mg ions when combined with a transport molecule. Thus the extracellular-intracellular gradient can be re-established more rapidly and efficiently, avoiding thereby the risks of sudden myocardium depolarization due to too high an extracellular electrolyte concentration following i.v. administration of large quantities of K^+ in particular.

The better electrolyte intracellular penetration afforded by our electrolyte transport therapy, as illustrated by clinical results, is probably responsible for the rapid improvement of cell metabolism—an essential factor in the re-establishment and maintenance of a physiological electrolyte gradient—and of normal repolarization processes. The recent studies of NAKAHARA *et al.* (61) on striated muscle would support these views. These authors tested only the K and Mg salts of L-aspartic acid which, on the basis of our previous remarks, do not appear as active on some tests as salts of the D,L-acid. They were, nevertheless, able to demonstrate in the stimulated striated muscle (gastrocnemius) of aspartate treated animals compared to controls: a) a much higher concentration in ATP; b) a nine-fold increase in residual creatin phosphate; c) higher K and lower Na intracellular levels; and d) a greater contraction amplitude and a faster recovery. Of a series of compounds tested, among which $KCl+MgCl_2$, the aspartates were the most active.

The part played by the aspartic acid moiety in the stimulation of metabolism is difficult to evaluate. LABORIT *et al.* consider that its action in intermediary metabolism—in the tricarboxylic acid cycle and in the Krebs-Hensleit cycle—is an important factor, whereas we tend to attribute to this aminoacid mainly a carrier rôle along the lines of our electrolyte transport theory. In any event, our study on pyruvic, lactic and alpha-ketoglutaric acid blood levels in patients, and the NAKAHARA *et al.* studies demonstrate the stimulation of cellular metabolism at the level of the tricarboxylic acid cycle by K+Mg aspartates. The increase in ATP described by these last authors could account for the return of cardiac excitability observed in some of our patients (Fig. 13c).

Therapeutic Consequences

Our own studies have shown that serum potassium levels below 17.8 per cent (4.5 mEq) may be associated with cardiac metabolism disturbances. If angina pectoris, myocardial infarct or certain forms of extrasystoles have not already developed, one or the other is likely to appear in patients with low plasma potassium values. Consequently such patients are most likely to benefit from our electrolyte transport therapy to which at present K+Mg aspartates appear to be best adapted.

On the basis of the experience gained so far, the following recommendations can be made for the administration of K+Mg aspartates:

I. Chronic Treatment of Primary Angina Pectoris or Subsequent to Myocardial Infarct

Our own study indicates not only the curative effects of electrolyte transport therapy on angina, but suggests also a possible preventive action since the incidence of myocardial infarct in the 84 patients treated over 18 months to 2 years was very low.

We believe now that this type of patient should be started on 3 gm/day of K+Mg aspartates orally, to be possibly increased to 4 or decreased to 2 gm/day, according to therapeutic response. Such therapy should be protracted, if not continuous.

II. Acute Treatment of Myocardial Infarct and of Severe Angina Pectoris

It is significant that TAPIN and PILLEN independently reached similar conclusions. If nothing else, the use of K and Mg aspartates would thus already be very valuable by the decrease they cause in the ischemic pain leading to the reduction or even the absence of need for narcotics and sedatives. These first results were obtained with low doses, and it is to be expected that with higher doses, results will be even better, as already indicated by some preliminary studies.

The intravenous route is recommended in such cases, and administration must be initiated as soon as possible; the electrolyte transport therapy that now we have adopted in acute infarction and severe angina

is based on the daily administration of 5 gm of K+Mg aspartates in 250 ml of 5 per cent glucose, levulose or sorbitol, by slow intravenous perfusion.

Such a treatment should be continued for a minimum of 4 to 5 days, and then oral maintenance therapy initiated at the dose indicated in I.

According to the observations of Bajusz (62), the administration of chlorides in heart necroses could also be useful in the treatment of myocardial infarct. Clinically, the K and Mg transport therapy requires, to a certain extent, the adjustment of decreased serum chloride levels, and we plan to study the effects of our electrolyte transport therapy with the combined administration of sodium free chlorides.

It should also be mentioned that in 1955–1956 Laborit had stressed the importance of a normal electrolyte gradient, and its relation to carbohydrate metabolism, for the maintenance of normal cardiovascular functions (63, 64). On this basis, he outlined a metabolic approach to the treatment of myocardial infarct (64, 65, 66), whose validity was stressed again in 1962 by Sodi-Pallares (67). Although Sodi-Pallares regards now 10 per cent glucose+insulin+K^+ as satisfactory, Laborit (65, 66) and Larcan (68), considering that in such conditions carbohydrate supply must be very high, recommend that the electrolyte treatment, in particular with the aspartates, should be combined in its early stage with large quantities of hypertonic glucose (10–30 per cent, 60 to 500 ml, i.v.)+1 U of insulin per 10 gm of glucose.

Obviously, the treatment that we recommend does not exclude the eventual use of anticoagulants and other forms of additional therapy that may also be required.

III. Treatment of Ventricular Extrasystoles

A therapeutic approach similar to that in II can be used, although the doses required for satisfactory response might be lower, and intravenous administration shorter. Doses of 1 to 2 gm of K and Mg aspartates can be administered intravenously directly without difficulty. Maintenance of oral therapy in doses as in I can be subsequently applied.

Tolerance: One of the important aspects of this electrolyte transport therapy is its lack of toxicity and of side-effects; whether the oral or slow intravenous route of K+Mg aspartates administration is used as recommended, tolerance is excellent. Rare gastrointestinal upsets may be observed with the oral preparation. The i.v. preparation should be used in slow perfusion when individual doses are higher than 1 to 2 gm.

Many cardiologists, however, are against the use of intravenous fluids in the treatment of myocardial infarct for fear of the development of pulmonary edema. We have never observed such accidents, to the contrary. Indeed, pulmonary edema results from cardiac insufficiency and the electrolyte transport therapy that we offer can be regarded as a specific treatment of cardiac insufficiency, especially when combined with glucose+insulin (65, 66). Such therapy, therefore, not only cannot lead to pulmonary edema, but offers an excellent therapeutic treatment for such accidents.

Summary

Both the metabolic and pathogenetic significance of an intracellular potassium and magnesium deficiency is discussed with special reference to cardiology. Aiming at a directed electrolyte therapy, potentially electrolyte transporting substances were studied. One of the most important compounds of this group is the 50:50 mixture of potassium aspartate and magnesium aspartate whose interesting experimental and clinical effects are demonstrated with the aid of various metabolic, electrocardiographic and therapeutical investigations.

References

1. Gould, S. E.: Pathology of the heart (Thomas, Springfield 1953).
2. Hort, W.: Pathological anatomy of heart infarct. Med. Welt *34:* 1641–1645 (1960).
3. Schmüderrich, B.: Sexualdualistische Abhängigkeit der Symptome der Herzinsuffizienz (Diss., Düsseldorf 1962) Ärztl. Forsch. *16:* 179–184 (1962).
4. Hochrein, M. and Schleicher, I.: Vertebral origin of angina pectoris. Med. Klin. *48:* 496–499 (1953).
5. Gundersen, P.: Acute myocardial infarction in a medical department in the years 1925–1927 compared with the year 1954; cit. Schmüderrich, B. Ärztl. Forsch. *16:* 179–184 (1962).
6. Bürger, M.: Geschlecht und Krankheit (Lehmanns, München 1958).
7. White, P. D.: Der Schlüssel zur Diagnose und Therapie der Herzkrankheiten (Steinkopff, Darmstadt 1957).
8. Froment, R.: Modern data on French coronary pathology. Principally statistical study. Acta cardiol. *14:* 39–42 (1959).
9. Larcan, A. et Huriet, C.: L'électrocardiogramme dysanabolique. Pénétrations ioniques et électrocardiogramme (Masson, Paris 1960).
10. Selye, H.: Electrolyte, Stress und Herznekrose (Schwabe, Basel 1961).
11. Blumberger, K.: Myocardial infarct and heart wall aneurysm after electrical current accident; a contribution to expert testimony with an appendix on changes of heart dynamics after electrical current accidents. Chirurg *25:* 481–486 (1954).

12. Selye, H.: Chemical prevention of cardiac necroses (Ronald Press, New York 1958).
13. Agranat, A.: Magnesium therapy for heart infarction. Med. Proc. (SA) *4:* 67–69 (1958).
14. Browne, S. E.: Letters to the editor. Magnesium sulphate in the treatment of angina. Lancet *7215:* 1313–1315 (1961).
15a. Malkiel-Shapiro, B. and Bersohn, I.: Magnesium sulphate in coronary thrombosis, notes and comments. Brit. med. J. *60:* 292 (1960).
15b. Malkiel-Shapiro, B. and Bersohn, I.: Magnesium sulphate in coronary thrombosis. Med. Proc. (Brit. Med. Ass.) *4:* 77 (1958).
16. Parsons, R. S.; Butler, T. and Sellars, E.: Magnesium sulphate therapy of coronary thrombosis. Med. Proc. (Brit. Med. Ass.) *5:* 487–488 (1959).
17. Teeger, A.: Antithrombotic activity of magnesium salts. Med. Proc. (Brit. Med. Ass.) *4:* 77–78 (1958).
18. Hirschfelder, A. D. and Haury, V. G.: Clinical manifestations of high and low plasma magnesium; dangers of epsom salt purgation in nephritis. J. Amer. med. Ass. *102:* 1138–1140 (1934).
19. Browne, S. E.: Magnesium and cardiovascular disease. Brit. med. J. *13:* 118–120 (1963).
20. Kühne, K.: Bad Oeynhauser Gespräche *III:* 108–109 (1958).
21. Wolff, H. P.: Bad Oeynhauser Gespräche *III:* 72–73 (1958).
22. Köhler, U.: Magnesium prophylaxis of heart infarct. Ärztl. Forsch. *14:* 513–517 (1960).
23. Nieper, H. A. and Blumberger, K.: Experimental basis and clinical use of electrolyte carrier compounds. 1. Metabolic activity of Mg and K-asparaginate, especially in coronary insufficiency. Ärztl. Forsch. *15:* 125–129 (1961). – 2. Normalizing effects of Mg and K-asparaginate on an atypical substrate balance, which appears in prolonged strophanthin treatment. Ärztl. Forsch. *15:* 305–309 (1961).
24. Laborit, H. et Huguenard, P.: Echanges ioniques, tonus vasculaire, métabolisme cellulaire. Bilan d'une étude expérimentale et aperçus thérapeutiques. Presses méd. *64:* 605–608 (1956).
25. Laborit, H.: Bases physiobiologiques et principes généraux de réanimation; vol. 1 (Masson, Paris 1958). – Stress and cellular function; vol. 1 (Lippincott, Philadelphia 1959).
26. Laborit, H.; Moynier, R.; Trzebski, A.; Guiot, G. et Baron, C.: Influence de la composition ionique du milieu extra-cellulaire et influence comparée de l'acide aspartique, de l'aspartate de potassium et du glucose sur l'épreuve de nage du rat blanc. C. R. Soc. Biol. *151:* 1383–1386 (1957).
27. Laborit, H.; Moynier, R.; Guiot, G.; Baron, C. and Niaussat, P.: Influence of various pharmacological agents on the swimming test of white rats. C. R. Soc. Biol. *152:* 486–487 (1958).
28. Laborit, H.: La fatigue. Etude expérimentale. Bull. Soc. méd. milit. *52:* 150–163 (1958).
29. Laborit, H. et Weber, B.: L'insuffisance hépatique des grands brulés. Lyon chir. *55:* 687–700 (1959).
30. Laborit, H.; Weber, B.; Niaussat, P.; Jouany, J. M.; Guiot, G.; Zawadowski, J. et Baron, C.: Note préliminaire sur l'étude expérimentale de quelques sels de l'acide D,L-aspartique. Anesth. Analg. *15:* 480–494 (1958).
31. Melon, J. M.: Essais cliniques avec l'aspartate de potassium et de magnésium dans les affections cardiovasculaires. Agressologie *1:* 443–454 (1960).
32. Weber, B.: Experimental and clinical study of aspartic acid salts (Foulon, Paris 1960).

33. Weber, B.; Laborit, H.; Jouany, J. M.; Niaussat, P. et Baron, C.: Modifications des signes électrocardiographiques de l'infarctus du myocarde expérimental chez le lapin par l'injection de sels de l'acide aspartique. C. R. Soc. Biol. *152:* 431–436 (1958).
34. Trzebski, A. and Lewartowski, B.: Increased anoxia resistance of the heart perfused with aspartic acid salts. Bull. Acad. Sci. Pol. *7:* 283–286 (1949).
35. Laborit, H.: Metabolism of ammonia and its disorders during states of shock. J. Méd., Bordeaux *136:* 687–688 (1959).
36. Weber, B.: Traitement des brulés. Agressologie *1:* 231 (1960).
37. Weber, B.; Laborit, H.; Jouany, J. M.; Regnier, M.; Broussolle, B.; Zavadovski, G.; Bonzanini, C.; Niaussat, P. et Baron, C.: Variations de l'ammoniemie provoquée par l'injection de chlorure d'ammonium chez le lapin. Anesth. Analg. *16:* 420–429 (1959).
38. Laborit, H. et Weber, B.: Etude expérimentale et clinique, prévention des accidents dûs à l'alimentation hyperprotidique par sonde. Anesth. Analg. *16:* 562–566 (1959).
39. Laborit, H.; Obrenovitch, L.; Leguen, P. et Jouany, J. M.: Action des sels potassiques et magnésiens de l'acide D,L-aspartique sur l'hyperammoniémie du choc hémarragique expérimental. C. R. Soc. Biol. *152:* 942–944 (1958).
40. Weber, B.; Laborit, H.; Jouany, J. M.; Niaussat, P. et Baron, C.: Action de certains sels de l'acide D,L-aspartique sur l'intoxication aigüe par le chlorure d'ammonium. C. R. Soc. Biol. *10:* 1361–1363 (1958).
41. Tapin, M.: Thèse, activité pharmacodynamique de l'acide aspartique sur le cœur isolé. Intérêt en clinique humaine dans le traitement de l'infarctus du myocarde (Barrois, Bar-le-Duc 1962).
42. Lamarche, M.; Royer, R. and Bas, M.: A comparison between the activity of the aspartates and of the nicotinic ester of diethylaminoethanol on cardiac manifestations of acute hypoxia. C. R. Soc. Biol. *CLVI:* 2099–2101 (1963).
43. Rosen, H.; McCallum, J.; Blumenthal, A. and Agersborg, H. P. K.: Effects of potassium and magnesium aspartates on the isolated guinea pig heart. Arch. int. pharmacol. thér. (in press).
44. Rosen, H.; Blumenthal, A. and Consalvi, A.: Effects of the potassium and magnesium salts of aspartic acid on ammonia intoxication in the rat. Acta pharmacol. (in press).
45. Loll, H. and Blumberger, K.: Modification of the serum level of intermediate products and enzymes by K-strophanthin. Ärztl. Forsch. *14:* 3–5 (1960).
46. Nieper, H. A.: Experimental bases and clinical use of electrolyte carrier compounds. Ärztl. Forsch. *15:* 510–514 (1961).
47. Greeff, K.: The action of potassium and magnesium aspartates on the glycoside intoxication of the heart. Proc. Germ. Soc. Pharmacol., April 1963 (in press).
48. Nieper, H. A. and Köhler, L.: Experimental basis and clinical use of electrolyte carrier compounds. 6. Investigation of potassium and magnesium nicotinylaspartate. Ärztl. Forsch. (in press); Agressologie (in press).
49. Nieper, H. A.: Experimental basis and clinical use of electrolyte carrier compounds. 5. Investigation of potassium and magnesium 2-aminoethylphosphate. Ärztl. Forsch. *16:* 641–642 (1962).
50. Hilmer, W. and Köhler, A.: Electrocardiographic patterns of the ST-T waves in disorders of potassium metabolism. Med. Welt *12:* 565–567 (1961).
51. Laborit, G. and Kind, A.: A special utilization of sodium 4-hydroxybutyrate. Agressologie *2:* 543–547 (1961).

52. Gessler, U.: Intra- and extracellular electrolyte changes in metabolic acidosis. Research on erythrocytes. Klin. Wschr. *39:* 232–234 (1961).
53. Jeanneret, P.: Water-electrolyte balance, tables of medically important values. Helv. med. acta *21:* 191–192 (1954).
54. Hartert, H.: Anticoagulant treatment of myocardial infarction. Med. Welt *5:* 251–254 (1962).
55. Laborit, G.; Kind, A. et Jouany, J. M.: Etude biologique des perfusions des sels potassiques et magnésiens de l'acide aspartique en clinique humaine. Anesth. Analg. *16:* 415–420 (1959).
56. Weber, B.: Communication personnelle.
57. Jacquin, F.: Communication personnelle.
58. Pillen, D.: The pathogenesis, prophylaxis and therapy of myocardial infarct. Med. Klin. *33:* 1413–1418 (1962).
59. Surawicz, B.: Low and high magnesium concentrations of various calcium levels. Effect on the monophasic action potential electrocardiogram and contractility of isolated rabbit hearts. Circulat. Res. *9:* 811–814 (1961).
60. Nieper, H. A. and Blumberger, K.: The effectiveness of electrolyte carrier compounds on myocardial metabolism, illustrated by magnesium and potassium aspartate. Verh. dtsch. Ges. Kreislforsch. *27:* 238–242 (1961).
61. Nakahara, M.; Yamada, S.; Sakahashi, H.; Nakamishi, Y.; Tokita, T. and Yoshihara, T.: Antifatigue effect of potassium-magnesium salt of aspartic acid on skeletal muscles and its mechanism of action. Agressologie *5:* 245–255 (1964).
62. Bajusz, E.: Nutritional factors in the pathogenesis of cardiac necroses. Z. Ernährungsw. *2:* 229; *3:* 1 (1962).
63. Laborit, H.; Favre, R.; Guittard, R. and Laborit, G.: Neuromuscular excitability, ionic balance and optimum temperature for tissue functions. Therapeutic consequences in hibernation therapy and surgery. Presse méd. *12:* 223–226 (1955).
64. Laborit, H. et Huguenard, P.: Sur certains effets myocardiques des injections intraveneuses rapides de KCl chez le chien. C. R. Soc. Biol. *150:* 513–516 (1956).
65. Laborit, H.: Intérêt majeur du glucose hypertonique en réanimation. Presse méd. *66:* 444–445 (1958).
66. Laborit, H.: Le traitement des insuffisances cardiovasculaires et de l'infarctus du myocarde par l'association insuline, glucose hypertonique, sels de potassium. Presse méd. *71:* 1–3 (1963).
67. Sodi-Pallares, D.; Testelli, M. R.; Fishleder, E. L.; Bisteni, A.; Medrano, G. A.; Friedland, C. and de Micheli, A.: Effects of an intravenous infusion of a potassium-glucose-insulin solution on the electrocardiographic signs of myocardial infarction. Amer. J. Cardiol. *9:* 166–167 (1962).
68. Larcan, A.: Le traitement métabolique de l'infarctus du myocarde, justification physio-pathologique et premiers résultats. Agressologie *4:* 387–416 (1963).

Author's address: Dr. med. Hans A. Nieper, Silbersee Krankenhaus, *Hannover*, and Dr. med. K. Blumberger Städtische Krankenanstalt, *Aschaffenburg* Germany