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## **AGEING AND DISEASE — A MACROMOLECULAR PROBLEM?**

by

**K.-S. Lachnit · A. Klausner · E. Proszowski · L. Rieder**

**VERLAG G. BRAUN  
POSTFACH 1709  
7500 KARLSRUHE 1  
30. JAHRGANG  
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Summary:

At a time long ago, so famous a man as Aristotle was already concerned with the problems of ageing and disease and in the course of the history of geriatrics a large variety of theories on the causative factors and changes involved in the process of ageing have been formed: damage and deficiency symptoms, wearing processes and degeneration, regulatory and metabolic disorders in the organs, tissues and cells are the suppositions mostly put forward to explain the phenomenon of ageing. In recent times, basic biological research provided evidence that age-dependent changes occur on a macromolecular level. From among the large number of investigations on changes in the function of the various macromolecules I only want to mention the "Fehler - Katastrophen" theory developed by ORGEL and the theory of life-sustaining processes by CUTLER.

Presuming from the assumption that macromolecular changes are mainly responsible for the ageing process in man, it seems obvious that only an overall macromolecular organotherapy offers the possibility of a causative treatment of ageing and disease. The history of organotherapy is believed to date far back, although it was only during the last 100 years that it could clearly be differentiated from magic medicine and mysticism. It is owing to K. THEURER that this macromolecular organotherapy was eventually established on a scientifically confirmed basis and introduced as "cytoplasmic therapy".

Address for correspondence:

Prim.Dr.K.-S. Lachnit, Dr.A. Klausner, OA.Dr.E. Proszowski  
und OA.Dr.L. Rieder  
Pflegeheim der Stadt Wien-Lainz, IV.med.Abt.  
(Vorstand: Prim.Dr.K.-S. Lachnit)  
Versorgungsheimpl. 1, 1130 Wien, Österreich

The publication of results on the therapeutic effect of cytoplasmic preparations in geriatric patients by several other investigators led us to start a series of studies on cytoplasmic therapy in ageing patients, even more so as we felt encouraged by the results of a pilot study carried out by us. It was the aim of this study to establish whether it was possible to exert a favourable influence on the physical and mental deterioration observed in patients of a large geriatric department. In view of the fact that manifestations of cerebral insufficiency and changes in the myocardium and coronary arteries can be detected in the large majority of geriatric patients, the experimental methods used were based on these two parameters. The results of this randomised double-blind study not only confirmed the underlying theories and findings of previous investigations but also provided valuable scientific data on this new method of geriatric treatment.

"Thus, it is justified to describe disease as an acquired old age, whereas old age is regarded as a natural disease. Moreover, certain diseases lead to the same effects as old age."

Strictly speaking, these words of Aristotle, who was the son of a physician, mark the beginning of the history of geriatrics, being defined as the science of the diseases and problems of old age. About 400 years later, GALEN from PERGAMUM, personal physician to Marcus Aurelius Antoninus and other Roman Emperors, reviewed all knowledge gained on this subject up to that time. Unlike Aristotle, he came to the conclusion that old age is an inescapable phase of life, which "everybody has to endure and which must therefore be regarded as the will of nature". Disease, however, he described as being contrary to nature, thus representing a disturbing factor in the natural course of life. Since then, the development of the science of geriatrics has been following a straight

course, which was partly characterized by periods of merely academic treatment of old age, partly by an indiscriminating belief in spectacular miracle drugs developed to "outwit old age". The question of the cause of the changes occurring in old age has, however, always been in the focus of scientific discussion. It seems worth while to study the various interpretations of the process of ageing, if only for historical reasons. Apart from damage and deficiency symptoms, there is a large variety of further reasonable and interesting theories - including those based on wearing and degeneration, regulatory and metabolic disorders or even intoxication - to explain the biological phenomenon of "old age". The fact that during the last few decades the emphasis in gerontological research was shifted to the field of macromolecules, which may partly be due to the development of new techniques, is certainly not to be regarded as a vagary of science. Regardless of whether ageing is ascribed to a disturbed function of the enzymes and structural proteins or changes in the messenger nucleic acids - be they regarded as an active factor or only an accompanying symptom of ageing - all processes of ageing are invariably associated with disturbances on a molecular-biological level. It must, however, be pointed out that this theory only marks the beginning of a new trend in research and many questions still remain to be investigated. From among the large variety of studies in this field I should like to mention two theories: the "Fehler - Katastrophen" theory developed by ORGEL (6), which is based on the supposition that the structure of the proteins changes with increasing age. Moreover, the biological functions of the proteins of aged cells are changed or even completely extinguished, which finally leads to a breakdown of the entire intracellular metabolism. CUTLER's theory of "life-sustaining processes" (3) presumes from the assumption that the maximum expectation of life, which varies between species, is correlated with a maintenance of the physiological equilibrium and repair mechanisms of the DNA in the cellular nuclei. "The duration of life is determined by the regenerative power of the genes".

In view of the fact that disturbances on a macromolecular level play the major part in the process of ageing, it seems obvious that only an overall macromolecular organotherapy offers the possibility of a genuine and causative treatment of age-dependent physiological and pathological changes. The history of organotherapy dates far back to times when magic medicine still had a predilection for bones, flesh and blood, or animals with a long expectation of life. There is a legend that Aesop was rejuvenated by Medea using the head of an old crow, but even more authentic sources mention the flesh of snakes as a remedy to prolong one's life - as for instance DIOSCURIDE, a famous physician and botanist. Leaving these centuries of mysticism in obscurity, I should now like to turn to BROWN-SEQUARD (2), who in 1889 reported the invention of an injection to the astonished members of the Paris Academy of Science, due to which he rapidly recovered from age-dependent depletion of strength even at the age of 72. This aqueous solution of triturated testes from dogs and guinea-pigs marked the beginning of scientifically based organotherapy. Its development is characterized by names like STEINACH, VORONOFF, METSCHNIKOFF, BOGOMOLETZ and many others, until in modern times Karl THEURER finally succeeded in developing a macromolecular cytoplasmic organotherapy. In view of the fact that the fundamentals and activities of research into the normalisation of cellular metabolism due to the restoration of impaired regulatory processes were already dealt with in sufficient detail in previous publications, I should now like to report on investigations into the induction of healing processes in patients of advanced age.

Aim:

It was the aim of our study to establish whether the physical and mental deterioration observed in patients of a geriatric department could be influenced favourably by a cytoplasmic therapy using macromolecular organ substances (Revitorgan dilutions, dry substances and lingual preparations, vitOrgan-Arzneimittelfabrik Dr. Theurer GmbH+Co KG, D-7302 Ostfildern 1/Ruit).

Patients and experimental methods:

A total of 109 patients (53 males and 56 females) of an age of 55 to 94 years (mean 77.7 years) were selected from among the patients of the 4th Medical Department of the Nursing Home for the Aged of the city of Vienna (table 1).

Table 1 Patient distribution (n = 109)

	n
Age: 55 - 94 years	
Average age: 77.7 years	
drop-outs	6
deaths	
(pre-study period up to the 2nd week)	3
refused to participate	1
Actual number of participants:	99
Verum group	55 (28 ♀, 27 ♂)
Placebo group	44 (23 ♀, 21 ♂)

As was to be expected, this department mainly comprised geriatric patients in need of care, where largely homogeneous cerebral and cardiac changes were revealed. This fact is of particular note, as in our experience cerebral and cardiac insufficiencies account for the major part of diagnoses revealed in patients of advanced age. For this reason, our investigations were mainly based on these two parameters. Other findings also frequently detected in connection with multiple morbidity, which is a characteristic of old age, were not taken into account (such as antibody changes, chronic infection of the urinary tract, hypertension and hyperlipaemia). Excluded from the study were moribund patients, who could not be expected to survive the 10-week observation period, patients who refused to cooperate, patients showing severe, irreversible organo-cerebral changes, and patients showing a tendency to severe renal and metabolic disorders as well as patients where no or only slight changes in the ECG could be detected.

These 109 patients were randomly assigned to the study groups using a double-blind procedure and stratification system taking account of the ward and sex of the patients. The code,

which was unknown to both the responsible investigator and the doctors and nurses involved in the study, was kept by the Institute of Statistics and Documentation of Vienna University. Due to thorough examinations during the pre-dosing period 6 further patients had to be excluded. Three patients died (1 patient in the 1st week due to acute exacerbation of a diabetic gangrene, 1 patient in the 1st week due to acute renal insufficiency, 1 patient in the 2nd week due to acute myocardial infarction), 1 patient (a former senior nurse) refused to take the drug, although she had originally given her consent to participate. Thus, the number of patients eventually taking part in the study amounted to 99. As most drop-outs happened to occur in the placebo group - which was revealed after completion of the study - the final distribution was 55 patients in the Verum group and 44 patients in the placebo group. Statistical evaluation showed age distribution in the two groups to be in good agreement. Moreover, largely corresponding findings were also revealed for the essential parameters of the ECG, cerebral symptoms and psychological tests during the initial examinations in the Verum and placebo groups, although this was not surprising in view of the large number of randomly assigned patients (fig. 1). The overall observation period was divided into a two-week pre-dosing period, a four-week treatment period and a four-week follow-up observation period. As can be seen from the diagram (table 2), thorough clinical examinations were performed once weekly, laboratory examinations three times in the course of the study (blood counts and biochemical parameters) at the end of each of the individual study periods. These were connected with examinations of the cerebral functions and ECGs - in each case between 8 and 9 a.m. - as well as psychological tests at the beginning and end of the study. The clinical examinations as well as the evaluations of the laboratory findings and cerebral manifestations (on the basis of the SCAG scale) were carried out by the responsible physicians, the ECG evaluation by the responsible investigator, and the evaluation of the psychological tests by an assistant medical director experienced in this field.

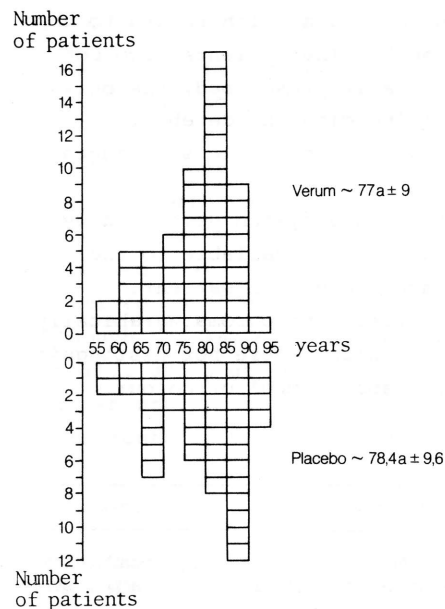


Figure 1 Age distribution

Table 2 Course of study (V = pre-study period)

week	V1	V2	1	2	3	4	5	6	7	8
clinical examination	x	x	x	x	x	x	x	x	x	x
laboratory examination		x					x			x
ECG	x	x	x	x	x	x	x	x	x	x
psychological test		x								x
medication			x	x	x	x				

The psychological tests chosen were taken from "Hamburg-Wechsler-Intelligenztest für Erwachsene" (7): General standard of knowledge to assess intelligence and receptivity; repetition of numbers, also in reversed order, to assess short-term memory; the mosaic test to assess non-verbal intelligence.

As a previous pilot study (4) had already provided proof of a highly significant effect of macromolecular organ substances on cardiac changes, the use of cardiac preparations was re-

tained for ethical reasons, in particular with regard to the large number of patients on placebo. The patients also continued to take other drugs originally prescribed, the only exception being preparations influencing the cerebral vessels and metabolism as well as psychotropic substances.

The preparations were selected using a system developed by vitOrgan (table 3). The drugs were made available to the various wards separately for each individual patient. Placebo (physiological saline solution or chromatographically pure human albumin) and active substance were not distinguishable from each other by appearance, shape, symbol or colour.

Table 3 Treatment plan

week	Monday	Wednesday	Friday
1	FegaCoren N* 1 amp., strength I	AntiFocal N* 1 amp., strength I	FegaCoren N 1 amp., strength I
2	AntiFocal N 1 amp., strength I	FegaCoren N 1 amp., strength I	AntiFocal N 1 amp., strength I
3	FegaCoren N 1 amp., strength I	AntiFocal N 1 amp., strength II	FegaCoren N 1 amp., strength II
4	AntiFocal N 1 amp., strength II	1 amp. (15 mg) Revitorgan Dry Substance No. 64 B*	1 amp. (15 mg) Revitorgan Dry Substance NeyThymun* 1 amp. (15 mg) Revitorgan Dry Substance No. 70*

Neytroph Drops + NeyCalm Drops as  
an interim medication

\* vitOrgan Arzneimittelfabrik, Ostfildern/Ruit

The data obtained in the individual patients of the study groups were recorded on a special test sheet. On completion of the study, all test sheets were passed on to the Institute of Medical Statistics and Documentation of Vienna University. The findings were evaluated using the chi-square test for comparison of frequency distribution between the study groups. +)

+) The biometrical system used was designed and evaluated by Dr. P. Bauer, Assistant Professor at the Institute of Medical Statistics and Documentation at Vienna University (Head of Institute: Professor Dr. F.X. Wohlzogen).

## Results

The following findings were revealed in the individual treatment and control groups:

1) ECG findings - PQ distance, QRS complex, ST segment and T wave were rated separately on a 4-point scale (0-3; 0 = no change, 1 = slight changes, 2 = moderate changes, 3 = marked changes). In the patients of the Verum group, we observed considerable improvements for the PQ changes (although the latter could not be detected in all patients from this group at the beginning of the study), considerable improvements in the QRS complex and markedly pronounced improvements in ST and T (fig. 2). The ECG findings in the placebo group mostly tended towards a slight deterioration

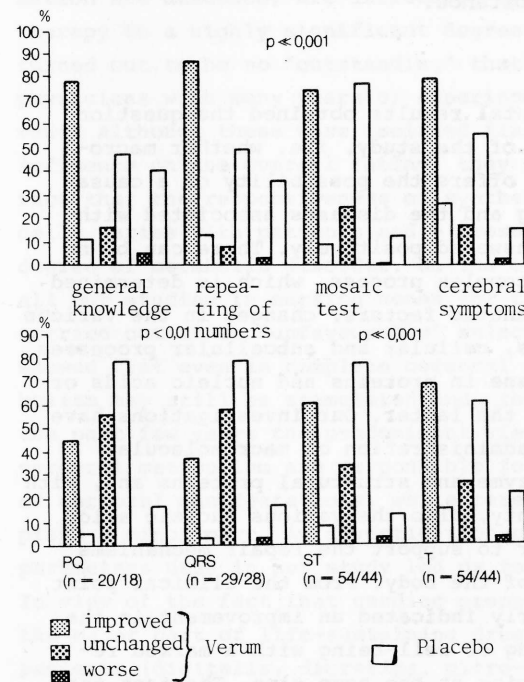


Figure 2 Results: Changes in the experimental parameters following organo-therapy



so that statistical comparison between the two groups revealed significant differences for PQ and QRS, highly significant differences for ST and T.

2) Highly significant differences between the two groups were also established for the general cerebral symptoms as well as for the psychological tests; in the Verum group, all these parameters were found to be improved at the end of the treatment period as compared to the pre-dosing period, whereas in the placebo group no such changes could be revealed.

3) The assessment of the general clinical parameters and laboratory findings revealed no indications of side-effects caused by the active substance.

#### Discussion

In view of the experimental results obtained the question raised at the beginning of the study, i.e. whether macromolecular organotherapy offers the possibility of a causative treatment of ageing and the diseases associated with this process, must be answered positively. There can be no doubt that ageing is a complex process, which is determined by constitutional and genetic factors, changes in the various organs and organ systems, cellular and subcellular processes and, above all, a decrease in proteins and nucleic acids or a disturbed function of the latter. Our investigations have shown that by means of administration of macromolecular organ substances the enzyme and structural proteins and, with a high degree of certainty, also the various nucleic acids can be replaced in order to support the repair mechanisms and regenerative power of the body. From the clinical point of view, our study clearly indicated an improvement in the patients' general feeling of well-being with a marked revitalizing effect occurring at the same time. The fact that many age-dependent complaints which - regardless of whether they are slight or severe - often have a worsening effect on apathy and depression in patients of advanced age, may sudden-

ly disappear completely, deserves to be given particular attention here. In many cases, the patients do not even remember their former "troubles". These subjective symptoms, however, gain scientific significance, if they are compared with the objective findings obtained in the psychological tests. As shown by a comparison of the general standard of knowledge between the verum and placebo groups, there was a highly significant improvement in the results, which is certainly not only attributable to the skill gained in performing the test but to a large degree to the favourable effect on the memory and ability to concentrate. Moreover, the weakening of the short-term memory, a typical characteristic of ageing, as well as general intelligence as determined in the mosaic test, in which the powers of reasoning and coordination are assessed, are influenced by cytoplasmic organotherapy to a highly significant degree. Individual results turned out to be so "outstanding" that they even surprised physicians with many years of experience in geriatric treatment. Although these were isolated findings, which had no influence on the overall rating, they provided proof of the fact that the responsiveness of synthetic processes in the cells varies with patients and - presumably - also with the degree of metabolic disorder. On the other hand, however, all our studies in nursing homes for the aged, which were carried out in an "unfavourable" selection of old people, showed that even in complete cerebral atrophy cerebral metabolism may still be stimulated and, thus, improved. During the past few years the predominant view was that changes in cerebral metabolism are responsible for the entire spectrum of cerebral manifestations, while cerebral blood flow only plays a minor part. An investigation of the second of the two parameters used in our study led us to a similar conclusion. In view of the fact that cardiac preparations account for the major part of life-sustaining drugs used in ageing patients (digitalis, diuretics, nitro-preparations, etc.), the use of the latter was basically retained for ethical reasons. Nevertheless, a comparison between the two groups permitted one conclusion to be drawn. The results obtained here confirmed the findings revealed in a previous study

where only cardiological parameters were used (4), which showed that organ substances may prove effective even in geriatric cardiology. As the possibility of the occurrence of cardiac decompensation could practically be excluded in our patients, who were continuously treated and supervised, the ECG was used as a parameter of cardiac efficacy. This fact is of particular note, as the repolarisation phase recorded on the ECG not only indicates coronary changes but also metabolic disorders in the myocardium. The evaluation of the ECG tracings showed a significant improvement for the PQ and ORS complexes, which was particularly remarkable in view of the fact that changes in these segments are mostly irreversible manifestations of former acute attacks (such as P changes, AV block, hypertrophy and bundle-branch block). The findings of repolarisation were also highly significant, which was to be expected on the basis of theory and previous experimental results. Here, organotherapy leads to a genuine compensation of myocardial and, perhaps, coronary metabolic disorders. In particular more recent theories about the pathogenesis of angina pectoris, myocardial infarction and sudden cardiac death due to coronary spasms (5), which may be the result of electrolytic and metabolic changes,\* indicate a tendency towards a reversal of "coronary theory", which still seems unsatisfactory, and will perhaps throw more light on the controversy about "coronary theory" on the one and "myocardial theory" on the other side.

A more detailed investigation of the substances administered further explains their effectiveness, thus confirming former theories about the therapeutic mechanism of organotherapy using macromolecular substances. "Fegacoren" contains hydrolysed extracts from tissue cells of the heart, aorta, thymus, and various internal metabolic organs. "Antifocal" is composed of cells from the diencephalon, cerebellum, cerebrum, spinal cord and, like the substance above, various metabolic organs. The same applies to the dry substances (enriched by cells from the placenta, adrenal gland and thymus) and lingual preparations. The fact that a therapeutic effectiveness was

\* localised or general

clearly detectable in our study provides proof of a relationship between macromolecular organotherapy and an influence on cerebral and cardiac metabolism and, thus, the patient's general feeling of well-being. Moreover, it should be pointed out here that the accompanying symptoms and side-effects of ill-reputed cellular therapy (1) like infections, sensitisation including even anaphylactic shock, abnormal antibody formation, etc. were not observed to occur in connection with cytoplasmic preparations, probably owing to their different nature and the processing techniques used. Clinical investigations and laboratory findings have shown that these substances are not likely to lead to adverse effects or damage of any kind. The laboratory data, however, which otherwise revealed no particular findings, gave indications of the following changes: a return of the liver and blood lipid values to normal levels and a tendency of alkaline phosphatase to increased values. As high alkaline phosphatase values may also be taken as an indication of an improved metabolism in the bones, both these effects can be attributed to an increase in metabolic activity.

To summarize it can be established that the results obtained not only fully confirmed previous investigations carried out by us but also all those published by other authors. Moreover, the study described here, which was performed in a typical selection of patients at a geriatric nursing home, showed a highly significant increase in the degree of cerebral and myocardial efficiency. Owing to cytoplasmic therapy, the possibility of a less complicated treatment of multiple morbidity in aged patients, which mostly requires a poly-pragmatic method, and a causative treatment of ageing and disease, does not seem remote. In view of the inadequate and, thus, unsatisfactory possibilities of treatment offered by the so-called "geriatric agents" our method represents and entirely new and, perhaps, more convincing approach to the problem of ageing.

\* which remain to be confirmed statistically