NEUROLOGIE UND PSYCHIATRIE FÜR DIE PRAXIS

psycho

DIAGNOSTIK PATHOLOGIE SOMATIK THERAPIE PHARMAKOLOGIE

Sonderdruck aus
Heft 4/79

peri med

Verlag Dr. med. D. Straube
Vogelherd 35, Postfach 3740
8520 Erlangen, Telefon 09131/69-1

THE TREATMENT OF CEREBRAL DISORDERS IN GERIATRIC PATIENTS

A clinical double-blind trial with macromolecular organ lysate (Theurer's method of cytoplasm therapy)

W. Jansen and G. W. Brückner
(Geriatric Hospital, Nuremburg)

A controlled double-blind study in three groups (active drug, placebo, control group without medication) of 35 preselected and randomised patients confirmed the therapeutic efficacy of macromolecular cell components. The Revitorgan preparations Neygeront "N", Dilution No. 6 (foetal heart), Dilution No. 11 (cerebral cortex), Dry Substances 6 and 64B (combination preparation), and Lingual Preparations 64, 69 and 96 were used in the treatment of geriatric patients with cerebral disorders affecting concentration, cerebral perception and

orientation, and statistically definable increases in cerebral performance were achieved.

Cytoplasm therapy is practically a natural result of research in the fields of immunology and molecular biology (Theurer, 1956). Its principle of action is now supported by broad fundamental research (Jachertz, 1963; Rüther, 1964; Letnansky, 1973,1974,1977; Wanderka, 1967, 1974; Wigge, 1975; Lipp, 1977) and a large number of hospital and GP studies, including Fuchs, 1975 (1); Lindstaedt, Wahn, 1975 (5); Ohntrup, 1974 (6); Hoffmann, 1978 (2).

The principle of this method of treatment is stimulation of endogenous repair mechanisms by administration of vital organ substances in a native, directly active form. Cytoplasm therapy is based on carefully separated macromolecular cell components administered in doses calculated with reference to immunological and molecular biological considerations. Reports on preliminary experience with this type of drug therapy in geriatric patients with cerebral impairment syndromes have been published by Jansen, 1969 (3), and others. Other authors agree that therapeutic success of a regenerative nature is achieved.

Protein synthesis rates fall with age. Recently, doubt has been cast on the belief that impairment of the parenchyma of the brain is due purely to vascular factors.

It is now known that these changes in the ageing brain are due to the following molecular causes:

- disturbed or impaired transmission of genetic information to the cell organelles involved in protein synthesis,
- increased frequency of errors in enzyme protein synthesis, and
- reduced ability of enzymes to adapt to increased metabolic

demands, and thus also reduced ability of the brain to maintain metabolic and functional homeostasis.

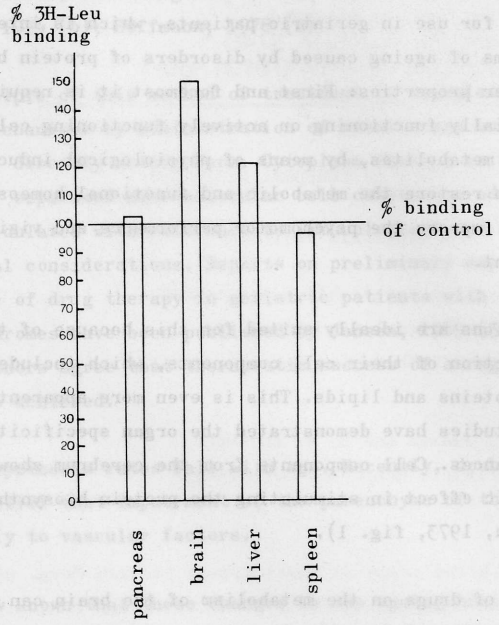
The clinical symptoms of molecular deficiency in cerebral impairment are a fall in overall performance, with rapid fatigue, reduced short and long term memory, disorders of attention and concentration, increased irritability and emotional lability, and extreme sensitivity to noise. These symptoms are usually accompanied by sleep disorders, headache and dizziness.

A therapeutic agent for use in geriatric patients, which is intended to influence symptoms of ageing caused by disorders of protein biosynthesis needs other properties: First and foremost it is required to stimulate potentially functioning or actively functioning cells to synthesise vital metabolites, by means of physiological induction stimuli, in order to restore the metabolic and functional homeostasis of the brain and to improve the psychomotor performance and vigilance of the ageing patient.

Protoplasm preparations are ideally suited for this because of the broad spectrum of action of their cell components, which include nucleinic acids, proteins and lipids. This is even more apparent now that broad animal studies have demonstrated the organ specificity of isolated cell substances. Cell components from the cerebrum showed a particularly specific effect in stimulating the protein biosynthesis of the brain (Axmann, 1973, fig. 1).

Although the effect of drugs on the metabolism of the brain can be demonstrated objectively and directly in animal studies, it is not possible to carry out experiments of the same type in man. In man, indirect methods, such as mental performance tests, have to be used to gain information on the effects on the brain. Our first steps towards psychometric definition of the effect of cytoplasm preparations

Figure 1: 0.5 ml (10^{-3} g/ml) of cytoplasmic organ extract was given to Sprague-Dawley rats by intraperitoneal injection. The rats were killed after 24 hours and the pancreas, brain, liver and spleen were removed and centrifuged at 700 G. The supernatant was used to determine protein biosynthesis by means of 3H-leucine binding.



in geriatric patients took the form of a pilot study (Jansen, Brückner, 1976)(4).

In order to present convincing evidence in a study today, a number of methodological requirements must be fulfilled. To do justice to all the criteria, a multiple study project is necessary, for which reason we chose a multivariant study design.

Methods

The study was double-blind, comparing macromolecular cell components (active drug), placebo, and control (no medication). The control group was included so that pure learning effects could be assessed methodically and separated from placebo effects. This then permits a definite quantitative statement on the effects of the test preparation. The following cytoplasm preparations were used: Revitorgan* Dilutions 6 and 11, Neygeront 64N, Revitorgan Dry Substances 6 and 64B, Revitorgan Lingual Preparations 64, 69 and 96. The patients in the placebo group received physiological saline solution instead of the Dilutions and Lingual Preparations, and chromatographically pure human albumin instead of the Dry Substances. There were 35 patients of either sex in each group (21 men, 84 women). Their mean age was 71.04 years. Three patients of comparable age, sex and intelligence were allotted one to each group on a random basis until the groups were complete.

Intelligence was assessed by the MWT method which is used in psychopathometry and is largely independent of mental and intellectual disturbances. This short test determines the patient's present intelligence quotient and permits assessment of his intelligence level prior to illness. This not only ensured fair distibution of intell-

*vitOrgan Arzneimittelfabrik Dr. Theurer GmbH + Co KG, Postfach 4240, D-7302 Ostfildern 1, Germany.

igence levels between the groups, but also provided a form of preselection, thus including only patients with an IQ that was at least just average.

A variety of methods was used to determine the efficacy of the therapeutic organ preparations.

Benton Test. This determines disorders in cerebral performance, where the patient's premorbid intelligence level is already known or has been determined by another test. It provides information on patients with cerebral disorders and dementive degeneration syndromes coinciding with the clinical examination and observation. The Benton Test does not depend on situation-induced, neurotic, transitory or chronic impairment of intelligence.

Flicker fusion frequency analysis. This test was first used in fatigue research. It has been shown that reduction of the threshold frequency in this test provides information on cerebral impairment (Bßger, 1975).

Mosaic Test from the Hamburg-Wechsler Intelligence Test for adults. This tests analytical and computative ability and is a good measure of general intelligence. It tests combination ability, concepts of space, and visual motor coordination.

Performance Test (Pauli Test). Tests the powers of concentration and ability for prolonged concentration, demonstrating the level of cerebral function (extended Pauli Test equipment).

All the psycometric methods used place high demands on the subject, and are largely unaffected by visual and auditory impairment. They have a high level of tester objectiveness.

The medical condition of the patients was assessed according to an

Table 1 : Double-blind clinical trial treatment schedule. Intramuscular injection of 2 ml each of Revitorgan Dilutions 6 (foetal heart), 11 (young brain extract) 64N (Neygeront^{R} - combination preparation containing total foetus, thymus, diencephalon, cerebral cortex, thyroid, amnion, gonads, adrenals, connective tissue, heart, kidney, aorta, liver, spleen, gastro-intestinal mucosa). Strength II is equivalent to 10^{-9} g/ml; Strength III is equivalent to 10^{-6} g/ml.

week 1	Mon 6/II Tues Wed 11/II Thurs Fri 64N/II Sat Sun	week 4	Mon Tues 11/II Wed Thurs Fri 64N/II Sat Sun
week 2	Mon Tues 6/II Wed Thurs Fri 11/II Sat Sun	week 5	Mon Tues 11/II Wed Thurs Fri 6/II Sat Sun
week 3	Mon Tues 64N/II Wed Thurs Fri 6/II Sat Sun	week 6	Mon Tues 64N/II Wed Thurs Fri 6/III Sat Sun
week 7	Mon Tues 11/III Wed Thurs Fri 64N/II Sat Sun		On all days without injections: 3 x 8 drops of L 64, 69, 96 per day, alternating.
	Mon DS 6 + 64		

indirect assessment scale covering a number of factors: inability to concentrate, weak short-term memory, lack of drive, depression, irritability, anxiety, disturbed social contact, difficulty in getting to sleep, interrupted sleep at night, headache, vertigo, fatiguability, lack of appetite.

The following laboratory data were recorded: haemoglobin, red blood cells, leukocytes, reticulocytes, platelets, bilirubin, alkaline phosphatases, SGPT, SGOT, triglycerides, BSR, creatinine, urea, total cholesterol. These data were obtained and assessed parallel to the psychometric investigations and medical assessment.

All cerebroactive substances were discontinued at least 14 days before the study commenced, and were not re-initiated during the course of the study. Medication was strictly according to plan. All patients commenced treatment on the same day (see tab. 1 for treatment plan). The first phase of treatment lasted 47 days, and was immediately followed by the second main assessment and recording of data. The second phase began on day 50, according to schedule, with Dry Substances 6 and 64B. The oral administration of the Drops continued for a further 25 days, until the third and final assessment.

Analysis of data

The marker variables measured were selected by factorial analysis, and horizontal comparison of the selected parameters between the three forms of treatment was done by comparison of the medians.

The assessment was non-parametrical, since the character of the data interval could not be predicted with certainty. The effective variation in efficacy during the study was assessed separately with the χ^2 test (2 x 2 contingency tables) for each marker variable for each of the three groups at each of the assessment times (main assessment

(MA) 1 : 2; MA 2 : 3; MA 1 : 3) in a vertical comparison. Variations between the three groups helped to define the drug effects.

Results

Factorial analysis of the 23 individual variables yielded 7 factors suitable for further assessment, 2 of which were heavily weighted. One factor, the general factor (G factor) took in almost the whole psychometric test battery, and thus does not distinguish between intelligence, concentration and other parameters of cerebral performance. The second factor mainly applies to variables from the assessment scale. Factor 1 accounts for a total of 56% of the total variance, and the two together 75.4%. There is thus little point in interpreting factors 3 - 7 individually; they are practically irrelevant for the assessment of this therapeutic agent.

Some improvement was observed in all three groups. Simple horizontal comparison of the medians revealed no statistically significant difference in the initial values, thus making differentiation on this basis difficult. The tendency to improvement in all groups is due to learning effects, for which allowance must be made when assessing psychometric test data.

Vertical comparison, on the other hand, permits definite differentiation of groups, and thus also assessment of the drug effect. In the long-term assessment (MA 1 : 3), i.e. assessment of one group over the whole course of the study, the only statistically highly significant improvement was in the active drug group, and not in either the placebo or control group.

In order to exclude the possibility of chance successes, the comparison included not only the marker variables, but also three of the factor 1 items from the psychometric test battery: the correct answers

in the Benton test, the total performance in the Mosaic test, and the correct answers in the Pauli test. The most heavily weighted items chosen for the assessment category in factor 2 were short-term memory disorder and disturbed night's sleep.

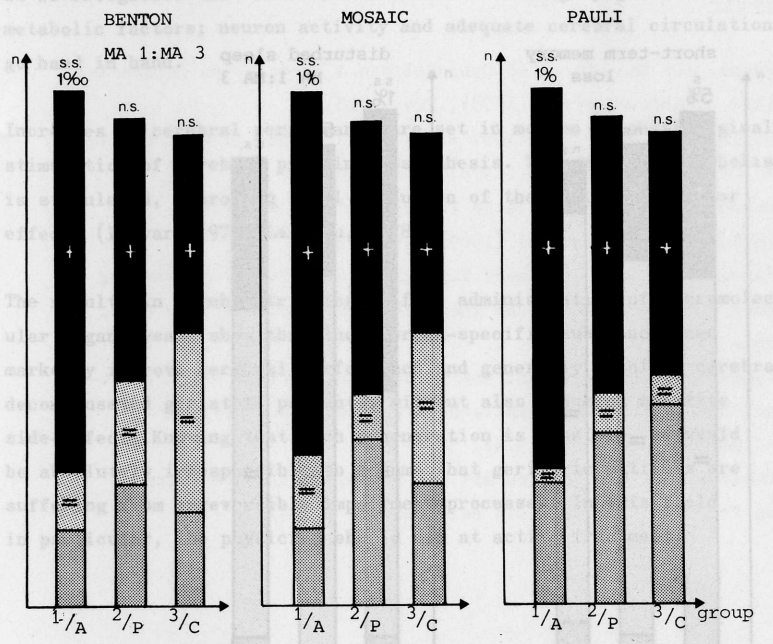
For each, the improved values were compared with the unchanged or worsened values between assessments 1 and 3. In the Benton test (loss of perception due to cerebral impairment) there was a statistically significant improvement in performance compared with the placebo and control groups. This obvious drug-induced effect definitely masks any simple learning effect. Significant drug-related improvements were also found in the Mosaic test and the Pauli test (fig. 2).

Medical assessment of the marker variable "short-term memory disorder" showed the same result as the psychometric assessment. In the variable "disturbed night's sleep", there was a reduction in disturbances in the long term in all three groups (fig. 3). This result can be interpreted as follows: the patients were more sensibly occupied and stimulated, and had such demands placed on them in the treatment and test situation that their sleep improved.

Laboratory findings. A wide range of the laboratory variables usually monitored, including total cholesterol, triglycerides, SGOT, SGPT, creatinine, bilirubin, haemoglobin, etc., was checked at regular intervals. In all cases, values were within normal limits for this group of geriatric patients. No extremes or extreme shifts were observed.

Tolerance. As was the case with the laboratory data, it can be stated with regard to tolerance that the bioavailability and pharmacokinetics were perfect, despite the general loss of active parenchyma in ageing patients. The biological preparations were tolerated excellently, and no incompatibility of any kind was observed.

Figure 2

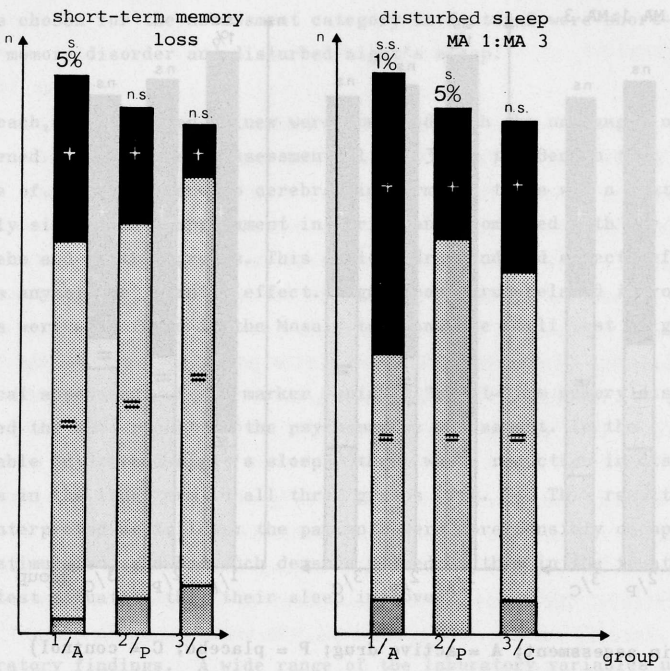


(MA = main assessment; A = active drug; P = placebo; C = control)

Discussion. "Ageing" is a phenomenon that probably includes a number of processes: exhausted mitosis capacity, reduction in neurosecretion, aplasia of the thymus, and disturbed interaction of the various organ systems.

It is also interesting that enzymes from young and old human liver cell cultures (Hayflick's phase 2 or phase 3) have the same enzymatic activity and immunological reactivity (Kahn, 1977). Electrophoresis shows that the brain proteins of young and old mice are identical (Vaughan, Calvin, 1977). These observations are not really in

Figure 3



(Abbreviations as in Figure 2)

accordance with the theory of programmed ageing by a systematic shutting off of genetic activity. The reduction in protein turnover in the ageing organism is thus probably due to the fact that there are not enough cell-specific induction stimuli at this stage in life. High-molecular organ cytoplasm preparations exercise an effect on the cell synthesis and metabolism, provided that the cells in question are still capable of a biological response.

It is recognised that cerebral circulation is largely governed by metabolic factors; neuron activity and adequate cerebral circulation go hand in hand.

Increases in cerebral performance are set in motion by physiological stimulation of cerebral protein biosynthesis. The neuronal metabolism is stimulated, improving local perfusion of the brain by mediator effects (Ingvar, 1978; Larssen, 1978).

The results in psychometric tests after administration of macromolecular organ lysate show that these organ-specific substances can markedly improve cerebral performance and generally vitalise cerebrally decompensated geriatric patients, without also inducing negative side-effects.Knowing that such regeneration is possible, it would be absolutely irresponsible to assume that geriatric patients are suffering from irreversible impairment processes. In this field in particular, the physician should aim at active treatment.

Authors' address: Dr. W. Jansen, Dipl.-Psych. G.W. Brückner,
Altenkrankenhaus der Stadt Nürnberg,
Veilhofstr. 34, D-8500 Nürnberg, Germany.

References

1. Fuchs, J.: The effect of Conjunctisan A Eyedrops on cataracts. (Med. Monatsschrift 5 (1975), 224 - 225)
2. Hoffmann, Z.: The treatment of diseases of the joints. (Zeitschr. f. Allgemeinmedizin 15 (1978), 847 - 851)
3. Jansen, W.: Zytoplasmatische Therapie in der Geriatrie. (Erfahrungsheilkunde 11 (1969), 396 - 398)
4. Jansen, W., G.W. Brückner: Tagungsbericht XXII. Jahrestagung über die Zytoplasmatische Therapie, Stuttgart, October 1976, 28 - 29.
5. Lindstaedt, R., K. Wahn: Über Behandlungserfolge bei Problempatienten mit zytoplasmatischen Therapeutika. (Zeitschr. f. Allgemeinmedizin 11 (1975), 545 - 548.
6. Ohntrup, H.: Erfahrungen mit der Zytoplasmatischen Therapie an Problempatienten. (Die Heilkunst 10 (1974), 1 - 3.