MINISTRY
OF HEALTH
•
THE NATIONAL
INSTITUTE
OF GERONTOLOGY
AND GERIATRICS
Bucharest

Romanian Journal of Gerontology and Geriatrics

2 tome 1
1980

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ROMANIAN JOURNAL OF GERONTOLOGY AND GERIATRICS

— biannual journal —

Str. Mănăstirea Căldărușani No. 9, R-79605-București, România

Romanian Journal of GERONTOLOGY and GERIATRICS

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LONGITUDINAL STUDY IN THE NATIONAL INSTITUTE OF GERONTOLOGY AND GERIATRICS OF ROMANIA

ANA ASLAN

National Institute of Gerontology and Geriatrics, Bucharest, Romania

Summary. Aging as a process which appears gradually during the life can be influenced through hygienic and therapeutical measures applied longitudinally.

For the researches carried out at the National Institute of Gerontology and Geriatrics, there were established several groups of subjects, to whom a complex of representative indices were applied in order to estimate the aging rhythm. The evolution of these indices was studied during the treatment with Gerovital H_3.

The longitudinal researches were carried out at different time intervals, the longest being at present of 27 years.

The groups of subjects under treatment differ in age, from 60 to 90–100 years. The main research is carried out in the Home of the Institute on subjects with the same environmental conditions and to whom different treatments were applied: Gerovital H_3, Vitamin E, epiphysis extract.

Other longitudinal researches are carried out on outpatients in polyclinics, factories or gerontological centres in the country.

All the subjects underwent periodically (half-yearly or yearly) clinical, psychological, functional, biochemical and hematological investigations.

Administration of Gerovital H_3 treatment led to the prevention of chronical degenerative diseases (which accelerate the aging process) or to their improvement, diminishing as well the thrombotic accidents, in the elderly. A reactivation or intensification of cellular regeneration processes (researches on cellular cultures) and of adaptation and defence mechanisms of the body takes place.

Gerovital H_3 has an antidepressive action, improving the psychological tests, the conditioned reflexes, the EEG track, the vascular reactivity and elasticity as well as the disturbances of coronary irrigation on ECG, etc.

In the treated subjects it was also noticed the increase of life expectancy and lengthening of physical and psychical activities. The lengthening of the life span was remarked in experimental researches, too.

Taking into account the metabolic properties of the therapy based on procaine, it is considered that by pointing out the above-mentioned effects one may reach a better understanding of the aging process (action on collagen, MAO inhibition, auto-antibodies reduction, release of calcium from the erythrocytic membrane).

Therapeutic research began on May 5th, 1951, on the elderly from a Home which in 1952 became the Institute of Geriatrics and later on, in 1974, the National Institute of Gerontology and Geriatrics; here, research efforts were directed towards 'the therapy and prophylaxis of aging'; the study of the aging phenomenon was included in the scientific research program of the Romanian Academy, under the directorship of C. I. Parhon, according to whom aging is a chronic dystrophic process (disturbances in cell metabolism), in the treatment of which vitamins, hormones and tissue extracts have to prevail. He believed in a therapeutic intervention which could delay and influence the aging process.

Experimental research was directed mainly towards assessing the role of the epiphysis, the thymus and the gonads; as a matter of fact, the above-mentioned therapeutics was the result of experimental studies.

Since 1948, I have taken part in the organization of the Institute as well as in most of the therapeutic work carried out here. We had to face all the difficulties inherent in any start, among which was the lack of comparable groups other than the aged. Most of the subjects under study did not present a normal aging pattern: the average age was in the 8th decade and life expectancy was limited. Nevertheless, despite the difficult start we tried to conduct cross-sectional researches on the functions of the organism, with emphasis on the nervous system, the cardiovascular and endocrine apparatus. We chose these criteria, the most representative and reproducible ones, with a view to applying them to the aged for therapeutic study and for studying the aging process.

Initial long-term studies using chemotherapeutic agents were tested in three groups of 28—40 selected elderly patients. They had previously received a variety of exploratory treatments, including spleen extract, pineal and thyroid hormones, procaine, vitamin E, and vitamin B complex. Of these three selected groups, one group was put on procaine, the second on vitamin E and the third on pineal gland extract (later this group became a control group), all being administered intramuscularly three times a week a total of 12 injections over a four-week period. Then, after a 10-day drug-free interval, the series of injections were resumed. Eight series of injections were given during the first year, and the program was continued during subsequent years.

In 1954, examining our observations, Parhon stated: "Regeneration of the organism occurred as a result of the treatment received, even hair repigmentation was obtained with certain substances (novocaine)". The capacity displayed by novocaine and vitamin E to attract fatty substances and render them soluble should be underlined. We believe they may be considered as defence factors against sclerosis. Mention should be made that in 1951 we did not use the double-blind technique; nevertheless the vitamin E and procaine groups were subjected to similar cycles of injections.

In 1956, I drew the following conclusions: from a clinical point of view, the treated subjects showed lust of life, diminished depression and anxiety, improved memory, increased physical and intellectual capacities, improved activity in the auditory, optical and olfactory analysers, diminished extrapyramidal stiffness, better trophicity of the skin and nails, controlled senile keratosis, growth of hair, increased muscular strength and joint mobility, normalized arterial blood pressure, increased appetite and weight [1].

It did not take too long to notice marked changes in the procaine group, in which hair repigmentation was noticed and reported, an effect of procaine which was unknown until then [2]. Later, Parhon et al. [3] published their *Results of psychological tests*, reporting also an improvement in memory and attention with this treatment. A large series of criteria were then developed to measure these changes objectively (psychological test batteries, studies of conditioned reflexes) [4].

By means of plethysmographic and oscillometric investigations, the vascular reactivity was measured [5]. Muscle strength and blood flow measurements were taken. Biochemical analyses to examine protein, lipid and glucose metabolism, as well as routine blood chemical analyses and blood counts were used. In addition,

life expectancy, morbidity and mortality tables were employed to analyze how the three groups compared with each other and with the population as a whole [6].

With respect to life expectancy, we tried two substances with metabolic action, i.e. vitamin E (60 mg) and procaine (Gerovital H_3 = procaine 2%, benzoic acid 0.12%, potasium metabisulphite 0.10%, disodium phosphate 0.01%). The action of these substances was observed over 8 years. Meanwhile, a control group

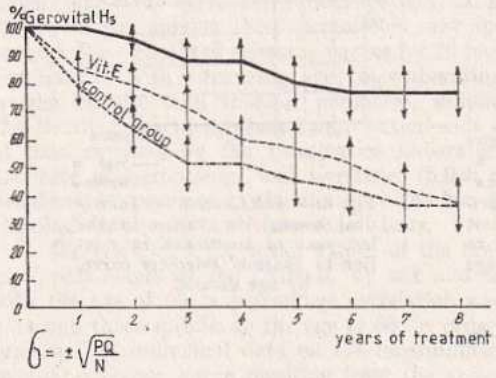

Fig. 1. — Survival curve.

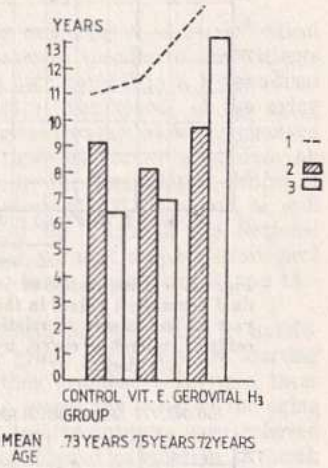

Fig. 2. — Life-span researches with Gerovital H_3 and vitamin E.

1, Ratio: effective life-span/probable life-span; *2*, life expectancy; *3*, effective life.

living under similar environmental conditions was kept under observation. Each group, except for the control group (37 subjects), was subjected to the respective treatment, according to the same schedule, that is: 3 injections per week, in series of 12 injections with 10-day breaks between the series. The average age was 76.8 in the Gerovital H_3 group, 75.2 in the vitamin E group (60 mg), and 72.4 in the control group (Figs 1, 2).

In order to assess the efficacy of the treatment we found it important to check the life expectancy of the whole group. The data on life expectancy were available in the mortality tables set up by the Central Board of Statistics after the population census [6, 7].

The life expectancy figure was compared to that of mean outlived years, with each case and separate group; we thus found out that the Gerovital H_3-treated group outlived the overall life expectancy by 30%; mention should be made that almost all the subjects investigated presented pathological phenomena which resulted in the shortening of the life span in the control and vitamin E groups. The benefits derived from Gerovital H_3 treatment were also shown by the improvement in pathological condition of the treated cases.

These studies were correlated with an experimental research conducted on 1840 white rats [8]. 50% of the animals were subjected to a treatment similar to

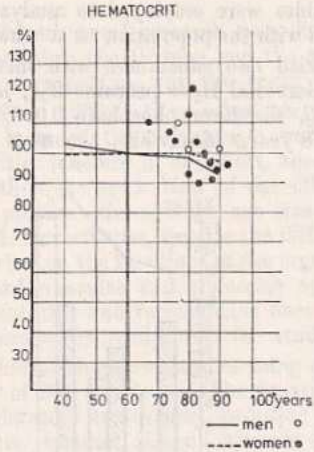

Fig. 3. — Distribution of individual hematocrit values in the last year of treatment, in relation to controls' reference curve, by age decade.

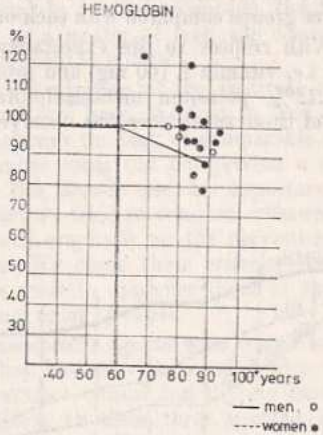

Fig. 4. — Distribution of individual hemoglobin values in the last year of treatment, in relation to controls' reference curve, by age decade.

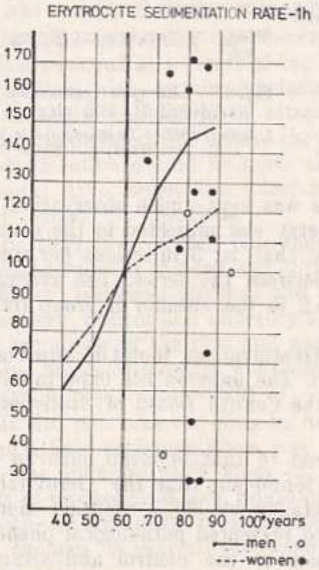

Fig. 5. — Distribution of individual erythrocyte sedimentation rate values in the last year of treatment, in relation to controls' reference curve, by age decade.

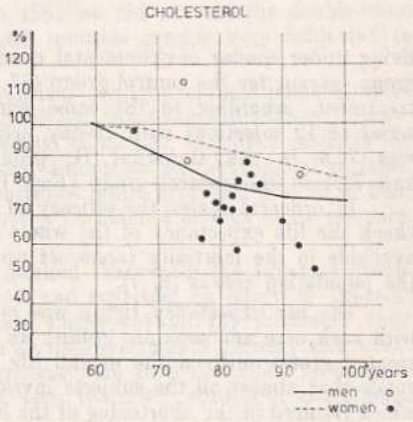

Fig. 6. — Distribution of individual cholesterol values in the last year of treatment, in relation to controls' reference curve, by age decade.

that used on human patients; the other half were used as controls (untreated group). A prolongation of the life span by 4 months (21%) as against the controls was noticed.

I would like to mention that one patient, aged 88, from the first group receiving Gerovital H_3 treatment since 1951, and 3 of 7 volunteers, aged 82, 79 and 92, are still alive. The subject aged 82, who at the age of 49 showed the symptoms of early aging, at present, after 21 years of treatment, has a normal aging pattern.

In collaboration with Safirescu, Breaz, König and Bârsan, a mathematical analysis was made of some of the biological parameters specific to the patients under long-term care, using each patient as his own control in a longitudinal study; in our opinion these parameters may indicate "the speed" of the aging process. We elaborated reference curves for 26 biological parameters which changed significantly with advancing age; in elaborating these curves we used data on weight, stature, and thoracic perimeter, supplied by the Computation Centre of the Health Department (based on a nation-wide analysis of 703,574 cases), as well as data supplied by the Informatics Laboratory of the Clinic of the National Institute of Gerontology and Geriatrics (5,026 cases without major pathological problems, hospitalized in the clinic for the last 20 years), hematological and biochemical constants and functional tests.

We calculated the mean values of the functional, biological and hematological parameters of the controls, by sex and age group every 5 years starting with the age of 60; a percentage correlation was then established between these data and those specific to the age of 60, in order to assess the speed of the aging process. The individual data on the longitudinally treated subjects were referred to the reference curve resulting from the above-mentioned calculation: a much slower aging rhythm was thus pointed out in the group of subjects treated with the biotrophic product Gerovital H_3.

The criteria under study (in 1975) for the Gerovital H_3-treated group were: hematocrit (Fig. 3), hemoglobin (Fig. 4), ESR (Fig. 5), sugar levels, lipemia, beta-lipoprotein, cholesterol (Fig. 6), triglyceride, protein (Fig. 7), albumin, globulin, urea, uric acid, oscillometry, basal metabolism, systolic pressure, diastolic pressure, CVA, VEMS, IPB, DVM, weight (Fig. 8), height (Fig. 9), thoracic perimeter, ECG, EEG, and anatomo-pathological data.

The research was conducted by a team of 17 research specialists * from the Clinic and from the Department for the Biology of Aging. The following facts were noticed in most of the treated patients: lowering of stature with advancing age was evidently slowed down, the process of losing weight slowed down, oxygen consumption was higher, cholesterol levels followed a lower downright curve, the diminution in muscular strength evidently slowed down.

The cases subjected to mathematical analysis were few, but they were kept under observation for 10—25 years. The total number of Romanian patients treated in the Institute amounts to 133,555 in 27 years.

Since the very beginning we approached the problems raised by the prophylaxis of aging. As a matter of fact, no difference should be made between the

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* Bălăceanu, C., Birsan, M., Breaz, S., Coculescu, L., Costiniu, M., David, C., Enăchescu, C., Enăchescu, G., König, V., Lăbuşcă, M., Lalu, P., Mihăilescu, V., Popescu, F., Sacerdoţeanu, F., Safirescu, T., Simion, S., Vrăbiescu, Al.

prophylactic and the curative treatments because any kind of therapy which should influence the aging process is, for the time being, a prophylactic therapy aimed at delaying the aging process, improving the functional and adaptive capacities, preventing the onset of chronic diseases and invalidities.

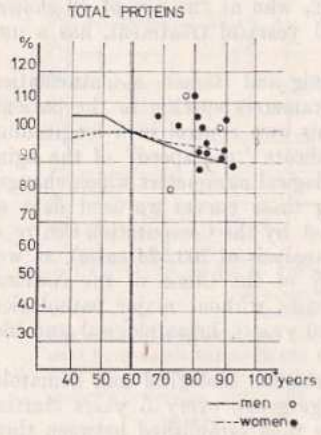

Fig. 7. — Distribution of individual total protein values in the last year of treatment, in relation to controls' reference curve, by age decade.

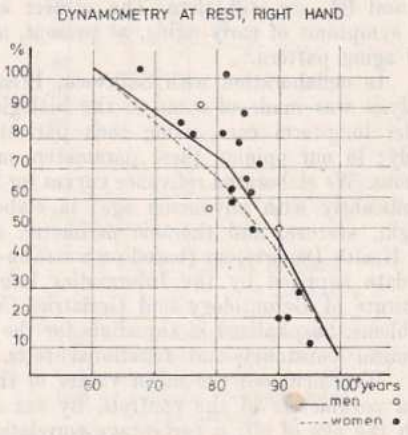

Fig. 8. — Distribution of individual dynamometric values in the last year of treatment, in relation to controls' reference curve, by age decade.

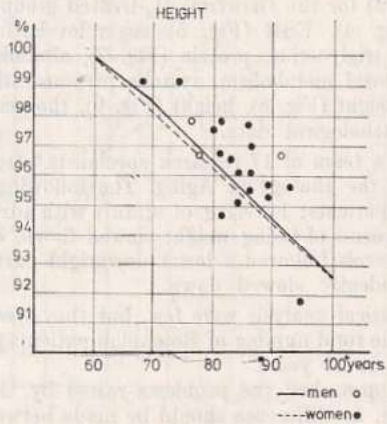

Fig. 9. — Distribution of individual height in the last year of treatment, in relation to controls' reference curve, by age decade.

We have pointed out the decrease of invalidity from 52% to 13% since 1956. We have also mentioned that during a severe influenza epidemic the mortality figure was 2.7% among the treated patients and 13.9% among the untreated ones [9].

From the immunological point of view, a significant increase of alpha- and beta-isohemagglutinins [10] in the patients actively immunized with group antigens was noticed as a result of long-term treatment. These facts account for the resistance to infection in the treated patients.

Repeated X-ray examinations showed alleviation of involutive osteoporosis [11].

Morphological examination of deceased patients who had been subjected to Gerovital H_3 treatment revealed: better preservation of the nervous structures, diminished vasoconstriction in kidney and endocrine glands, reactivation of the mycocardial fibre as well as fewer atherosclerotic lesions on the aorta [12]. It was also noticed that the aged with accidental fractures recovered in 45—60 days by endosteal callus formation. This observation was experimentally verified [13].

The studies conducted in collaboration with Nedler and Todea [14] on experimentally induced arthritis showed that in 30% of the cases this did not occur, whereas in 85% the articular phenomena were cured as a result of the treatment. We also showed the general effect of the substance on the fur, and on the weight of the organs.

Prophylactic treatment was tried for the first time on 100 workers aged 45—60: the results, assessed in comparison with a control group were quite favorable. The prophylactic treatment was then instituted in 145 gerontological centres. We carried out a statistical mathematical analysis on a group of 150 workers (70.7% men and 29.3% women) subjected to a 10-year treatment. Based on the study of the dynamics of some somatophysiometrical criteria, Ciucă and Ghenciu made a synthetic assessment of the health status of the elderly before and after treatment with Gerovital H_3. A high percentage was specific to both tests before the treatment, 82.1% men and 79.5% women with medium health status; 15.1% men and 9.1% women with normal health status; 11.4% men and 2.8% women with major pathological problems. A continuous improvement in the medium health status was seen in 15.1% of the men and in 9.1% of the women; it also improved as a result of the 5 to 10 years' treatment in 54.6% of the men and in 48.8% women. The conclusion which can be drawn is that long-term treatment contributes to the improvement of the health status. The working capacity was dynamically assessed and certain physiometrical age criteria were calculated as against the respective criteria. Thus, the dynamometric tests subsequent to the 2-year treatment showed an increase in muscular strength to 124 in men (age group 50—54) and to 90.6—94.4 in women (same age group).

Vital capacity decreased with advancing age in both sexes: men 3431—3183, women 2900—2778. As a result of the treatment the values increased to 3544 and 3200 in men aged 50—54, and to 3000—2878 in women aged 50—54; the most significant accumulation was noticed after 2 years of treatment.

Arterial blood pressure, the vital capacity index, the average values in oscillometry, and height were also investigated.

The above-mentioned data were the result of a 23-year longitudinal research carried out at the National Institute of Gerontology and Geriatrics in Bucharest. They showed that the product and the method of treatment were well tolerated by the aged. They also demonstrated that the process of aging can be delayed by reducing the incidence and alleviating the progress of chronic diseases, particularly when the treatment is prophylactically applied.

Riassunto. La vecchiaia è un processo evolutivo che s'installa pian piano lungo la vita e puo essere influenzato tramite delle misure di igiena e terapia, applicate in modo longitudinale.

Nel quadro delle ricerche efettuati nell'Instituto Nazionale di Gerontologia e Geriatria, sono stati constituiti più gruppi di soggetti, su di cui si è applicato un sistema di test di indicatori rappresentativi, allo scopo di valutare il ritmo d'invecchiamento.

In seguito si è studiata l'evoluzione degli indicatori durante il trattamento con Gerovital H_3.

Le ricerche longitudinali si sono sviluppate in vari intervalli di tempo, il più lungo è arrivato oggi a 27 anni.

I gruppi in trattamento sono constituiti da soggetti di varie età da 60 a 90—100 anni. Le ricerche basi si sono efettuate nell'asilio per i vecchi dell'istituto, su soggetti viventi nelle stesse condizioni ambientali, sui quali si sono applicati i trattamenti con Gerovital H_3, vitamina E, e estratto di epifisi.

Le altre ricerche longitudinali sono attuate in ambulatorio o sul posto di lavoro (Policlinico, imprese, centri geriatrici).

Le investigazioni cliniche, psicologiche, funzionali, biochimiche e ematologiche sono state fatte sui soggetti, ogni semestre.

La somministrazione del trattamento con Gerovital H_3 ha portato alla prevenzione delle malattie croniche degenerative che accelerano il processo d'invecchiamento e, per le età avanzate — ad un importante miglioramento delle dette e alla diminuzione degli incidenti trombotici. Col trattamento longitudinale ha luogo una riattivazione e un rinforzamento dei processi di regenerazione cellulare (ricerche su culture di cellule) e dei mecanismi di adattamento e difesa dell'organismo.

Sui soggetti trattati con Gerovital H_3 si è costatato un efetto antidepresivo, il miglioramento dei test psicologici, dei riflessi condizionati e dei tracciatti EEG, l'aumento della forza muscolare, l'equilibrio delle funzioni endocrine, il miglioramento della reattività e dell'elasticità vascolare, il miglioramento dei disturbi di irrigamento coronario sull'EEG, ecc.

Si è costatato ancora l'aumento della speranza di vita e il prolungamento dell'attività fisica e psichica. Il prolungamento della durata di vita è stato notato anche nelle ricerche sperimentali.

Tenendo conto delle proprietà metaboliche della terapia in base alla procaina, si considera che la messa in evidenza degli efetti prodotti puo portare alla conoscenza approfondita del processo d'invecchiamento (azione sul colageno, inibizione MAO, riduzione auto-anticorpi, ecc.).

REFERENCES

1. Aslan, A., *Eine neue Methode zur Prophylaxe und Behandlung des Alterns mit Novocain—Stoff H_3 — eutrophische und verjüngende Wirkung.* Therapiewoche, Karlsruhe, 1956, *1/2*, 14—22.
2. Aslan, A., Parhon, C.I., *Novocain, a factor against acromotrichia* (in Romanian). Bul. St. Acad. R.P.R., Bucharest, 1955, **5**, *4*, 557—568.
3. Parhon, C.I., *Biologia virstelor.* Ed. Academiei, Bucharest, 1955, p. 417.
4. Aslan, A., Parhon, C.I., Vrăbiescu, Al., *Central nervous activity in young and old people, studied by the method of vascular conditioned reflexes. The influence of hormone and vitamin treatments in old persons* (in Romanian). Com. Acad. R.P.R., Bucharest, 1955, **5**, *2*, 417—424.
5. Aslan, A., Vrăbiescu, Al., *Oscillometric research in old people by effort test* (in Romanian). St. Cerc. Endocrinol., 1955, **6**, *1—2*, 215—221.
6. Aslan, A., *Theoretical and practical aspects of chemotherapeutic techniques in the retardation of the ageing process — Gerovital H3.* In: *Theoretical Aspects of Aging*, ed. by Morris Rockstein, Academic Press, New York, 1974, p. 145—156.
7. Aslan, A., Jantea, F., Nicolae, D., *Recherches sur la microbiocénose intestinale et la sanogenèse chez les vieillards.* Abstracts Seventh Intern. Congr. of Geront., Vienna, 1966, Vol. 2, p. 251.

8. Aslan, A., Vrăbiescu, Al., Domilescu, C., Cîmpeanu, L., Costiniu, M., Stănescu, St., *Long-term treatment with procaine Gerovital H_3 in Albino rats.* J. Geront., 1965, **20**, *1*, 1–8.
9. Aslan, A., Cosmovici, N., Lalu, P., Bunescu, G., *Development of the influenza virus epidemy in the Bucharest Institute of Geriatrics (February–March 1959)*, Intern. Conf. on Geront., Akadémiai Kiadó, Budapest, 1965, p. 409–413.
10. David, C., Enăchescu, G., *Immunologische Untersuchungen bei Bejahrten. Dynamische Aspekte der Reaktivität bei antigen Stimuli aus dem 0AB-Blutgruppensystem. Therapeutische Stimulierungsmöglichkeiten der immunologischen Reaktivität.* Verhandlungen der Deutschen Gesellschaft für innere Medizin 74. Band. Verlag J.F. Bergmann, München, 1968.
11. Aslan, A., David, C., Hatmanu, D., *Dysmetabolic osteoporosis of involution.* Intern. Conf. on Geront., Akadémiai Kiadó, Budapest, 1965, p. 445–451.
12. Aslan, A., Crăciun, E., David, C., *Sur la thanatogenèse pathologique du vieillard.* Inf. Méd. Roum., 1959, *3*, 16–17.
13. Aslan, A., *Recherches concernant le processus de vieillissement et sa prophylaxie.* Report at the VIIIth European Congress of Clinical Gerontology, Neptun, Romania, 1977.
14. Aslan, A., Nedler, M., Todea, L., *The effects of procaine on experimental arthritis induced in albino rats* (in Romanian). Com. Acad. R.P.R., Bucharest, 1951, **1**, *11–12*, 1110–1116.

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ASLAVITAL FOR CHILDREN IN MENTALLY DEFICIENT SUBJECTS

ANA ASLAN, AL. VRĂBIESCU, MARINA DOBRE

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Summary. The study was conducted on 100 school girls aged 7 to 14 with mild or average mental deficiency.

According to the double-blind method used, 50 children were treated with Aslavital for children and 50 with Placebo.

The medication was administered as pills (2 per day) for 3 weeks alternatively, with shots of 4 ml Aslavital for adults and aged. One day break weekly.

The treatment was administered in the course of 180 days, each subject receiving 85 shots and 190 pills.

The etiology and the clinical diagnosis were established based on the medical examination.

The psychological tests pointed out the psychic deficiencies and their extent; the tests were focused on the assessment of the mental level, memory, concentration, attention, psychomotor control and coordination.

The tests were done prior to and after the treatment.

No significant difference between the 2 groups under study was noticed prior to treatment.

The psychological tests resumed at the end of the treatment revealed obvious improvements in Aslavital-treated children as concerns the dynamics of the intellectual activity, psychomotor control and coordination, memory and ability to concentrate, motor style in accomplishing a psychomotive task.

The teachers also noticed improvements in the behavior of Aslavital-treated children as well as a higher responsiveness to the educational training.

No significant changes as against initial tests were noticed in children receiving Placebo.

In a previous double-blind study the authors showed that the geriatric product Aslavital influenced effectively the dynamics of the intellectual activity and its motor projection, as well as the adaptative function of the central nervous system of children suffering from mild or average mental deficiency. Consecutively, better results in school activities were noticed with the treated as against Placebo groups [1].

Based on the results mentioned, Ana Aslan has started the elaboration of an activated derivative of Aslavital adjusted for the treatment of mentally deficient children *. The present paper reports the results of the double-blind study carried out with this new product.

* "Aslavital for children", patent. Authors: Ana Aslan, M.D., D.Sc. and Florica Mihăilescu, Ph.c.

MATERIAL AND METHOD

The study was conducted on a group of 100 school girls aged 7 to 14 from a boarding school for mentally deficient children in Bucharest**. These subjects were selected from 210 children subjected to clinical, neurologic, psychological, and electroencephalographic investigations following the diagnosis of mild or average mental deficiency without underlying diseases. The case histories mentioned encephalopathic sequellae, obstetrical traumas, cranio-cerebral traumas, ethilic or mentally deficient parents, unappropriate family environment, parents with disturbed behavior, conflicts between parents, disorganized families, hygienic and educational deficiencies.

The psychological examination aimed at investigating mental level based on Raven's coloured progressive matrices. The group under study included children with IQs ranging from 0.44 to 0.70, corresponding to mild or average mental deficiency [2].

The psychological examination was focused on assessment of:

— memorizing ability, according to "voluntary memory" test (V.M.);

— attention, according to "attention, double checking" test I and II (A.d.c.) and "attention-efficiency" (A.e.);

— relationship between motor behavior and intellectual development, according to "tapping lines — motor level and style".

These tests were selected for pointing out the dynamics of the intellectual activity, perception, thought and their motor projections by means of measuring movement coordination and manual ability in the more or less precise accomplishment of psychomotive tasks [3, 4].

All psychological tests were done prior to and after the treatment.

Simultaneously, the teachers watched the progress in school training.

According to the double-blind method the children were randomly divided into 2 groups, each including 50 subjects.

All children were first tested for Aslavital tolerance; subsequently one group received Aslavital for children, 2 pills per day, 3 times weekly, alternatively with 4 ml Aslavital in i.m. shots 3 times per week. The treatment was administered in the course of 11 months, discontinued on Sundays and during holidays.

Each child received 190 Aslavital pills and 85 Aslavital shots.

The children from the second group received the same amount of pills and shots with Placebo. During the study no other neurotropic medication was administered.

The products were administered by the medical staff, based on the parents' consent.

RESULTS AND DISCUSSION

After the individual interpretation, the results of the psychological tests prior to and subsequent to treatment were subjected to the statistical analysis based on the "t" test.

** Boarding school for mentally deficient children No. 6. Director: Prof. Emilia Catrinescu.

The following facts were pointed out:

1) The results of the psychological tests before the beginning of the experiment were similar for all children included in the 2 groups (Table 1);

2) No statistically significant improvement occurred in the Placebo group (Table 2);

Table 1

Results of psychological tests prior to treatment

Test	Aslavital for children	Placebo	Statistical significance
V.M.	3.36 2.34	3.44 2.38	N.S.
A.d.c. I	0.126	0.117	N.S.
A.d.c. II	0.326	0.322	N.S.
A.e.	83.96	84.16	N.S.
T.l.m.l.s.	70.14 58.08	90.58 60.00	N.S. N.S.

Abbreviations: V.M. = Voluntary memory
A.d.c. = Attention, double-checking, I, II.
A.e. = Attention, efficiency
T.l.m.l.s. = Tapping lines, motor level and style.

Table 2

Results of psychological tests prior to and after Placebo

Test	Before Placebo		After Placebo		Statistical significance
	m.	s.d.	m.	s.d.	
V.M.	3.45 2.38	±0.06 ±0.05	3.44 2.48	±0.06 ±0.06	N.S. N.S.
A.d.c. I	0.117	±0.08	0.125	±0.09	N.S.
A.d.c. II	0.322	±0.02	0.327	±0.02	N.S.
A.e.	84.16	±2.86	81.76	±2.74	N.S.
T.l.m.l.s.	90.58 60.00	±4.28 ±4.02	77.76 62.82	±3.57 ±4.08	N.S. N.S.

Abbreviations: See Table 1

3) The results of all the psychological tests improved significantly in the group treated with Aslavital for children (Table 3).

The scores of the psychological tests in the treated children pointed out: significant improvement in memorizing ability and sustained mental activity,

Table 3

Results of psychological tests prior to and after Aslavital for children

Test	Before		After		p
	m.	s.d.	m.	s.d.	
V.M.	3.36 2.34	0.71 0.55	4.10 3.20	0.64 0.52	<0.01 <0.01
A.d.c. I	0.126	0.12	0.086	0.09	<0.05
A.d.c. II	0.326	0.24	0.239	0.2	<0.05
A.e.	83.96	±3.04	97.42	±3.31	<0.05
T.l.m.l.s.	70.14 58.08	±5.61 ±4.25	54.22 40.18	±5.23 ±3.06	<0.05 <0.02

Abbreviations: See Table 1

corrected attention deficiencies included; increased psychomotor control and coordination; improved motor style in accomplishing the psychomotive target.

The details given by the didactic staff on the 2 groups under study pointed out favorable elements concerning the evolution of the educational process in the subjects treated with Aslavital for children. The difficulties in concentrating attention and memorizing, apathy and slowness, proneness to isolate oneself diminished and the results became ever better for all classes.

The teachers noticed obvious personal traits, occurring in the treated children, their active participation in school activities their effort to obtain good marks, the real improvement of their ability to learn (arithmetical reasoning, memorizing, attention).

The increased resistance to exertion and lower receptivity to intercurrent diseases in Aslavital-treated children should be mentioned as a general observation made by the didactic staff.

The neurological and electroencephalographic examinations performed at the end of the study pointed out no progress in the preexisting changes in the children under study.

Mention should be made that the medication had no side effect throughout the period of study.

In elaborating Aslavital and Aslavital for children, Ana Aslan made use of her observations on the effects of Gerovital H_3 in depressive states, decrease in memorizing ability and some diseases of the nervous system in the aged, as well as its action on memory, attention, learning ability noticed in children under treatment for other diseases, such as vitiligo, alopecia, etc. The children with average school performances had very good results; a girl aged 11 was able to learn foreign languages.

In order to obtain Aslavital, the amount of potassium ions required by the release of acetylcholine was increased [5]; the author also added glutamic acid, the role of which is well known in neuron metabolism and acetylcholine release. This acid is taken up by the nervous cell. Mention has been made of its effects on rigidity in Parkinson's disease and in delaying epileptic attacks. It also plays an important part in disamination, a part strengthened by vitamin B_6.

Aslavital for adults and aged, a product available as pills, contains vitamin B_6 and mesoinositol as procaine activators [6].

It was demonstrated that in order to function normally the nervous cell requires a biochemical substratum in which pyridoxine plays an important part. As therapeutic effect the amendment of rigidity way noticed in Parkinsonian patients.

Experiments on rats pointed out the improvement of conditioned reflexes under the action of pyridoxine and glutamic acid [7].

Vitamin B_6 has its part in the functioning of neurons and skin, in the trophicity of the nervous cells of the motor cortical and diencephalic areas, in the physiology of the worn out heart, in disamination processes, neuromuscular dystrophies, myopathies.

Mesoinositol is an antiasthenic agent particularly active in cases of muscular fatique. Being an anabolic agent it stimulates growth processes.

The experimental studies on growth in rats pointed out a certain relationship between mesoinositol and paraaminobenzoic acid. Growth of mice requires 6 factors of the vitamin-B complex: B_1, B_2, B_6, choline, PP, pantothenic acid. If either inositol or paraaminobenzoic acid alone is added to the above mentioned vitamins, growth is more difficult. If both paraaminobenzoic acid and inositol are added, growth is normal.

Mention should be made that higher amounts of mesoinositol are found in young tissues as against old ones.

When elaborating Aslavital for children, one of the authors adapted Aslavital formula by activating the synergic action of some components with procaine action in order to intensify the neurotropic effects.

Aslavital for children includes in a new formula and one single form (sugar-coated pills) the synergic components of Aslavital vials and pills for adults and aged; the drug is thus more efficient and easier to administer to children.

In conclusion, the double-blind study of the treatment with Aslavital for children in mentally deficient subjects yielded good results pointed out by the psychological tests and a higher efficiency of the educational training, indicating the improved trophicity and functioning of the central nervous system. A quicker rehabilitation of the mentally deficient children was thus possible.

Résumé. L'étude a été effectuée sur 100 petites filles de 7 à 14 ans souffrant de déficience mentale légère ou moyenne.

On a utilisé la méthode « double blind », un lot de 50 enfants étant traités à l'Aslavital à usage pédiatrique et 50 ayant reçu un facteur « Placebo ».

La posologie a été la suivante: deux fois par jour une dragée pendant trois semaines, alternativement avec l'administration d'injections de 4 ml (utilisées aussi pour les patients adultes et âgés). Chaque semaine un jour d'interruption.

La durée du traitement a été de 180 jours, chaque patient recevant, au cours de ce laps de temps, 85 injections et 190 dragées.

L'étiologie et le diagnostic clinique ont été établis à la suite d'une examination médicale.

Les tests psychologiques ont mis en évidence les déficiences psychiques et leur degré; les tests ont été concentrés sur l'évaluation du niveau mental, de la mémoire, la concentration, l'attention, le contrôle psychomoteur et la coordination.

Les tests ont été effectués avant et après le traitement.

Les tests psychologiques évalués à la fin du traitement ont mis en évidence des améliorations visibles chez les enfants traités à l'Aslavital, aussi bien dans le domaine de la dynamique

intellectuelle que dans le contrôle psychomoteur et la coordination, dans le domaine de la mémoire et de la capacité de concentration et en ce qui concerne le style de la motricité dans l'accomplissement d'une tâche psychomotrice.

Le corps enseignant a aussi remarqué une amélioration dans le comportement des enfants traités à l'Aslavital, de même qu'une plus grande réceptivité au processus éducatif.

Chez les enfants ayant reçu le facteur « Placebo » on n'a pas observé des modifications significatives.

REFERENCES

1. Aslan, A., Vrăbiescu, Al., Dobre, M., Polovrăgeanu, El., *The Aslavital treatment in the recovery of mentally-deficient children*. Romanian J. Geront. Geriatrics, 1980, **1**, *1*, 93–98.
2. Raven I.C., *Guide to Using the Coloured Progressive Matrices Set A.Ab., B.* H.K. Lewis & Co. Ltd. London, WCIE 6 BS, 1962.
3. Roşca M., *Psihologia deficienţilor mintali*. Ed. didactică şi pedagogică, Bucharest, 1967.
4. Zazzo R., *Les débiles mentaux*. Esprit, 1965.
5. Alfonskaia L., *Le changement de l'action de la procaïne sur les fibres nerveuses sous l'action des ions de K, Cl, et SO_4* (in Russian). Soc. Med. Ref. Oboz 4-a 134, 1949.
6. Aslan A., *Bases théoriques actuelles de la thérapie à la procaïne dans la prévention de la sénescence*. In: *Aslavital*, printed by the National Institute of Gerontology and Geriatrics and the Ministry of Chemical Industry, Bucharest, 1977.
7. Chiosa L., Neuman M., *Vitamine şi antivitamine*. Ed. medicală, Bucharest, 1955.

ROMANIAN J. GERONT. GERIATRICS, 1980, 1, 2, p. 195—204

RESEARCHES ON THE ANTITHROMBOPHILIC ACTIVITY OF THE BIOTROPHIC THERAPY WITH GEROVITAL H_3 AND ASLAVITAL

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Summary. Applying the main humoral thrombophilic indicators, the authors studied comparatively on 65 old subjects with advanced atherosclerosis, the antithrombogenic action manifested by the biotrophic drugs Gerovital H_3 and Aslavital.

This antithrombophilic action, more obvious with Aslavital, has been pointed out by the statistically significant improvement of the principal humoral indicators of the thrombophilic status: the increase of ADP-induced thrombocytary agglutinability, hypofibrinolysis, hypercoagulability of the structural type, the deficit of physiological anticoagulants and dyslipidemia.

The mean value of these indicators in the investigated subjects as well as the average global rate on the whole sample of all thrombophilic parameters, were displaced after 30 days of biotrophic treatment from the net thrombophilic zone to the moderate zone; the percentage of subjects initially presenting humoral pathological signs fell sharply after 30 days of treatment.

Comments are made on the possible mechanisms of action of the biotrophic products, at the thrombophilic level, of the humoral disturbances and on the thrombosis risk prevention, in old atherosclerotic patients on a long-term biotrophic treatment.

Clinical observations concerning the marked reduction of thrombo-embolic vascular accidents in aged atherosclerotic patients undergoing long-term treatment with biotrophic substances like Gerovital H_3 and Aslavital, have necessarily imposed a demonstration by bio-humoral methods, of the active intervention of these drugs not only in the development of metabolic disturbances within the framework of involution dystrophy [1, 2] and of the atherogenic process [3], but also upon the basic pathogenic factors of thrombogenesis: hemodynamic, hemorrheologic, parietal and especially hematic factors.

Continuing a series of studies we attempted in the present work to carry out a comparative research on the antithrombogenic activity of two original biotrophic preparations — Gerovital H_3 and Aslavital.

MATERIAL AND METHODS

A total of 65 aged patients (30 males and 35 females) were selected and investigated. Their average age was 67.1 years and they showed advanced clinical symptoms of atherosclerosis, predominantly located in the brain and in the heart vessels, most of them with vasculo-thrombotic accidents in their antecedents.

The major and necessary criterion for selecting the cases was the presence of the thrombophilic humoral syndrome, that was pointed out by the following hematologic and biochemical tests:

(1) The index of thrombocytic agglutinability in relation to ADP, according to the method of Veiner and Caen [4] as modified by de Nicola et al. [5].

(2) Plasma coagulability of the chronometric type, as determined by:

(a) the heparin tolerance index *in vitro* (Soulier);

(b) the "r + k" constant on the thrombelastogram.

(3) Plasma coagulability of the structural type evaluated by:

(a) the "am" constant of the thrombelastogram;

(b) the thrombocytic thrombodynamic activity, simultaneously measured in the same patient by thrombelastography of platelet-rich and platelet-poor plasma.

(4) Plasmatic fibrinolytic activity evaluated by the lysis time of the streptokinase-treated recalcified plasma. This investigation was performed with the aid of the thrombelastograph.

(5) Assessment of the physiologic plasma anticoagulants:

(a) endogenous heparin (determined by the Pieptea method);

(b) progressive antithrombin III (by the Kondi method).

(6) Evaluation of dyslipidemia by determining:

(a) total blood cholesterol (the Rappaport technique);

(b) the beta/alpha lipoprotein ratio (paper electrophoresis and photometric recording with a Zeiss integrating device).

Physiological range and values in the thrombophilic range of the above-mentioned parameters are represented in Table 1.

In view of studying the antithrombophilic effects of the biotrophic medication, as demonstrated by possible changes in the humoral thrombophilic status, the 65 patients were divided into three groups:

— group I consisted of 20 patients undergoing biotrophic therapy with Gerovital H_3;

— group II consisted of 30 patients undergoing treatment with Aslavital; and

— group III consisted of 15 patients who served as controls.

Treatment with Gerovital H_3 or Aslavital was applied parenterally and consisted of two series of 12 vials each, administered by daily intramuscular injections, with a 5—6 days' interval between the series. The control of the humoral parameters was made 3, 5, 8, 15 and 30 days after the beginning of the treatment. The patients were hospitalized during the applications. The clinical and biologic control of patients in the control group (who did not receive biotrophic treatment) was performed at the same intervals.

In view of facilitating the statistical representation of the results obtained, the following code was used: indication of individual values of each of the applied parameters by 1, 2 or 3, in relation to the presence in the range of physiological values, in the moderately thrombophilic range, or in the clearly thrombophilic range. It is easy to see that with this system of representation mean values for each group, for every parameter, as well as the global mean values for each group of all thrombophilic parameters applied will be found either in the 1—2 range or in the 2—3 range, if they belong to the moderate thrombophilic or to the clearly thrombophilic category, respectively. The values will be represented by 1 if they are considered within the physiologic range.

Table 1

Values of the physiologic range and of the thrombophilic range for the parameters applied

Thrombocytic agglutinability index to ADP	Chronometric type coagulability	Structural type coagulability	Fibrinolysis	Physiologic anticoagulants	Cholesterolemia. Beta/alpha lipoprotein ratio
	Thrombelastogram		*Lysis time*	*Heparin*	Ch. over 350 mg% Beta/alpha over 4
Over 11	r+k<20 mm *Heparin tolerance index* over 1.4	am>65 mm *Thrombocytic thrombodynamic activity* over 35 mm	over 90 min.	<3 u/ml A III<60%	
	Net thrombophilia				
8–11	*Thrombelastogram*		*Lysis time*	*Heparin*	Ch. = 260– – 350 mg% Beta/alpha: 3–4
	r+k = 20–25 mm *Heparin tolerance index* 1.2–1.4	am = 60–65 mm *Thrombocytic thrombodynamic activity* 30–35 mm	60–90 min.	3–5 u/ml A III = 60–80%	
	Moderate thrombophilia				
5–7	*Thrombelastogram*		*Lysis time*	*Heparin*	Ch. = 16–250 mg% Beta/alpha: 2–3.5
	r+k = 25–40 mm *Heparin tolerance index* 0.8–1.2	am = 50–60 mm *Thrombocytic thrombodynamic activity* 20–30 min.	50–60 min.	5–8 u/ml A III = 80–100%	
	Physiologic range				

RESULTS

The statistical evaluation of the data obtained by the application of tests of statistical significance has evidenced the following results:

1. — After 30 days of biotrophic therapy, there was a decrease of the percentage of cases that had initially presented pathological humoral indicators (moderate or net thrombophilia), both in group I and in group II. Although this decrease was noted in all the biological parameters applied, it appeared to be statistically significant ($p < 0.01$) for 5 of the indicators: the index of thrombocytic agglutination to ADP, hypofibrinolysis, the deficiency of physiological anticoagulants, dyslipidemia and structural-type hypercoagulability, in the group of patients who were treated with Aslavital, and for only three indicators: hypofibrinolysis, the index of thrombocytic aggregability and dyslipidemia, in group I treated with Gerovital H_3 (see Figs. 1 and 2). No similar changes were noted for any of the humoral parameters applied in the control group III (see Fig. 3).

2. — The statistically significant decrease ($p < 0.01$) after 30 days of treatment, as compared with the initial figure of the mean global value for each

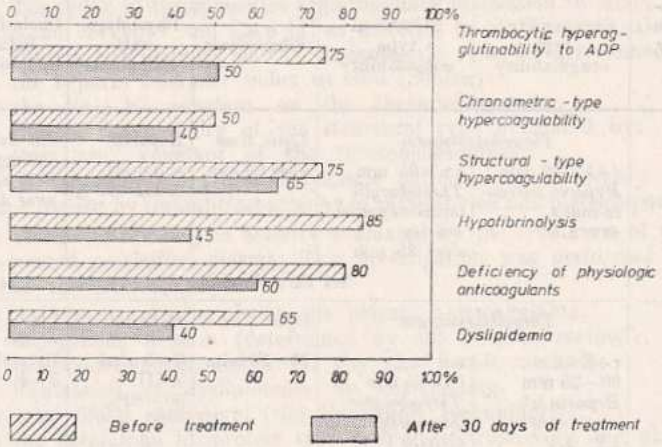

Fig. 1. — Percentage of cases presenting pathological humoral indicators (moderate or net thrombophilia) in the group of patients, before and after 30 days of biotrophic therapy with Gerovital H_3.

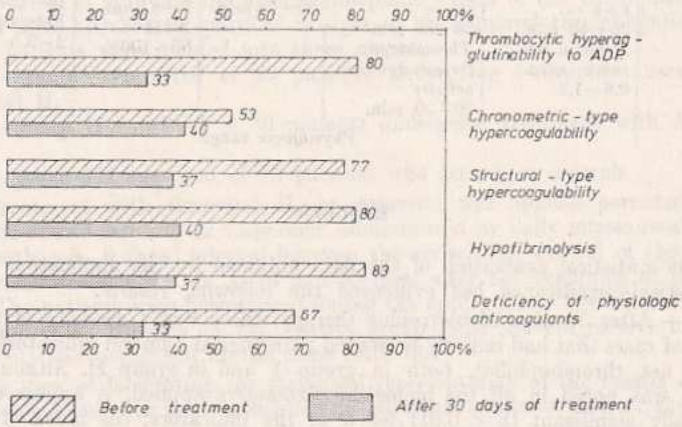

Fig. 2. — Percentage of cases presenting pathological humoral indicators (moderate or net thrombophilia) in the group of patients, before and after 30 days of biotrophic therapy with Aslavital.

group, of the thrombophilic parametets applied, both in group I and in group II (see Fig. 4, *a* and *b* — arrows).

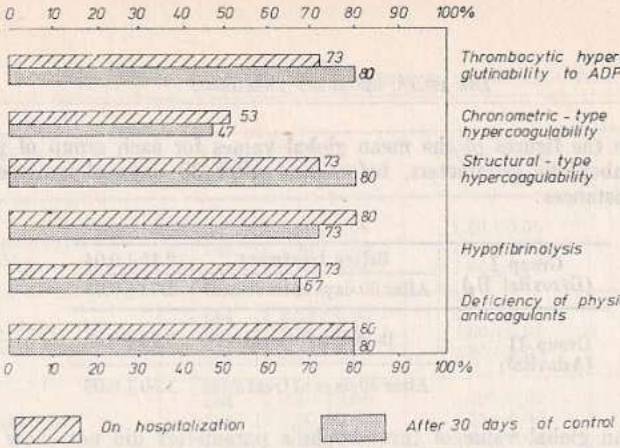

Fig. 3. — Percentage of cases presenting pathological humoral indicators (moderate or net thrombophilia) in the group of non-treated controls, on hospitalisation and after 30 days of control.

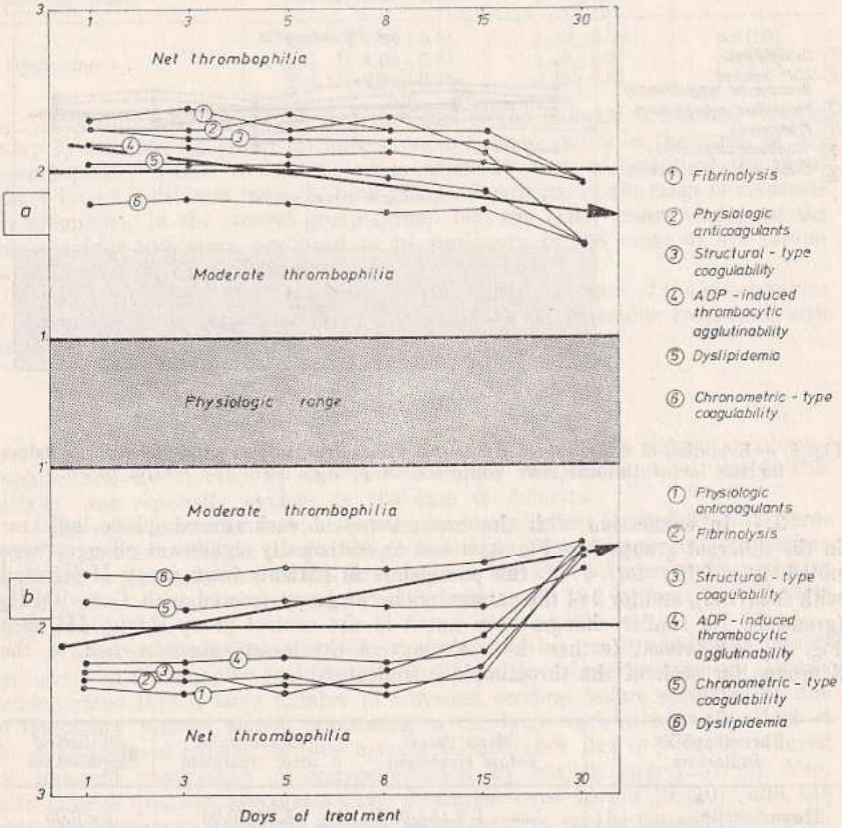

Fig. 4. — Evolution of mean values of humoral parameters, as well as of global mean values for the lot of thrombophilic indicators, under the influence of biotrophic therapy with Gerovital H_3 (*a*) and with Aslavital (*b*).

Here are the figures of the mean global values for each group of patients, for the thrombophilic parameters, before and after 30 days of treatment with biotrophic substances:

Group I (Gerovital H_3)	Before treatment	2.15±0.04
	After 30 days of treatment	1.74±0.05
Group II (Aslavital)	Before treatment	2.16±0.05
	After 30 days of treatment	1.50±0.06

The mean global value of thrombophilic parameters did not show statistically significant variations in the third group of patients in the course of the 30 days of control (Fig. 5).

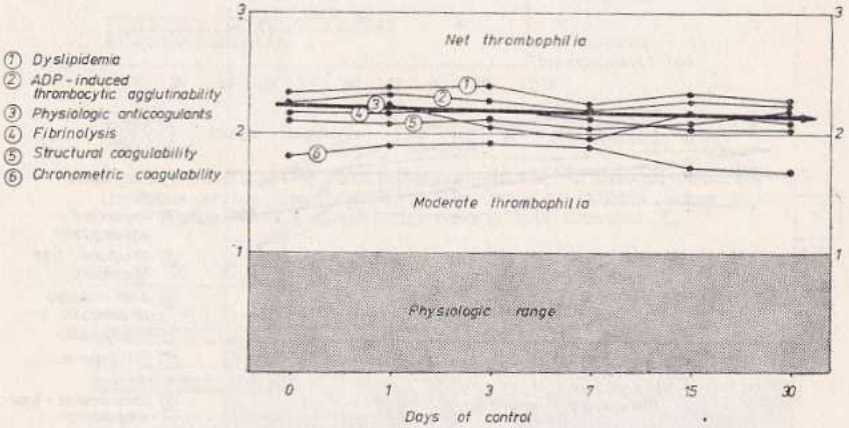

Fig. 5. — Evolution of mean values of humoral parameters, as well as of global mean values for the lot of thrombophilic indicators, in patients from the control group.

3. — In connection with the mean value of each thrombophilic indicator in the different groups (see Fig. 4, *a* and *b*) statistically significant changes were noted ($p < 0.01$) for 4 of the parameters in patients from group II (treated with Aslavital), and for 3 of the parameters in the group treated with Gerovital H_3 (group I). No similar changes were noted in the control group (group III) (see Fig. 5). We present further the variations of the mean values in each of the 3 groups for each of the thrombophilic indicators:

Thrombophilic indicators	Mean value before treatment	Mean value after treatment	Statistical significance
Thrombocytic agglutinability index to ADP	Lot I 2.15±0.03	1.90±0.04	$p<0.05$
	Lot II 2.23±0.05	1.46±0.05	$p<0.01$
	Lot III 2.26±0.04	2.26±0.06	non-significant

Thrombophilic indicators	Mean value before treatment	Mean value after treatment	Statistical significance
Chronometric-type coagulability	Lot I 1.80±0.06	1.60±0.05	p: n.s.
	Lot II 1.80±0.05	1.60±0.05	p: n.s.
	Lot III 1.80±0.04	1.66±0.06	p: n.s.
Structural-type coagulability	Lot I 2.25±0.05	1.90±0.04	$p<0.05$
	Lot II 2.26±0.06	1.50±0.04	$p<0.01$
	Lot III 2.13±0.06	2.20±0.05	p: n.s.
Hypofibrinolysis	Lot I 2.30±0.06	1.60±0.06	$p<0.01$
	Lot II 2.30±0.05	1.53±0.06	$p<0.01$
	Lot III 2.26±0.06	2.14±0.06	p: n.s.
Deficiency of physiological anticoagulants	Lot I 2.25±0.03	1.95±0.03	$p<0.01$
	Lot II 2.25±0.04	1.50±0.05	$p<0.01$
	Lot III 2.20±0.04	2.00±0.06	p: n.s.
Dyslipidemia	Lot I 2.05±0.04	1.60±0.06	$p<0.01$
	Lot II 1.66±0.04	1.40±0.03	$p<0.05$
	Lot III 2.35±0.05	2.20±0.04	p: n.s.

4. — One must notice the fact that out of the humoral indicators, five (in group I) and four (in group II) have presented mean values in the range of net thrombophilia, before treatment, while after 30 days of treatment the mean values for all indicators were, in both groups of patients, in the range of moderate thrombophilia. In the control group (group III) the mean values of five of the thrombophilic indicators continued to be stationary in the range of net thrombophilia after 30 days of control.

5. — One should also note that the substantial decrease of the mean values of thrombophilic indicators occurred after 15 days of biotrophic treatment with either of the two preparations (Gerovital H_3 or Aslavital).

DISCUSSION

The above results made it possible for us to underline a certain antithrombophilic activity exerted by the two biotrophic substances under study. This activity was especially evident in the case of Aslavital.

The experiments have evidenced the favourable effect exerted by both Gerovital H_3 and Aslavital on the pathologic deviations of two important parameters employed in the evaluation of the thrombophilic status of atherosclerotic patients: the rise of the thrombocyte agglutinability index and the hypoactivity of plasmatic fibrinolysis.

It is generally accepted that platelet aggregation is an early and highly important event in the complex chain leading to *in vivo* thrombus formation [6]. It was demonstrated that a large number of transient cerebral failure episodes are due to temporary platelet emboli originating in the large neck arteries [7]. Most of the ADP-perfused animals develop myocardial infarction due to ischemia induced by transient suppression of microcirculation by platelet aggregates [8]. Also, ADP-induced platelet aggregates may determine renal lesions [9, 10]; and the same aggregates may frequently become factors involved in the Sanarelli-Schwartzman type reactions and in the mechanisms of rejection of grafted kidneys.

An evident relationship between the incidence of thromboses and the increased thrombocytic agglutinability was described by Wright [11] in the stage following surgical interventions, a condition that certainly implies an increased risk of thrombosis. Similar observations have also been made following myocardial infarction [12, 13, 14], and in other "thrombogenic" conditions such as atherosclerosis, diabetes, occluding vascular diseases, homocystinuria, etc. [15, 16].

A large number of authors have noted a high concentration of plasma lipids in patients with thromboses [17, 18, 19]. Farbiszewski and co-workers [20] noted that beta-lipoproteins increased the platelet aggregating capacity of ADP, as well as that of thrombin. This effect could partially explain the thrombophilic tendency of atherosclerotic patients with a high level of betalipoproteins, as well as the positive antithrombogenic effects of the hypobetalipoprotein therapy. Other authors [21] noted a clear relationship between the concentration of triglycerides and the increased platelet aggregability in conditions of hyperlipemia. Apparently the length of the fatty acid molecule is an important factor in such cases.

With regard to the decrease of the thrombocyte aggregability index in relation to ADP in the presence of biotrophic medication (Gerovital H_3 and Aslavital) future research will evaluate if this is due to one of the following mechanisms:

1. — Inhibition of induction, that is of the interaction between the inducing agent (ADP in our case) and the platelet membrane, resulting in the triggering of the "release reaction". This is essentially a competition mechanism between the energy which is necessary for the phosphorylation processes and transport of adenosine, and that which is necessary for the thrombocyte aggregation [22]. A well-known group of substances, that of pyrimido-pyrimidines (dipyridamole or persantine, RA 433, RA 233), is capable of inhibiting by the above-mentioned mechanism the platelet aggregability induced *in vitro* by ADP.

2. — Inhibition of the intra-platelet transmission of the "message" carried by aggregating agents, a phenomenon which is closely related to a well-known nucleotide, cyclic AMP, a substance which serves as effector for a large number of enzyme systems, capable of inhibiting platelet aggregability induced *in vitro* by ADP. It is known at present that the inhibiting action of prostaglandin E_1 (PGE_1) is related to the metabolism and functions of cyclic AMP.

3. — Inhibition of energy production in the platelet by interference of the two major metabolic pathways which provide energy: glycolyis and oxidative phosphorylation. The phenomenon lies at the basis of the antiaggregating effect of some antiinflammatory and antidepressant drugs.

4. — Finally, the inhibition of ADP release outside the cell (as is the case of several drugs such as acetylsalicylic acid, antiinflammatory agents, antidepressants, serotonin and heparin).

Further studies will be able to evidence possible relationships between the MAO-inhibiting action of Gerovital H_3 and of Aslavital on the one hand and the interference of physiological substances of the serotonin type with the phenomenon of platelet aggregability on the other hand. It is possible that biotrophic medication interferes with the thrombocytic aggregation by an alteration of the serotonin level.

With regard to the shortening of the lysis time of streptokinase activated recalcified plasma, this cannot be explained by a modification of the plasma fibrinogen level (a time-consuming process which occurs in many patients during prolonged treatment), and it should be considered as a result of activation of factors

in the fibrinolytic system, or as a result of the influence on the complex mechanisms which are involved in the activity of factor XIII, F.S.F.

The *in vivo* increase of physiological anticoagulants induced by biotrophic preparations (specially by Aslavital) may be the result of release from storage of heparin-like substances, rather than of stimulation of mastocytic (heparin-forming) cell production, although some studies confirm the increase in the number of medullary mastcells in patients who have followed a prolonged treatment with Gerovital H_3.

The improvement of dyslipidemia, with decreased cholesterol level and reduction of the beta-alpha lipoproteic ratio, which occur *in vivo* after 30 days of treatment with both biotrophic substances, should also be considered in the frame of the antithrombogenic activity of these substances since well-known relationships exist between dyslipidemia, coagulation and fibrinolysis, as well as the above-mentioned interferences between hyperlipemia and thrombocytic hyperagglutinability.

CONCLUDING REMARKS

Starting from the above data the following conclusions can be drawn:

1. — The two biotrophic drugs — Gerovital H_3 and Aslavital — have a certain antithrombophilic action.

2. — This activity, more obvious with Aslavital, was pointed out by statistically significant improvement of the major humoral indicators of thrombophilia: the increase of the ADP-induced thrombocytic aggregability index, hypofibrinolysis, structural-type hypercoagulability, dyslipidemia and the deficiency in physiological anticoagulants. The mean value of these indicators in each group of patients ,as well as the mean global value of all thrombophilic parameters, were displaced, after 30 days of biotrophic treatment, from the range of net thrombophilia to that of moderate thrombophilia. Also, statistically significant decreases were noted — after a 30-day treatment — in the number of patients who had initially displayed pathological thrombophilic indicators (either net or moderate thrombophilia). The antithrombophilic effect mostly manifested itself — for both substances — after the first 15 days of biotrophic treatment.

3. — Considering the prevention of the risk of thrombosis as the sole practical objective aimed at by the therapy of advanced forms of atherosclerosis in the aged, one may conclude, on the basis of the results obtained, that the use of biotrophic substances, especially of Aslavital, should be considered by the current medical practice as an efficient antithrombophilic therapy.

Résumé. Par l'application des principaux indicateurs humoraux thrombophiliques sur 65 patients athéroscléreux âgés, les auteurs font une étude comparative de l'action antithrombophilique des substances biotrophiques Gérovital H_3 et Aslavital.

Cette action antithrombogène, plus manifeste dans le cas de l'Aslavital, a été mise en évidence par l'amélioration significative du point de vue statistique des principaux indicateurs humoraux de la thrombophilie: l'accroissement de l'agglutinabilité thrombocytaire à l'ADP, l'hypofibrinolyse, l'hypercoagulation du type structural, le déficit d'anticoagulants physiologiques et la dyslipidémie.

La valeur moyenne de ces indicateurs pour les lots de sujets étudiés, ainsi que la valeur moyenne globale des paramètres thrombophiliques se sont déplacées, après 30 jours de traitement biotrophique, de la zone de thrombophilie nette à la zone de thrombophilie modérée.

On a signalé aussi une diminution significative, à la suite du traitement, du pourcentage des patients à indicateurs humoraux pathologiques.

On discute les mécanismes d'action des substances biotrophiques au niveau des dérèglements humoraux thrombophiliques, ainsi que la prévention du risque de thrombose chez les athéroscléreux âgés à l'aide du traitement biotrophique à long terme.

REFERENCES

1. Aslan Ana, Symposium "Biotrophic Therapy in Geriatrics", Bucharest, Dec. 29, 1970.
2. Aslan Ana, *Theoretical and practical aspects of chemotherapeutic techniques in the retardation of the aging process.* In: *Theoretical Aspects of Aging*, edited by Morris Rockstein. Academic Press, Inc, New York, San Francisco, London, 1974, p. 145–156.
3. Aslan Ana, David C., Enăchescu Georgeta, *Modifications humorales chez les athéroscléreux âgés sous l'influence du traitement biotrophique à Aslavital.* In: *Gerontology*, edited by B. Steimann. Hans Huber Publishers, Bern, Stuttgart, Vienna, 1973, p. 412–415.
4. Veiner H., Caen J., *Utilisation d'un test photométrique pour l'étude de l'effet de l'ADP sur les plaquettes sanguines.* Nouv. Rev. Franç. Hémat., 1963, **3**, *2*, 149–158.
5. De Nicola P., Frandoli G., Gibelli A., Turazza G., Giarola P., *L'Aggregazione piatrinica da ADP e sue modificazioni da agenti farmacologici; ricerche cliniche e sperimentali.* Giornale dell'arteriosclerosi, 1967, **V**, *4*, 425–482.
6. Cepelàk V., *Patogenesi della trombosi.* In: *Coagulazione e trombosi*, edited by P. de Nicola, Edizioni Pem, Roma, 1971, p. 845–869.
7. Gunning A.J., Pickering G.W., Robb-Schmith A.H.T., Russel R.R., *Mural thrombosis of the internal carotid artery and subsequent embolism.* Quart. J. Med., 1964, **33**, 155.
8. Mustard J.F., Rowsell H.C., Murphy F.A., *Reversible platelet aggregation and myocardial ischemia.* Circulation, 1964, **30**, Suppl. 3, 23.
9. Glynn M.F., Jorgensen L., Buchanan M.R., *Platelet aggregation, renal function and hypertension.* Fed. Proc., 1966, **25**, 554.
10. Moore S., Mersereau W.A., *Platelet embolism and renal ischemia.* J. Path. Bact., 1965, **90**, 579.
11. Wright H.P., *Changes in the adhesiveness of blood platelets following parturition and surgical operations.* J. Path. Bact., 1942, **54**, 461.
12. Ardlie N.G., Kinlough R.L., Schwartz C.J., *In vitro thrombosis and platelet aggregation in myocardial infarction.* Brit. Med. J., 1966, **1**, 888.
13. Bouvier C.A., Rosner P., Berthaud S., Ritschard J., Scherrer J.R., Hauser E., *Anomalies du comportement plaquettaire lors de l'infarctus du myocarde.* Cardiologia, 1967, **50**, 232.
14. O'Brien J.R., Heywood J.B., Heady J.A., *The quantitation of platelet aggregation induced by four compounds: a study in relation to myocardial infarction.* Thromb. Diath. Haemorrh., 1966, **16**, 752.
15. Breddin K., *Experimental and clinical investigations on the adhesion and aggregation of human platelets.* Exp. Biol. Med., 1968, **3**, 14.
16. Hartmann R.C., *Tests of platelet adhesiveness and their clinical significance.* Semin. Haemat., 1968, **5**, 60.
17. Beckett A.G., Lewis J.G., *Mobilization and utilization of body fat as an aetiological factor in occlusive vascular disease in diabetes mellitus.* Lancet, 1960, *2*, 14.
18. Bunag R.D., Dougglas C.R., Inai S., Berne R.M., *Influence of pyrimido-pyrimidine derivative on deamination of adenosine by blood.* Circulation Res., 1964, **15**, 83.
19. Corvilain J., Champenois A., Loeb H., Abramow M., *Effect of fasting on levels of plasma non-esterified fatty acids in normal children, normal adults and obese adults.* Lancet, 1961, *1*, 534.
20. Farbiszewski R., Skyzydlewski Z., Worowski K., *The effect of lipoprotein fractions on adhesiveness and aggregation of blood platelets.* Thromb. Diath. Haemorrh., 1969, **21**, 89.
21. Coccheri S., D'Anruono G., Alessandri M., Garcia-Conde-Bru J., *The initiation of clotting in lipaemic blood: contact phase and platelet participation.* Hémostase, 1966, **6**, 339.
22. Gaetano G., Vermylen J., Verstraete M., *L'inhibition de l'agrégation plaquettaire: données expérimentales et perspectives cliniques.* Nouv. Rev. Franç. Hémat., 1971, **XI**, *3*, 339–364.

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L'ÉTAT DE SANTÉ DE 12 CENTENAIRES DU NORD DU VIÊT-NAM

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Résumé. 12 centenaires appartenant à des régions différentes du Nord Viêt-nam: régions de plaines, régions montagneuses, et villes, ont été étudiés au point de vue de l'état de santé. Nous avons quelques remarques préliminaires:

— La plupart vivent dans les régions de plaine et les régions montagneuses où la vie est assez calme et l'air salubre; la plupart sont des travailleurs manuels et sont rarement malades.

— Les manifestations de la sénescence appartiennent surtout aux lésions dégénératives, particulièrement au niveau du système de locomotion, aux organes de sens (vue — ouïe), au système cardio-vasculaire et aux poumons.

— La région de Ha giang où l'on trouve des centenaires en plus grand nombre a été sommairement étudiée: le climat y est sec, l'air salubre, l'atmosphère calme. Cependent le niveau d'hygiène y est assez bas. Dans ces conditions d'environnement favorables, si les règles d'hygiène sont mieux observées, peut-être la santé de nos centenaires serait encore meilleure.

La gérontologie actuelle s'intéresse de plus en plus à l'étude des grands vieillards, espérant y trouver les caractéristiques de l'organisme à cet âge particulièrement avancé et y trouver peut-être les secrets de la longévité.

C'est dans ce but que nous étudions ici l'état de santé de 12 centenaires au Nord Viêt-nam dont l'âge, le sexe et le lieu d'habitat sont résumés dans le tableau ci-dessous:

No	Prénom et nom	Date de naissance Calendrier lunaire		Age	Sexe	Lieu d'habitat
1	Nguyễn thị Ân	1867	Đinh Mão	111	Femme	Thái bình
2	Trần thị Duyệt	1870	Canh Ngọ	108	Femme	Nam định
3	Trương thị Nhâm	1870	Canh Ngọ	108	Femme	Hà-nội
4	Phạm thị Trà	1878	Tân Tỵ	100	Femme	Hà-nội
5	Tống văn Túc	1875	Ất Hợi	103	Homme	Nam định
6	Nguyễn thị Xuân	1873	Quý Dậu	105	Femme	Nam định
7	Thào văn Xếch	1877	Đinh Sửu	101	Homme	Hà giang
8	Vù thị Máy	1878	Tân Tỵ	100	Femme	Hà giang
9	Giàng thị Máy	1858	Mậu Ngọ	120	Femme	Hà giang
10	Xùng thị Xùng	1873	Quý Dậu	105	Femme	Hà giang
11	Phùng tắc Phằng	1864	Giáp Tý	114	Homme	Phú thọ
12	Nguyễn thị Toàn	1877	Đinh Sửu	101	Femme	Nghệ An

On remarque:

— Parmi les 12 centenaires, 3 seulement sont des hommes, 9 sont des femmes. La prédominance du sexe féminin chez les grands vieillards est une constatation courante.

11 exercent durant leur vie un travail manuel, un seul est intellectuel, faisant le métier d'instituteur et de guérisseur de médecine traditionnelle.

— Tous vivent à la campagne ou dans des régions montagneuses. Ce n'est que pendant les dernières années que 4 d'entre eux vivent dans les villes.

Les résultats de nos recherches sont ci-dessous succinctement analysés.

I. LES MENSURATIONS CORPORELLES

1. Le poids varie de 35 à 45 kg, la moyenne étant de 38 kg. Tous les auteurs s'accordent sur ce point qu'il n'y a pas d'obèses parmi les centenaires.

2. La hauteur:

— En station debout: varie de 140 à 168 cm, la moyenne étant de 148 cm.

— En station assise: varie de 66 à 81 cm, la moyenne étant de 74 cm.

La cyphose très fréquente chez nos centenaires est la cause de la petite taille.

3. Mesure de la circonférence thoracique:

— à l'inspiration forcée: de 76 à 87 cm,
moyenne 81 cm,

— à l'expiration forcée: de 74 à 81 cm,
moyenne 78 cm.

— La circonférence thoracique moyenne est de 75 à 84 cm.

On note la différence minime entre l'inspiration et l'expiration. La cause en est probablement l'emphysème sénile si fréquent chez les personnes âgées.

4. Mesure des différents contours des membres:

— à la cuisse: de 32,5 à 46 cm, moyennes 38 cm,

— au mollet: de 25 à 29 cm, moyenne 26 cm,

— au bras fléchi: de 21 à 24,5 cm, moyenne 22 cm.

En général les membres sont plutôt maigres, l'atrophie musculaire étant fréquente et ceci influe sur la force musculaire qui est diminuée.

5. Mesure de la force musculaire:

— bras droit de 4 à 20 kg, moyenne 6 kg,

— bras gauche de 10 à 19 kg, moyenne 15 kg

6. Index de Pignet:

— varie de 18 à 50, moyenne 28,

— Index Q—V—C = de I à 34,5, moyenne 7.

II. LE SYSTÈME CARDIO-VASCULAIRE

1. Le pouls radial varie de 63 à 86 par minute, moyenne 70/minute.

2. La tension artérielle varie de 120/70 à 200/90 mmHg, la moyenne étant de 140/80 mmHg. Aucun sujet n'a la pression diastolique dépassant 90 mmHg.

3. L'auscultation du cœur révèle chez un sujet, un souffle diastolique au 2e espace intercostal droit, dû à une insuffisance aortique d'origine probablement athéromateuse.

4. La palpation des artères radiales humérales, temporales permet de constater chez 9 personnes l'état scléreux des artères roulant sous les doigts.

5. L'électrocardiogramme est, en général, normal. On ne trouve qu'un axe dévié à gauche chez 2 sujets. Le résultat des mesures électrocardiographiques est résumé dans le tableau ci-dessous:

Sujet	Rythme	Fréquence	Axe angle	Durée				ST	T	
				P	PQ	QRS	QT			
1	Sinusal	72	+15°	0,06	0,18	0,06	0,38	—	+	Normal
2	,,	68	+60°	0,08	0,20	0,06	0,40	—	+	,,
3	,,	66	+10°	0,06	0,18	0,08	0,40	—	+	,,
4	,,	74	+80°	0,06	0,20	0,10	0,42	—	+	,,
5	,,	64	+70°	0,08	0,20	0,08	0,40	—	+	,,
6	,,	72	−50°	0,10	0,20	0,06	0,42	—	—	axe gauche
7	,,	74	+85°	0,08	0,18	0,08	0,36	—	+	Normal
8	,,	70	+ 5°	0,08	0,16	0,06	0,38	—	—	,,
9	,,	72	−20°	0,08	0,18	0,08	0,38	—	+	axe gauche
10	,,	70	+65°	0,08	0,20	0,08	0,40	—	+	Normal
11	,,	80	+10°	0,10	0,18	0,08	0,38	—	+	,,
12	,,	76	+65°	0,09	0,16	0,08	0,38	—	+	,,

6. Radiographie du cœur (face et profil).

Chez tous, la radiographie du cœur montre une dilatation de la crosse aortique. Chez 4 sujets, on observe l'arc moyen gauche bombé, probablement dû à la dilatation de l'artère pulmonaire consécutive à l'emphysème pulmonaire. Chez un sujet, on trouve l'arc inférieur gauche agrandi, probablement dû à l'hypertrophie-dilatation du ventricule gauche.

L'index de Gredel est de 50% chez 3 sujets, 60% chez un, et 70% chez un autre.

7. Phonocardiogramme fait chez 3 sujets a donné des résultats suivants:

	QB_1	Rapport amplitude B1/B2			B_3	B_4
		Pointe	IIe EICD	IIe EICG		
Truong thi Duyêt	0,045	1	0,75	0,45	(−)	(−)
Nguyên thi Ân	0,050	0,86	0,38	0,30	(−)	(+)
Tông văn Tûc	0,070	0,26	0,33	0,30	(−)	(+)

On remarque que le temps QB_1 est normal, l'amplitude de B_1 est inférieure à B_2 le rapport B_1/B_2 1. Chez deux sujets, on enregistre le 4e bruit.

8. Le carotidogramme est pratiqué chez 3 sujets. On remarque que:

— le temps pré-éjection est normal,
— le temps éjection normal,
— le quotient hémodynamique normal,
— le rapport IA/BA un peu élevé,
— le temps sommet allongé (normal = 0,10 seconde)
— le temps mi-sommet allongé (normal = 0,05 seconde)
— le temps de transmission B_2 — I raccourci (normal = 0,01—0,04 seconde).

9. Le jugulogramme, pratiqué chez un sujet révèle:
T2 — v = 0,17 seconde = allongé (normal 0,05 seconde),
T2 — y = 0,30 seconde = allongé (normal 0,10 seconde), faisant penser au temps de remplissage auriculaire et ventriculaire allongé.
10. Examens de biochimie:
— Le cholestérol = de 126 à 176 mg pour 100 ml de plasma
— Lipides totaux = de 0,64 g à 0,76 g,
— Le lipidogramme (électrophorèse des lipoprotéines):
le rapport des fractions β/α aux environs de 1,86. En général, les résultats sont normaux.

III. L'APPAREIL RESPIRATOIRE

1. Examen clinique:
— Fréquence respiratoire de 18 à 22 par minute,
— La percussion trouve chez 11 sur 12 sujets, une hypersonorité due à l'emphysème pulmonaire, particulièrement fréquent chez les personnes âgées,
— Chez 2 sujets, on trouve une diminution du murmure vésiculaire à l'auscultation.
— 4 sur 12 sujets ont des expectorations épaisses pendant l'hiver, 2 seulement fument mais le nombre de cigarettes est négligeable.
2. Radiographie des poumons.
Tous ont une hyperclarté pulmonaire correspondant à l'emphysème pulmonaire constaté en clinique et des hiles chargés, images possibles de bronchite chronique.
3. Exploration fonctionnelle:
— La capacité vitale est de 530 à 2100 ml. En général elle est diminuée.
— La vitesse expiratoire maximale seconde (VEMS) est de 320 à 400 ml, l'indice de Tiffeneau va de 32 à 60%.
— l'air courrant est dans les environs de 350 ml.
En général, il y a diminution des performances ventilatoires. Cependant, il faut noter que les épreuves d'exploration fonctionnelle sont difficiles à pratiquer chez les grands vieillards qui n'observent pas rigoureusement les recommandations techniques.

IV. L'APPAREIL LOCOMOTEUR

6/12 ont la cyphose
1. Examen des articulations:
— Degré de flexion vertébrale: 0 à 2 cm, moyenne 0,2 cm,
— Degré d'extensibilité thoracique: 0,2 cm à 1,5 cm,
— Angle de flexion du genou: de 20° à 45°,
— Angle d'extension du genou: de 140° à 175°,
— Angle de flexion au niveau de la hanche: de 40° à 50°,
— Angle d'extension au niveau de la hanche: de 150° à 180°,
— Angle de flexion au niveau du coude: de 28° à 30°,
— Angle d'extension au niveau du coude: de 175° à 180°
Dans l'ensemble, la mobilité des articulations est restreinte.

2. La radiographie des os et des articulations montre la fréquence de l'ostéoporose et des ostéophytes, surtout aux vertèbres, sous forme de « bec de perroquet ».

Les os du crâne sont plus transparents, surtout au niveau des mâchoires, signes d'ostéoporose accentuée.

V. LE SYSTÈME NERVEUX

— Aucun n'est atteint de troubles démentiels, si fréquents chez les personnes très âgées.

— Les tests de la mémoire au moyen de 10 mots que les sujets doivent répéter montrent une déficience nette de la mémoire. L'interrogatoire montre, en outre, que nos centenaires gardent encore une bonne mémoire des événements passés depuis très longtemps alors qu'ils oublient vite les événements récents.

— Chez 3 sujets, on note des troubles d'orientation, chez 2 autres, des troubles de langage, 2 ont des tremblements des membres; 3 ont des réflexes ostéotendineux abolis. Chez aucun sujet, on n'observe des troubles de sensibilité, des troubles moteurs, sphinctériens, trophiques, ni des signes d'atteinte des nerfs crâniens.

— L'électroencéphalogramme fait chez 5 personnes montre, chez un sujet des ondes bêta en grand nombre et d'une façon diffuse; chez 2 sujets, la fréquence des ondes thêta. On n'y trouve pas d'ondes delta.

VI. LES AUTRES SYSTÈMES

1. Examen hématologique:

— Les nombre d'érythrocytes se situe entre 2.660.000 et 3.600.000, la moyenne étant de 3.200.000. L'anémie chez le vieillard est une constatation classique et est souvent difficile à traiter,

— Le nombre de leucocytes varie entre 3.400 et 6.200, la moyenne étant de 3.800.

— Dans la formule leucocytaire, on note le pourcentage de neutrophiles entre 59 et 78%. Ce qui est à remarquer, c'est que les polynucléaires ont en général de 4 à 6 segments. Le pourcentage d'éosinophiles est assez élevé (de 5 à 11%). Pour certains auteurs, le grand nombre d'éosinophiles chez les personnes âgées est un signe de bon pronostic.

— Le taux d'hémoglobine varie de 72% à 82%,

— Le pourcentage de lymphocytes T est de 34 à 49%, c'est-à-dire légèrement bas (normal = 55%) et celui de lymphocytes B est de 17,3% à 19,3%, légèrement bas lui aussi, comparé à la norme de 25% chez les Vietnamiens.

La plupart des auteurs constatent chez les personnes âgées une diminution des lymphocytes T et une augmentation des lymphocytes B.

— Le taux de complément varie de 26,7 à 32,8, légèrement diminué,

— Le dosage des immunoglobulines montre que le taux d'IgG est de 1230 à 1400 mg %

IgA — 268—368 mg %

IgM — 91—114 mg %

— Le test de transformation lymphoblastique donne des pourcentages de 34% à 71,7%, la moyenne étant de 50%.

— La vitesse de sédimentation varie de 5/10 à 30/46 mm.

2. Le système urinaire:

— L'examen clinique ne révèle rien d'anormal

— L'urée sanguine varie de 26 mg % à 41 mg %

— La créatinémie varie de 0,9 mg % à 1 mg %

— L'albuminurie est négative chez tous les sujets, sauf chez un, où elle est de 0,03 g/l

3. Les glandes endocrines:

— L'examen clinique ne révèle rien d'anormal. Aucun n'a de goitre endémique, même chez ceux qui vivent dans les régions montagneuses.

— La glycémie se situe entre 94 mg % et 112 mg %. La glucosurie est négative.

— Le métabolisme basal est entre −8% et +16%

— Les 17 cétostéroides urinaires sont aux environs de 4,8 mg/24 heures chez la femme et 8,18 mg chez les hommes.

— Les protides totaux varient de 6,12 g % à 6,65 g %. Le protéinogramme par électrophorèse est sensiblement normal.

4. Les organes de sens:

— L'examen ophtalmologique trouve 4 cas avec réduction du champ visuel, 3 avec enophtalmie; tous ont le trachome. Presque tous ont la dégénérescence de la cornée, la cataracte; 3 ont la dégénérescence de la rétine. La tension rétinienne est normale.

— L'examen oto-rhino-laryngologique révèle un épaississement du tympan chez tous les sujets.

Chez 3 personnes, on trouve la déviation de la cloison nasale.

L'audiométrie a été faite chez 3 personnes: chez tous, on enregistre des signes d'une surdité plus ou moins nette; troubles de transmission, lésion de l'oreille interne.

VIII. ÉTUDES PRÉLIMINAIRES DE L'ENVIRONNEMENT

Tous les gérontologistes s'accordent pour admettre le rôle de l'environnement dans le processus de la sénescence. La plupart des centenaires habitent les régions montagneuses, surtout à Ha giang. Nous y sommes venus pour faire l'étude préliminaire de l'environnement.

La température à l'intérieur des maisons est de 30—35°C au mois d'Avril, à l'extérieur, elle est de 31—35°C. La température humide est de 24—27°C, à l'intérieur et 24—26°C à l'extérieur, on remarque le peu de différences entre la température à l'intérieur et à l'extérieur des maisons.

Le degré d'humidité est à 52 à 61% à l'intérieur et de 47 à 56% à l'extérieur — c'est donc un climat chaud et sec.

La vitesse du vent est de 0,61 m/seconde à 1,44 m/seconde. En somme, les habitations sont assez aérées.

La pression atmosphérique varie de 718 à 721 mmHg.

En ce qui concerne l'habitation, la plupart des maisons ont la façade orientée ouest ou nord-ouest. En général, l'orientation des habitation n'ont pas une préférence particulière. On les bâtit à l'endroit le plus favorable à la construction sans se soucier de l'orientation.

La surface habitée est très variable, allant de 1,9 m^2 à 6 m^2 par habitant.

Le volume d'air varie de 3,5 m^3 à 12 m^3 par habitant.

L'atmosphère y est plutôt calme, les habitations des Mèo sont souvent très isolées les unes des autres.

Le niveau d'hygiène de la région de Can-ty où sont rassemblés de nombreux centenaires, laisse à désirer: les puits manquent, on se sert de l'eau des rivières; l'eau est contenue dans des tonneaux de bois, les fosses d'aisance manquent. Les moustiquaires sont en nombre insuffisant.

La superstition règne encore, les cérémonies religieuses sont souvent organisées dès qu'il y a un malade dans la famille.

Summary. A health survey has been carried out on 12 centenarians living in various areas in North Vietnam, comprising plains, mountainous regions and cities.

The following are some preliminary remarks:

— Most of them are handworkers living in the plains and mountainous regions where life is relatively quiet and the atmosphere salubrious. They have been seldom ill.

— Senescence manifestations are due to degenerative lesions found particularly in the system of locomotion, the sensory organs (sight, hearing), the cardio-vascular and respiratory systems.

— The Hagiang area where live the majority of centenarians has been studied in some aspects: the climate is dry, the atmosphere calm, but hygienic conditions are relatively poor. If these were be improved, one can expect a better standard of health for these centenarians.

ROMANIAN J. GERONT. GERIATRICS, 1980, **1**, 2, p. 213–219

CLINICAL PECULIARITIES OF HYPO- AND HYPERTHYROIDISM IN THE AGED

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Summary. The paper deals with the clinical and functional peculiarities of hypothyreosis and hyperthyroidism in the aged.

The clinical elements that are common to old age and hypothyreosis are mostly less accentuated, but lasting. They should be thought of, and in their presence the assay of a thyroid hormonal substitution confirms our diagnosis.

Hyperthyroidism in the old presents itself in a special way, full of nuances, only leanness and tachycardia maintaining the value they have in the adult's clinical symptomatology.

Neuropsychical elements, a diabetic mask, may often appear in the aged and old people's hyperthyroidism.

Metabolic peculiarities, the tired-out regulation exerted by the diencephalic centres, account for the reduced, non-characteristic symptomatology and for the presence in the aged, of unusual clinical forms of thyroid syndromes, which may start from small injuries that have the possibility of upsetting a very labile balance.

The researches of the last decades made it possible to aver that endocrine reactivity is persisting for a long time, which allows the appearance of thyroid clinical symptoms of functional hypo- or hyperactivity even in the most advanced ages.

We do not dispose, as yet, of a unanimously adopted conception as to thyroid pathology in aged and old people. This is moreover a chapter of endocrinology that is an especially discussed one, full of nuances, and in which often bedside experience alone is taking the decisive part.

Thyroid pathology in the aged should be considered in the particular conditions of an alteration of the central regulating mechanisms, of the neurohormonal ways of stimulation as well as of receptivity [1, 2, 3].

The many ways of iodine metabolism modification [1, 4] also contribute to a great extent to the shading of the phenomenological picture.

The researches [2, 5, 6] on the hypophyseal-hypothalamic and hypophyseal-adrenocortical couple during the ageing process facilitate a broad and fundamental understanding of the clinical features of diseases in the elderly.

The perturbation of the functional balance of vegetative centres determines a vicious regulation, a diminished response and a precarious biological balance — which account to a great extent for the lability and poorness of the clinical symptoms in the pathology of the aged and the old. The thorough clinical examination and individualization of certain clinical peculiarities in dysthyroid aged patients lead to the appropriate strategy in exploring thyroid function [7].

A. CLINICAL PARTICULARITIES OF HYPOTHYREOSIS IN THE OLD

It is long ago that the similarity between old age and some symptoms of the thyroid functional hypoactivity was noted.

C. I. Parhon [8, 9] showed that a series of involution symptoms are caused by some of the endocrine glands, "and anyway the role of thyroid insufficiency in the old-age symptomatology seems to be not a small one".

Starr and collab. [10] present some symptoms which are common to old age and thyroid insufficiency: dry and wrinkled skin aspect; asthenia, constipation, subjective vasomotor disorders, the teeth falling-off, degenerative disturbances (osteopathies, vascular sclerosis).

References are sporadic as to the incidence of hypothyreosis in the old, and those which may be found do not permit a distinction between the forms that appear in the elderly and those manifested in adults, the latter being usually included jointly.

Moreover, Starr and collab. [10] sustain that the old do not usually suffer from hypothyreosis. William and Rollis [11], however, admit a possibility for hypothyreosis to begin in the third age.

On the basis of a number of 3,417 cases examined over a period of $2\frac{1}{2}$ years, Lloyd and Goldberg [12] mention a rather high percentage of hypothyroid people: 1.7%, as compared to only 0.5% hyperthyroid ones. By sex, they find a clear preponderance of hypothyroid women over men (5:1). By age group, most of the cases of hypothyreosis are found from 65 to 75 and from 80 to 85 years. With 60 subjects studied [4] and chosen from the 8th, 9th and 10th decades of age, who suffered from various forms of chronic ischemic cardiopathy, the incidence of thyroid functional hypoactivity was of 11.6%.

In our opinion, the reports about the hypothyreosis incidence in old age are not quite realistic, and invite further studies and statistical researches. Attention should be insistently drawn to the presence of hypothyreosis in the old, as most of the patients are directed to consulations with another diagnosis — rheumatism, chronic bronchitis, anemia —, while they actually present a thyroid insufficiency in various degrees.

We recall — for its evocative form — the great frequency of old with myxedema entering in a coma, as compared to the adults.

The most difficult aspect is that of light clinical forms, which may manifest themselves quite differently, often fallaciously. In the presence of a precocious or accelerated ageing, it is good to give our attention also to a possibly existing hypothyreosis. Clinical forms showing a single or few symptoms are a rule with the old — a simple constipation may actually conceal hypothyreosis.

The poor and unrelieved, yet persistent, clinical symptomatology is common to other clinical patterns, but with some particularities for those diseases. It should be felt, studied and — why not — even verified by a therapeutic approach, which in most cases confirms the clinical supposition. Clinical examination and therapeutic assay are decisive elements in determining the diagnosis of a hypothyreosis in an aged or old subject, the more so as the biological tests as well as those of thyroid dynamics are often inconsistent and unconvincing.

With some effort, there may be distinguished and systematized some elements which are to be looked for in the elderly, and which are often the expression of a certain degree of thyroid functional hypoactivity.

(a) Concerning the integuments, the skin, nails and mucosae, besides the common old-age symptoms, we may notice a particular dryness of axillae and hands. Exceptionally, the adult's edema will be found, still the parchmentlike, upholstered aspect of the hands, macroglossia and progressive hypoacousia should retain our attention.

The latter raises interesting diagnostic problems; with the substitutional thyroid treatment, we stated remarkable ameliorations of the auditory acuity.

Hypoacousia suggested us [4] a possible thyroid functional deficiency in 11 subjects of 65, most of them females. The decreasing hearing acuity was present for over 6 years, not very severe but constant and bilateral, and continuously preoccupied the patients. The thyroid dynamic test was unsignificant, even inconsistent, the clinical picture poor, and the therapeutic approach alone was directly amazing in 8 cases, with a clear betterment of the hearing acuity.

(b) From the part of the locomotor apparatus, the need for stretching one's limbs, the difficulty in making the first movements when getting up, dysarthria may be a consequence of a muscular infiltration and less of a circulatory insufficiency. When emphasizing a delayed muscular decontraction, Achille's jerk confers a great value to the bedside examination.

(c) The digestive tube, when minutely examined, reveals useful and interesting details. A complete barium transit may show modified segments of the alimentary tract: a lengthening of some parts, disappearance of haustration at the colon level, stagnations of an inadmissible duration on the small intestine tract. All of these are suggesting a marked hypotonia of the digestive tube.

(d) The patient may present a physical, psychic and intellectual asthenia, lack of interest, loss of sensitivity, memory and hearing disturbances, without any signs of cerebral or cardial circulatory insufficiency.

Demanet and Bastenie [13] could not establish, by a clinical study, any relation between arterial pressure and hypothyroidism.

The frequently clinically noticed association of hypertension with thyroid insufficiency should be interpreted in relation with the increased systolic pressure in consequence of the hemodynamic modifications in the elderly with physiosclerosis [4].

(e) We relatively often meet with an anemia of a macrocytic type. The favourable response to the substitutive treatment may be appreciated by the patient losing weight, ECG modifications in the sense of a bettered myocardial nutrition and increases in the amplitude of the rapid ventricular complex, and some changes of the facies or ameliorations of the clinical symptoms which had suggested us the diagnosis. Paraclinical data are often unsignificant or even discordant [4]. We retain among them the radioactive iodine uptake, as the more exact, giving positive results in 66% of the cases; in 13% of the subjects, iodine uptake maintains itself within normal limits, while in 21% the track takes a pronounced inferior marginal character [4].

We generally found normal thyroid scintigram, basal metabolism and iodemia.

All of these symptoms taken separately are little telling and may be considered as simple old-age manifestations. When taken together and correlated, they are not marely orientative but even indicative of hypothyreosis. This is why they should be thought of, looked for, analyzed. In the presence of a bedside and laboratory suspicion of hypothyreosis, the diagnosis is determined by a favourable response to a substitutional therapy, which in its turn is to be administered with a special judiciousness, progressively.

Our prudence and cautions during the substitutional treatment with thyroid preparations are required because of the possible accidents, of the type of a major coronary failure, or of an adrenal insufficiency, due to an inadequate response of the heart and of the adrenal glands.

B. PARTICULARITIES OF HYPERTHYROIDISM IN THE OLD

Comprehensive studies of hyperthyroidism have been carried out by numerous authors [11, 14, 15].

The adult's obvious symptoms: agitation, cardiovascular hyperreactivity, may be present in the aged too; however, we often meet with clinically incongruous, oligosymptomatic, noncharacteristic forms.

It is not very long since those aspects in the old were related to a different type of hyperthyroidism, which is the result of a hyperreactive nodule. The existence of both hyperreactive histological forms is a well-defined fact in the adult's as well as in the elderly's pathology [1]. It is true that the nodular form occurs more often in the old, still this is neither characteristic of nor responsible for the symptomatology peculiarity. The same covert, masked forms, may have as an anatomic substrate the diffuse aspect of functional hyperactivity or nodules with functional hyperactivity, disseminated in the thyroid mass and surrounded by zones with a functional hypo- and normal activity.

The frequency of hyperthyroidism after the age of 50 was appreciated in different ways in the course of time. After a period of beginning, when the reports on the frequency were relatively poor, the researches of the last decades show rather high percentages; this is probably related to an increased patient's readiness, an improvement of the investigation methods (Table 1).

Table 1

The hyperthyreosis frequency in aged and old subjects according to various authors

Authors	No. of cases	Follow-up period	Age (y.)	No. of subjects	%
Sattler (1909)	3,474	—	40	—	28.5
MacKenzie (1916)	438	—	60	4	1
Gilbert-Dreyfus (1930)	143	—	60	3	2
Clute and Swinton (1935)	1,957	4 years	60	145	7
Cookson (1939)	400	1930–1938	60	66	16.5
Dumitru M. (1979)	60	1970–1979	70	34	6.6
Young (1941)	2,507	(a) before 1926	60	—	3
		(b) 1926–1940	60	—	12
Seed and Linday (1949)	818	(a) 1925–1934	60	—	7
		(b) 1938–1948	60	—	17.4
Iversen (1953)	1,822	1933–1945	60	137	9.8
De Gennes and coll. (1961)	413	1957–1960	60	86	20.8
Pitiș et al. (1963)		1963	60	295	25.5

The clinical symptomatology in the aged and old people may be especially colourful, shaded and subtle. Oligosymptomatic forms (diarrhoea) or such with neuropsychical manifestations should not surprise us.

The principal symptoms of hyperthyroidism in advanced ages are shown in Table 2.

As to the loss of weight, the authors agree that it is one of the important, always present symptoms. According to De Gennes et al. [2], the loss of weight may attain 40 kgs; Pitiş et al. [14] reports a 37 kgs loss of weight in 5 months.

As a rule, the major symptoms are presented in different ways, they having often a frequency under 50%.

Table 2

Hyperthyroidism symptoms in the elderly

	Pitiş et al. (1963) %	Personal researches %	De Gennes et al. (1961) %
Leanness	100	100	100
Tachycardia	37.9	62	84.9
Goiter	34.5	38	52.3
Asthenia	50.9	46	55.8
Exophthalmus	31.1	28	64.0
Tremor	50.9	40	34.1
Neurovegetative disturbances			
Hypersudation	23.0	31	17.4
Thermophobia	16.4	27	58.0

From Tables 1 and 2 it may be easily and clearly appreciated the frequency and the symptoms of hyperthyroidism in the aged, according to the various authors.

The confuse, misleading, secondary clinical signs are given in this context a particular importance.

But in the hyperthyroidism case, too, some clinical aspects which are relatively frequent in the old may be outlined:

(a) The apathetic aspect of the old hyperthyroid patient, who is quiet, with a reduced motor activity, and may be depressed or dim from the psychic standpoint. These features are associated with the absence of tremor and ocular signs.

(b) The masked aspect is a clinical form of hyperthyroidism of a maximum importance.

Cardiovascular disturbances lacking a precise etiology and resisting to treatment, with paroxysmal rhythm disorders, may conceal hyperthyroidism, according to Fiedberg. The cardial damage is 10 times more frequent in people over 60 suffering from hyperthyroidism, than in adults [14].

The high frequency of the thyroid cardiopathy — 31.4% (De Gennes), 25% (Pitiş et al.) — induce us to consider it, besides leanness, as one of the most characteristic symptoms for the elderly.

A diabetic, psychotic, psychoneurotic mask could also point to the elderly's hyperthyroidism. Some laboratory investigations prove to be of great help in determining the diagnosis [4].

The fixation of radioactive iodine may be considered as a telling test. De Gennes and collab. [2] assign great importance to the fixation of radioactive iodine after 6 hrs, showing that in the first hours the fixation is reduced, a fact confirmed by our own studies.

Determination of P.B.I. as well as basal metabolism also proves to be useful. The cholesterol low values acquire with advanced ages the importance of the increased values in myxedema with the adult.

CONCLUSIONS

(1) It may be appreciated that age induces some thyroid involutive modifications, which according to most of the authors, may be discovered by histologic, functional and clinical data.

(2) The endocrine reactivity, which is present up to the most advanced ages, creates a possibility for the presence of thyroid syndromes of functional hypo- or hyperactivity, with a few peculiarities as compared to the adult.

(3) The thyroid pathology in the elderly proves to be a chapter full of nuances, subtle and rich in surprises. Secondary clinical phenomena acquire a first-rate importance, and have to be looked for, analyzed and put together for enabling the diagnosis to be determined.

(4) It may be surprising, but the beginning of thyroid symptoms is abrupt, small injuries having the possibility of easily changing an unsteady balance, difficultly maintained in the biological conditions of the aged and old people.

(5) The reduced, non-characteristic symptomatology, the presence of unusual clinical forms find the most judicious explanation — as shown by Marinescu — in diencephalic modifications, in the tired-out regulation exerted by the respective centres.

Riassunto. Nel lavora sono presentati gli aspetti clinico-funzionali descrivendosi alcune caratteristiche cliniche che possono suggeriri ed indicare l'esistenza dell ipotireosi o dell'ipertiroidismo negli anziani.

Gli elementi clinici communi alla vecchiaia ed all'ipotireosi sono molto spesso meno accentuati, pero persistenti; essi devono essere considerati, ed in presenza di loro la prova per una sostituzione ormonale tiroidea conferma la nostra diagnosi.

L'ipertiroidismo si presenta negli anziani in un modo speciale, ricco di sfumature; soltanto la megrezza e la tachicardia mantengono lo stesso valore che nella sintomatologia clinica dell'adulto.

Degli elementi neurologici, una maschera diabetica, possono apparire spesse volte nell'ipertiroidismo dei pazienti avanzati in età ed anziani.

Le particolarità metaboliche, la regolazione inerte esercitata dei centri diencefalici rendono conto della sintomatologia ridotta, non-caratteristica e della presenza negli anziani di forme insolite di sindromi tiroidei, che possono aver principio in piccoli disturbi che hanno la possibilità di rovesciare un equilibrio molto labile.

REFERENCES

1. Dumitru M., *The thyroid function in chronic ischemic cardiopathy in the aged and old patient.* Doctoral Thesis (in Romanian), Bucharest, 1972.
2. De Gennes M.M., Batines M.L., Moreau L., Dechamps H., *L'hyperthyroïdie du sujet âgé de plus de 60 ans (A propos de 86 cas).* Presse Méd., 1961, **53**, 2425.
3. Mortensen J.C., Wolner L.B., Bennet W.D., *Gross and microscopic findings in clinically normal thyroid gland.* J. Clin. Endocrinol., 1955, **15**, 1270.

4. DUMITRU M., *The thyroid in the aged.* Rev. Roum. Endocrinol., 1973, **10,** *5*, 441—449.
5. MARINESCU GH., *Studies on the biochemical mechanisms of aging and rejuvenation* (in Romanian). Bul. Soc. Rom. Neurol., 1933, **IV,** 172.
6. STERESCU N., *Peculiarities of endocrine homeostasis in the aged* (in Romanian). St. Cercet. Fiziol., 1965, *2*, 107.
7. FRAGU P., ALPEROVITCH A., GARDET P., CHARBORD P., PARMENTIER C., TUBIANA M., *The strategy of exploring thyroid function.* Nouv. Presse Méd., 19 Nov. 1979, **8,** *45*, 3723—27.
8. PARHON C.I., *Old Age* (in Romanian). Ed. Viaţa Românească, Iaşi, 1925.
9. PARHON C.I., *The Biology of the Ages* (in Romanian). Ed. Academiei, Bucharest, 1955.
10. STARR P. AND COLLAB., *Clinical experience with blood protein — Bound iodine determination as routine procedure.* J. Clin. Endocrinol., 1950, **10,** 1237.
11. WILLIAM C., ROLLIS M.D., *The aged thyroid gland.* Geriatrics, 1968, Sept., 124.
12. LLOYD W.H., GOLDBERG I.J., *Incidence of hypothyroidism in the elderly.* Brit. Med. J., 1961, **11,** 1256.
13. DEMANET J.C., BASTENIE P.A., *Étude clinique de l'influence de l'hypothyroïdie sur la tension artérielle.* Presse Méd., 1969, **49,** 1809.
14. PITIŞ M., SPANDONIDE T., CIOVÎRNACHE M., DINULESCU E., *Research on hyperthyroidism in the aged* (in Romanian). St. Cercet. Endocrinol., 1963, **14,** 355.
15. SPANDONIDE T., *The relations between the thyroid functional tonus and the evolution of the vascular system age pathology.* Doctoral Thesis (in Romanian), Bucharest, 1968.

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THE INFLUENCE OF GEROVITAL H_3 TREATMENT ON BLOOD AND URINE CATECHOLAMINES IN HYPERTENSIVE AND NORMAL OLD PEOPLE

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Summary. Serum epinephrine, norepinephrine, dopa, dopamine, 5-hydroxytryptamine and urine epinephrine, norepinephrine, homovanilmandelic acid (HVA) and 5-hydroxyindolacetic acid (HIAA) were evaluated in 369 hypertensive and normal subjects (244 women and 125 men aged 40 to 90), prior to and after Gerovital H_3 treatment.

A moderate increase was noticed in serum and urine catecholamines, correlated with an increased sympathetic ergotropic tonus.

Previous researches have pointed out that a characteristic feature of the aging process is tonus decrease in the sympathetic ergotropic system. The phenomenon is due to the progressive diminution of catecholamines, specific mediators in this system, explained by an increase with age of monoamine oxidase (MAO), the main CA enzyme.

Our researches started both from Hrachovec and MacFarlane's studies [1, 2] which, in 1973, demonstrated the inhibitive action of Gerovital H_3 on MAO in the rat brain, and from results obtained in 1977 by a staff from the National Institute of Gerontology and Geriatrics [3, 4, 5], who investigated some blood and urine catecholamine variations, before and after Gerovital H_3 treatment.

MATERIAL AND METHOD

The research was carried out on a number of 369 patients, 125 men and 244 women, 45–95 years old, who were hospitalized in the National Institute of Gerontology and Geriatrics between 1978 and 1979.

Of the investigated patients 43.9% were cardiovascularly orthogeric and 56.1% hypertensive in the first stage.

Neither of the patients presented organic cardiovascular sufferings or major impairments of other organs or systems. All the patients underwent a Gerovital H_3 biotrophic cure, consisting in the daily administration of one intramuscular Gerovital H_3 vial, for 12 days. During this period and in the lapse of time preceding the investigations (7–10 days), the patients were not given any other medication.

In blood we found adrenaline, noradrenaline, dopa, dopamine and serotonin, according to Van Euler fluorimetric method modified by Price and Price. In urine

we detected adrenaline, noradrenaline, homovanilmandelic acid (HVA), and hydroxyindolacetic acid (HIAA).

Determinations were made before starting the treatment and 24 hours after finishing it (urine and blood taken 24 hours after the last injection).

RESULTS

Determinations made after the end of Gerovital H_3 biotrophic therapy showed moderate rises in all the products, dosed both in blood and urine.

In blood, adrenaline and noradrenaline increased in 73% of the patients, dopamine in 51% and serotonin in 71% (Fig. 1).

In urine, adrenaline increased in 93% of the patients, noradrenaline in 90 %, homovanilmandelic acid in 56%, and hydroxyindolacetic acid in 53% (Fig. 2).

The other cases presented unchanged or decreased values, which did not exceed 18% of the initial values.

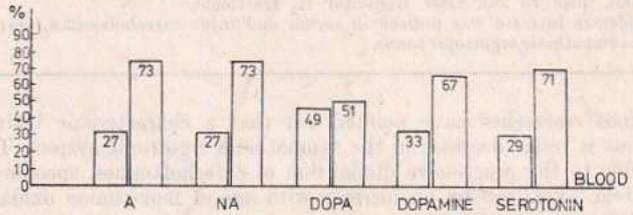

Fig. 1. — Serum catecholamine concentration in blood prior to and after Gerovital H_3 treatment.

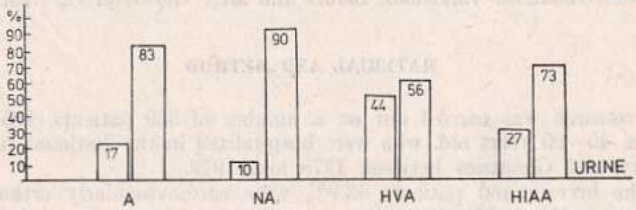

Fig. 2. — Serum catecholamine concentration in urine prior to and after Gerovital H_3 treatment.

No notable differences were found regarding variations from one sex to the other.

There were no remarkable differences between normal and hypertensive people, either.

Neither of the patients in the two groups presented notable variations of the arterial pressure.

We used a Tc test to estimate the statistical significance of the difference between the means preceding the treatment and those succeeding it (Table 1).

Table 1

The statistical calculus for Tc significance test

Parameters	Average values prior to and after treatment		σ^2	tc	P
Blood adrenaline	0.734	0.799	0.017	2.90	0.97
Urine adrenaline	4.42	6.23	2.31	4.52	0.97
Blood noradrenaline	0.723	0.876	0.14	2.40	0.97
Urine noradrenaline	24.95	35.24	11.6	5.14	0.95
Blood serotonin	0.98	1.19	0.13	3.84	0.97
Urine hydroxyindolacetic acid	135.05	162.08	83	1.89	0.95

We obtained a statistical significance with a probability value of 0.95 for HIAA samples in urine, and nonsignificant values for HVA, dopa and dopamine in blood.

Mention must be made of the fact that our research work still continues.

DISCUSSION

The increase of catecholaminemia and catecholaminuria is obvious after small and daily procaine doses (1.5 mg/kg body/24 h), represented by Gerovital H_3. The level does not exceed the double of the initial value for any of the dosed products, therefore we can notice a moderate rise.

Except for the above-mentioned mechanism, MAO inhibition might exercise its hypercatecholaminemia-inducing action by diminishing the uptake process of the catecholamines secreted at the level of synoptical slits, being a risk factor for the concentration of these substances in blood and urine.

An activity similar to MAO inhibition is possible at the level of other inactivating enzymes of catecholamines, such as catechol-O-methyl-transferase (COMT).

Finally, we assume a positive action at the level of tyrosinehydroxylase, the enzyme which catalyses tyrosine change into L-dopa, and is therefore a clue in the initiation or inhibition process of catecholamines metabolic chain.

All these actions induced by Gerovital H_3 result in the storage of catecholamines and produce a rise in the ergotropic tonus in spite of its clinical and biological consequences.

The arterial pressure of hypertensive patients was not influenced by these relatively small rises in catecholaminemia.

The fact is known that the catecholaminic system as a hypertensive factor plays an important role only in the pathogenesis of secondary hypertension in

pheochromocytoma, which represents about 0.2% of all arterial hypertension forms and is less obvious with old people.

Important catecholamine rises (300—500%) can be noticed in this affection, which are not accompanied by high blood pressures, except for 70% — 80% of the cases.

This explains the fact that moderate rises of catecholamines after Gerovital H_3 do not imply high blood pressure values.

The Gerovital H_3 stabilizing hypotensive action might be explained by a predominant stimulative action of adrenergic 2-beta receptors in arterioles, which are vasodilators.

Considering the Gerovital H_3 relation to some hypotensive drugs and the above-mentioned facts, the following problems should be taken into account: the non-selective beta-blocking agents such as propanol block the vasodilator 2-beta receptors in arterioles by releasing the vasoconstrictive alpha-receptors and produce a vasoconstrictor effect which can be increased by the hypercatecholaminemia induced by Gerovital H_3. This effect may result in the increase of peripheral resistance which produces hypertension. Without influencing the 2-beta receptors in arterioles, therefore without changing the peripheral vasomotor equilibrium, the new generation of beta-blocking agents (Metoprolol, Lopresor, Betabloc) can be associated with Gerovital H_3.

We must also point out that Gerovital H_3 is less related to hypotensive drugs producing removal of catecholamines, which are inactivated after leaving the axons (reserpin, guanetidin); Gerovital H_3 blocking action on the inactivating enzymes (MAO, COMT) could excessively increase catecholaminemia.

CONCLUSIONS

Gerovital H_3 treatment induces moderate rises in catecholamines, especially with old people.

In AHT the simultaneous stimulative action of peripheral beta and alpha systems induced by the "stored" catecholamines, as a result of Gerovital H_3 biotrophic treatment, produces stability and in some cases decrease in the peripheral resistance which influences diastolic arterial pressure.

In this respect, mention must be made of the researches carried out in our clinic on a group hospitalized in a long-term ward. The patients undergoing a Gerovital H_3 cure displayed significant low systolic and especially diastolic arterial pressure values.

The relation to some hypotensive substances should be judiciously analysed in the light of the above-mentioned pharmacodynamic processes.

Riassunto. Su un numero di 369 soggetti, di cui 244 donne e 125 uomini, di età tra 40 e 90 anni, ipertensivi e normali, sono dozate: l'adrenalina, noradrenalina, Dopa, Dopamina, e 5 Idrossitripamina nel sangue el'Adrenalina, Noradrenalina, l'Acido Omovanilmendelico e l'acido 5 idrossindolacetico nell'orina, prima e dopo il tratamento con Gerovital H_3.

Si è costatato un moderato aumento delle catecolamome nel sangue e nell'orina, insieme all'aumento del tono ergotropo simpatico.

REFERENCES

1. Hrachovec J.P., MacFarlane M.D., *Gerovital H3. A possible explanation of its action based on reversible inhibition of monoamine oxidase.* Int. Symp. of Gerontology, Bucharest, June 1972, p. 273.
2. MacFarlane M.D., Hrachovec J.P., *The mechanism of MAO inhibition by Gerovital H3.* Int. Symp. of Gerontology, Bucharest, June 1972, p. 545.
3. Safirescu Th., Bîrsan M., Chira Al., Hartia L., Staneschi D., Vascan C., Ionescu Theodora, Păuşescu E., Chirvasie R., *Variations of catecholaminemia and catecholaminuria under the influence of Gerovital H3 treatment.* Abstr. VIIIth Europ. Congr. Clinical Gerontology, Neptun, 1977, p. 102.
4. Vascan C., Bîrsan M., Chira Al., Hartia L., Staneschi D., Ionescu Theodora, Păuşescu E., Chirvasie R., Safirescu Th., *Blood and urine catecholamine variations with age.* Abstr. VIIIth Europ. Congr. Clinical Gerontology, Neptun, 1977, p. 60.
5. Aslan A., Hartia L., Bîrsan M., Safirescu Th., Ionescu Theodora, Vascan C., Chira Al., Staneschi D., Breaz S., Păuşescu E., Chirvasie R., *Catecholamine variations with old people displaying idiopathic arterial hypertension under the influence of Gerovital H3 and other hypotensive drugs treatment* (in Romanian). Ses. INGG, Bucharest, April 1978.

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CATECHOLAMINE VARIATION RELATED TO AGE

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Summary. The research was conducted on 63 women and 37 men aged 39 to 99 with no affection able to induce significant modifications of catecholamines, selected among the patients of the clinical section of the NIGG. Their blood epinephrine, norepinephrine, dopamine and 5-hydroxytyramine (serotonin) as well as blood and urine metabolites: homovanilmandelic acid and 5-hydroxyindolacetic acid were investigated according to Van Euler method modified by Price and Price. The results show more reduced quantities in the elderly than in adults, with differences between sexes and age-decades. The highest decrease is specific to epinephrine and norephinephrine during the 89–99 decade in men and the 79–89 decade in women. Dopa and dopamine decrease more with men than with women. The peculiarity of the above-mentioned decades is generally the psychic depression, clinically concealed by various minor somatic pictures. The catecholamine variations play quite an important part in the pathogenesis of psychic depression.

Ana Aslan and C. Bălăceanu [1] pointed out at the Eighth European Congress of Clinical Gerontology the beneficent effects of Gerovital H_3 treatment on psychic depression in aged persons by moderate and reversible monoaminoxidase inhibition. Similar effects have been confirmed by Bucci and Saunders [2], Hrachovec [3], MacFarlane [4, 5], Zung et al. [6].

Robinson et al. [7] pointed out an increased MAO activity as well as a low norepinephrine level with advancing age resulting from the activity of the age-modified enzymes, with a tendency to psychic depression.

Praage et al. [8] advanced a comprehensive theory on the connection between biogenous amines and psychic depression in old people; as a result, quite a large number of researches were carried out leading to a better understanding of the metabolism and action of this group of substances.

Neurotransmitters are mostly produced within the cells; only a small amount of neurotransmitters and of their metabolites is present in blood and urine, the rest remains both in the brain and the cerebrospinal fluid (CSP). The blood-brain barrier may be completely blocked for the catacholamines and their metabolites with 5 g of probenecid for 6 hours, which allows a complete examination in the CSF.

The most important metabolites investigated were the dopamine-derivative homovanilmandelic acid (HVA) and the serotonin-derivative 5-hydroxyindolacetic acid (5-HIAA).

Bowers and Gerbode [9] found lower 5-HIAA with old people than with adults; the finding accounted for the susceptibility of old people to psychic depression.

MATERIAL AND METHOD

The research was conducted on 63 women and 37 men aged 39 to 99 with no affections able to induce significant modifications of catecholamines, selected

among the patients of the clinical section of the NIGG. Their blood epinephrine, norepinephrine, dopamine and 5-hydroxytyramine (serotonin) as well as blood and urine metabolites: HVA and 5-HIAA were investigated according to Van Euler method modified by Price and Price.

With adults, the normal figures in 24 hours were: 4—8 gamma for urine epinephrine, 20—50 gamma for urine norepinephrine, 50—80 nanograms/ml for homovanilmandelic acid and 100—500 nanograms/ml for 5-hydroxyindolacetic acid.

Distribution of subjects by age-decade and sex

Age-decade	Women	Men	Total
39—49	5	4	9
49—59	16	7	23
59—69	24	8	32
69—79	8	9	17
79—89	9	6	15
89—99	1	3	4
General total	63	37	100

Urine catecholamine excretion according to age (mean values — gamma/24 hours)

Age-decade	Epinephrine		Norepinephrine	
	Women	Men	Women	Men
39—49	7.44	3.7	20.18	23.32
49—59	5.23	4.51	25.87	21.98
59—69	4.75	4.08	23.14	16.44
69—79	5.25	4.52	41.87	23.27
79—89	4.67	4.48	35.78	14.92
89—99	—	4.67	—	18.97

Epinephrine excretion is lower in old people than in adults: its linear evolution ranges from 3.7 to 4.67 gamma/24 h in men and 7.47 to 4.48 gamma/24 h in women, slightly decreasing with age.

Urine H-vanilmandelic acid and 5-hydroxyindolacetic acid excretion according to age (mean values — nanograms/24 h)

Age-decade	H-vanilmandelic acid		5-hydroxyindolacetic acid	
	Women	Men	Women	Men
39—49	45.68	40.50	105.12	198.25
49—59	36.20	55.50	178.95	171
59—69	40.63	28.99	135.96	133.99
69—79	49	43.95	141	72.36
79—89	38.57	37.75	138	149
89—99	—	42	—	188.67

The norepinephrine excretion is lower in old people than in adults: the lowest values were found in old men, ranging from 14.92 to 23.32, while in women from 20.18 to 41.87 gamma/24 hours, slightly increasing with age.

Homovanilmandelic acid values are low with both sexes, ranging from 36.20 to 45.68 nanograms/24 hours in women and from 28.99 to 53.51 nanograms/24 hours in men; both values are below those specific to adults.

5-hydroxyindolacetic acid values range from 105.12 to 178.95 nanograms/24 hours in women and from 72.36 to 198.25 nanograms/24 hours in men; these values are also lower than in adults.

Blood catecholamine variation according to age (gamma/1000 ml)

Age-decade	Epinephrine	Norepinephrine	Dopa	Dopamine	Serotonin
		Women			
39–49	0.72	0.87	0.15	0.03	0.87
49–59	0.73	1.18	0.10	0.04	0.84
59–69	0.75	0.84	0.13	0.08	0.087
69–79	0.83	0.89	0.08	0.03	0.98
79–89	0.09	0.68	0.11	0.05	0.94
		Men			
39–49	0.70	0.83	0.11	0.02	0.97
49–59	0.76	0.67	0.14	0.14	0.93
59–69	0.66	0.80	0.12	0.05	0.50
69–79	0.79	0.97	0.16	0.03	0.87
79–89	0.84	0.84	0.11	0.02	0.79
89–99	0.62	0.59	0.16	0.05	0.91

The dotted line marks the lowest values.
The underlined figures have the highest values.

CONCLUSIONS

All catecholamines decrease with age. The highest decrease is specific to peinephrine and norepinephrine during the 89–99 decade in men and the 79–89 decade in women.

As only one woman was in the last decade, the case was not taken into consideration.

Dopa and dopamine decrease is relatively equal with both sexes.

Indolamine-serotonin varies irregularly: with women, the maximum is specific to the 69–79 decade, whereas the minimum to the 49–59 decade; with men, the maximum appears during the 39–49 decade and the minimum during the 59–69 decade.

The peculiarity of the above-mentioned decades is generally the psychic depression, clinically concealed by various minor somatic pictures. The catecholamine variations play quite an important part in the pathogenesis of psychic depression.

Zusammenfassung. Die Untersuchung wurde an 100 Patienten durchgeführt, welche keine Leiden (Krankheiten) hatten, die die Veränderung des Katecholaminen Bildes hätten hervorrufen können. Die 63 Frauen und 37 Männer wurden aus den Reihen der Patienten der I.N.G.G. Klinik ausgewählt. Epinephrin, Norepinephrin, Dopamine und 5-Hydroxythyramin, wie auch die Produkte ihres Stoffwechsels im Blut und im Urin (Homovanilmandelic-Säure und 5-Hydroxyindolacet Säure) wurden nach der von Price und Price veränderten van Euler Methode, untersucht. Die Ergebnisse zeigten eine starke Verminderung der Quantitäten bei den Bejahrten im Vergleich zu den Erwachsenen, mit Unterschieden zwischen Geschlechts- und Altersstufen. Für die Altersgruppen: 89—99 Jahre bei Männern und 79—89 Jahre bei Frauen ist die stärkste Abnahme von Epinephrin und Norepinephrine kennzeichnend. Im Vergleich zu den Frauen fallen Dopa und Dopamine bei Männern mehr ab. Als ausgefallene Charakteristik bei den oben erwähnten (Jahrzehnten) Altersgruppen ist eine allgemeine psychische Depression hervorzuheben, welche klinisch von verschiedenen, unwichtigen, somatischen Erscheinungen maskiert ist. Die vielfältige Veränderung der Katecholaminen spielt eine besonders wichtige Rolle bei der Pathogenese der psychischen Depression.

REFERENCES

1. Aslan Ana, Bălăceanu C., *Les états dépressifs du troisième âge*. Rapports au VIII-ème Congrès européen de gérontologie clinique, Neptun, Roumanie, 1977.
2. Bucci I., Saunders J.C., *A psychopharmacological evaluation of 2-diethylaminoethanol-paraaminobenzoate (procaine)*. J. Neuropsychiat., 1960, **51**, 276—281.
3. Hrachovec J.P., *Inhibitory effect of Gerovital H3 on monoaminoxidase of rat brain, liver and heart*. Physiologist, 1972, **15**, 3.
4. MacFarlane M.D., *Possible rationale for procaine (Gerovital H3) therapy in geriatrics: inhibition of MAO*. J. Amer. Ger. Soc., 1973, **XXI**, 9, 414.
5. MacFarlane M.D., *Procaine (Gerovital H3) therapy: mechanism of inhibition of monoaminoxidase*. J. Amer. Geriat. Soc., 1974, **XXII**, 8, 365—371.
6. Zung W.K. et al., *Pharmacology of depression in the aged: evaluation of Gerovital H3 as an antidepressant drug*. Sympos. on Theoret. Aspects of Ageing, Miami, Florida (U.S.A.), Febr. 1974.
7. Robinson D.S. et al., *Ageing monoamine and monoaminoxidase levels*. Lancet, 1972, **I**, 290.
8. Praage A.J. et al., *Catecholamines and psychic depression*. Life Sci., 1967, *6*, 581.
9. Bowers M.B., Gerbode F.A., Nature, 1968, **219**, 1256.

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TROUBLES DE CONDUCTION INTRAVENTRICULAIRE PAR RAPPORT À L'ÂGE

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Résumé. On a évalué la prévalence des suivants troubles de conduction intraventriculaire sur un nombre de 1401 sujets d'âges différents (de 40 à 89 ans), groupés par décennies: la déviation axiale gauche accentuée (l'axe QRS situé entre −30° et −90°) la déviation axiale droite accentuée (axe QRS situé plus de +100°), le bloc de branche droit, le bloc de branche gauche, le bloc de branche droit associé à la déviation axiale gauche accentuée et le bloc de branche gauche associé à la déviation axiale accentuée.

On a constaté un accroissement des troubles de conduction intraventriculaire par rapport à l'âge, le plus important accroissement étant celui de la déviation axiale gauche.

On met en discussion certains problèmes de diagnostic différentiel concernant l'hémibloc gauche antérieur, qui peut coexister avec un infarctus ancien du myocarde inférieur, de même que la contribution du vectocardiogramme.

Les derniers temps on accorde une grande importance aux troubles de conduction intraventriculaire, d'un côté, par suite de l'individualisation de certaines altérations électrocardiographiques (EKG) qui autrefois n'avaient pas une signification spéciale, par exemple les hémiblocs gauches, et de l'autre côté, par suite de l'importante contribution du vectocardiogramme (VKG) dans la découverte des formes « pures » de conduction ou de leur association avec d'autres processus d'une signification plus sévère; ces processus peuvent accompagner ou déterminer les troubles de conduction intraventriculaire, comme l'infarctus du myocarde, qui n'est pas toujours évident à l'électrocardiogramme. En ce qui concerne l'infarctus ancien du myocarde inférieur son expression peut interférer l'expression de l'hémibloc gauche antérieur (HBGA). Il faut souligner que l'activité électrique du cœur dans les troubles de conduction intraventriculaire repose sur le concept du caractère trifasciculé du système de conduction intraventriculaire [26].

Certaines recherches relèvent un accroissement avec l'âge, des troubles de l'activité électrique du cœur [6, 7, 8, 12, 13, 18, 22, 28] et des troubles de conduction intraventriculaire [2, 3, 6, 7, 8, 13, 15, 18, 22, 23, 28, 29]. Il faut mentionner que la prévalence de ces troubles présente des variations déterminées par le caractère des lots étudiés — sujets sans affections cardiaques, sujets examinés dans des études épidémiologiques, ou des sujets qui présentent des troubles cardiovasculaires, hospitalisés dans des cliniques de spécialité.

Parmi les troubles de conduction intraventriculaire aux âgés, la déviation axiale gauche accentuée (DAGA-l'angle de l'axe QRS en plan frontal situé entre −30° et −90°), déterminée le plus souvent par un hémibloc gauche antérieur, est prédominante la prévalence de celle-ci dépassant 30% pour l'âge avancé [2, 3, 8, 13, 15, 18, 22, 23] en étant de 1% pour l'âge jeune [17].

En ce qui concerne le bloc de branche droit (BBD), on a constaté un accroissement de la prévalence avec l'âge, jusqu'à 10,5% (2) tandis que pour les jeunes la prévalence est très réduite (0,2%) — décennie IIIe [17].

Dans le bloc de branche gauche (BBG) la prévalence est de 10,9% [2] chez les âgés, par rapport à 0,1% chez les jeunes [17].

Ce travail a pour but l'étude de la prévalence des troubles de conduction intraventriculaire d'un lot de sujets âgés groupés par décennies.

Chez certains d'entre eux qui présentaient des difficultés de diagnostic électrocardiographique, par exemple la présence de l'onde r d'amplitude basse dans des dérivations inférieures ou certains aspects particuliers du complexe QRS (c'est le cas du bloc de branche gauche associé à hémibloc gauche antérieur) on a enregistré aussi le vectocardiogramme (système Frank).

MATÉRIEL ET MÉTHODE

Les recherches ont été faites sur 1401 patients hospitalisés dans l'Institut National de Gérontologie et Gériatrie; parmi eux se trouvaient des orthogères et des patients avec des affections cardiovasculaires. Les sujets ont été groupés par décennies d'âge de la Ve jusqu'à la IXe (tableau I).

Pour la sélection des cas à déviation axiale gauche antérieure on a utilisé les suivants critères électrocardiographiques [12, 14]: *a)* L'axe QRS en plan frontal située entre $-30°$ et $-90°$, dans l'absence du cœur pulmonaire chronique ou du syndrome WPW. *b)*, le complexe rS dans les dérivations II et III. *c)* la durée des complexes QRS $< 0{,}12$ sec.

Pour la sélection des cas à hémibloc gauche postérieur (HBGP) on a considéré les cas à l'axe QRS en plan frontal $> +100°$.

Pour la sélection des cas de BBD on a utilisé les critères électrocardiographiques [12, 14]: *a)* la durée de complexes QRS $\geqslant 0{,}12$ sec. *b)* l'aspect RsR ou QR en Vi; *c)* la sous dénivellation ST et l'inversion de l'onde T et Vi; *d)* des ondes S larges en I, aVL, V5, V6.

Les critères vectocardiographiques utilisés pour la sélection des cas ont été [10, 30] pour la déviation axiale gauche antérieure: *a)* l'orientation inférieure des vecteurs initiaux de la boucle QRS. *b)* la rotation antihoraire de la boucle QRS; *c)* la déviation anormale à gauche et supérieure du vecteur maximum QRS dans le quadrant supérieur gauche;

— pour l'infarctus du myocarde inférieur: *a)* l'orientation au-dessus de l'axe $0-180°$ des vecteurs initiaux de la boucle QRS, en plan frontal; *b)* la rotation horaire de la boucle QRS en plan frontal.

— pour la coexistence de l'hémibloc gauche antérieur avec l'infarctus inférieur: *a)* l'orientation au-dessus de l'axe $0-180°$ et la rotation horaire des vecteurs initiaux de la boucle QRS en plan frontal; *b)* la rotation antihoraire et le ralentissement de l'inscription des vecteurs terminaux; *c)* la position du vecteur QRS maximum dans le quadrant supérieur gauche; *d)* la boucle QRS située dans sa majorité au-dessus de l'axe $0-180°$.

— pour l'hémibloc gauche postérieur on a utilisé le critère de la position de la boucle QRS dans le quadrant inférieur, droit, postérieur (10)

— pour le bloc de branche droit et le bloc de branche gauche on a utilisé les critères de Chou et coll. [10].

RÉSULTATS

Dans le tableau 1 on présente la prévalence des troubles de conduction intraventriculaire chez 1401 patients examinés, groupés par décennies d'âge.

Tableau 1

La prévalence (%) des troubles de conduction intraventriculaire chez 1401 sujets par rapport à l'âge

ans	40—49	50—59	60—69	70—79	80—89
N	81	185	415	510	210
DAGA	3,7	7,6	17,3	20,2	31,9
BBD	—	—	2,9	2,9	4,3
BBD + DAGA	—	—	0,9	0,6	1,9
BBG	—	0,5	2,2	1,8	3,3
BBG + DAGA	—	—	0,5	0,8	2,4
DAD	—	0,5	0,2	—	—

On constate une prévalence relativement petite des troubles de conduction intraventriculaire pour les décennies V et VI, plus grande quand même que celle des âges jeunes; par exemple: pour la déviation axiale gauche antérieure, la prévalence chez les jeunes gens (décennie III^{e}) est approximativement de 1% [23]. Importante c'est la prévalence appréciable de la déviation axiale gauche antérieure de la VII^{e} décennie, quand elle dépasse 17%, jusqu'à 31,9% IX^{e} décennie.

La prévalence du bloc de branche droit est plus grande que celle du bloc de branche gauche; elle atteint 4,3% dans la IX^{e} décennie pour le bloc de branche droit par rapport à 3,3% pour le bloc de branche gauche.

La prévalence pour l'hémibloc gauche postérieur est de 0,5%.

En ce qui concerne l'aspect vectocardiographique chez les cas de HBGA à aspect électrocardiographique discutable, on a fait des enregistrements vectocardiographiques chez 105 patients et on a constaté dans le plan frontal, chez 31 de cas (29,5%) l'aspect HBGA coexistant avec l'infarctus ancien du myocarde inférieur.

En ce qui concerne le problème controversé de l'association BBG à HBGA, on a constaté dans le plan frontal l'aspect vectocardiographique indicatif de HBGA, avec la boucle QRS située dans le quadrant supérieur gauche.

DISCUSSION

Les troubles de conduction intraventriculaire montre un accroissement de leur prévalence avec l'âge. Parmi ceux-ci, le DAGA est le plus évident. C'est ainsi que Bensaid et coll. [2] ont constaté chez les sujets âgés de 90—99 ans, sans cardiopathie, la présence de HBGA dans un pourcentage de 30,7%, Mihalick et coll. [22] ont constaté une fréquence de HBGA de 11% chez 671 sujets au-dessus de 65 ans, hospitalisés ou non, mais sans affections cardiaques.

Dans une étude épidémiologique sur 4678 sujets entre 20 et 80 ans, Ostrander a constaté un important accroissement de la prévalence de DAGA par rapport à l'âge, atteignant dans les décennies VIII et IX 25,74%. Bhat et coll. [3]

constate sur 455 sujets au-dessus de 65 ans une prévalence de HBGA de 27,5%. Nous avons revelé un accroissement progressif de la prévalence de DAGA par rapport à l'âge jusqu'à 35% [30] dans la IX^e et X^e décennie.

Il nous apparaît que l'altération de l'état fonctionnel ou structural du cœur influence l'accroissement de DAGA par rapport à l'âge. C'est ainsi qu'il est à mentionner les études corrélatives qui revèlent l'importance de la relation entre les altérations anatomiques et la présence DAGA [15, 16, 29]. On mentionne aussi certaines études épidémiologiques [4, 5] qui n'appuient pas sur ces constatations. En outre Mihalick et coll. [22] n'associent pas DAGA à la cardiopathie clinique des âgés, en constatant un accroissement de la fréquence de DAGA au cours de la vieillesse. Ostrander [23] conclut que 59% de 248 sujets avec DAGA ont présenté aussi d'autre anomalies électrocardiographiques marquant la cardiopathie; l'augmentation de DAGA par rapport à l'âge a été observé tant à DAGA isolée que à DAGA associée à la cardiopathie.

L'hémibloc gauche postérieur a été trouvé de Bhat et coll. [3] chez 0,65% des patients âgés, le faisceau gauche postérieur étant le moins vulnérable du système de conduction intraventriculaire.

Selon différents auteurs, le bloc de branche droit, comme défaut isolé de conduction, marque une augmentation différente chez les âgés. Par exemple Bensaid et coll. [22] constate une prévalence de 5,5% chez les sujets au-dessus de 90 ans, Bath et coll. [3] de 10,5%, Campbell, et coll. [8] de 1,9%, Golden et coll. [13] de 7%, Kitchin et coll. [18] de 2,3% et Mihalick et coll. [22] de 7,1%.

Pour les âges jeunes la prévalence de BBD est considérablement petite, de 0,2% (III^e décennie). Chez nous le BBD a varié entre 2,9 et 4,3%.

Le bloc de branche gauche a été trouvé de 10,9% par Bensaid et coll. [2], de 7,9% par Bhat et coll. [3] de 1,4% par Campbell et coll. [8], de 7% par Golden et coll. [13, 18] de 4,9% par Mihalick et coll. [22] et de 1,4% de Kitchin et coll. [18]. Chez nos cas, le BBG a varié entre 0,5% — 3,3%. Pour les âges jeunes la prévalence de BBG a été trouvée considérablement petite, de 0,1% dans la III^e décennie [17]. Bhat et coll. [2] ont trouvé la coexistence de BBD et de HBGA en proportion de 9% chez les âgés au-dessus de 65 ans. Chez nous on l'a trouvée plus petite, entre 0,6 et 1,9%. On considère cette combinaison d'un pronostic plus réservé que les autres troubles de conduction. Ainsi Rosembaun et coll. [25], Kulbertus et coll. [20] ont relevé que le bloc cardiaque total est souvent précédé d'un bloc dans deux des faisceaux du système de conduction. Lasser et coll. [21] ont revelé l'existence d'un bloc atrioventriculaire transitoire ou complet pour 59% des malades qui ont présenté BBD et HBGA.

Kulbertus et coll. [19] ont constaté, durant une période d'observations de 4 à 8 ans, une incidence de 21% pour le bloc complet, chez les patients à BBD et HBGA.

En ce qui concerne la relation entre HBGA et l'infarctus du myocarde inférieur, on ne peut pas établir toujours avec précision le diagnostic électrocardiographique différentiel, car l'aspect de l'ekg est influencé tant par HBGA que par l'infarctus du myocarde [1, 9, 11].

L'infarctus du myocarde guéri présente des difficultés de diagnostic ekg, afin d'établir la présence ou l'absence de l'infarctus, dépendant seulement de l'étude des déflexions QRS ou des ondes Q dans les dérivations périphériques inférieures II, III et aVF, les ondes Q anormales se trouvant seulement dans une ou deux dérivations inférieures, étant quelquefois absentes même dans ces dérivations. On a constaté que 10% des cas à infarctus inférieur du myocarde peuvent avoir un

aspect rS dans les dérivations II, III et aVF, qui en présence de DAGA peuvent être diagnostiquées d'une manière erronée, comme HBGA [1, 27].

L'utilisation des critères ekg caractéristiques à la coexistence de l'HBGA avec l'infarctus inférieur du myocarde [1], c'est-à-dire la position des vecteurs initiaux au-dessus de l'axe P-180°, avec la rotation initiale horaire et puis, dans la IIe moitié de la boucle à rotation antihoraire, les vecteurs de la branche afférente étant situés au-dessus de la branche efférant de la boucle de QRS, ayant l'aspect général de corne à concavité en bas, offre la possibilité de la réalisation du diagnostic différentiel.

Celle-ci est d'autant plus nécessaire que la preuve de l'inspiration profonde utilisée pour établir la signification de l'aspect QS dans les dérivations II, III et aVF — la présence ou l'absence de l'infarctus du myocarde — n'est pas toujours concluante, ainsi que le montrent les recherches coronarographiques et ventriculographiques pour tels malades [27].

Summary. The prevalence of the following intraventricular conduction disturbances was stated for 1401 subjects of different ages (from 40 to 89 years old), grouped in decades: marked left axis deviation (QRS axis situated between −30° and −90°), marked right axis deviation (QRS axis situated above +100°), right bundle branch block, left bundle brunch block, the right bundle branch block associated with marked left axis deviation and the left bundle branch block associated with marked left axis deviation.

In general, it was noticed an increase in prevalence of intraventricular conduction disturbances with age, the most relevant being the left axis deviation.

We tackled some problems concerning differential diagnosis caused by the left anterior hemiblock, which can coexist with old inferior myocardial infarction and we underlined the role played by vectocardiogram in these circumstances.

BIBLIOGRAPHIE

1. Benchimol, A., Desser, K.B., *Coexisting left anterior hemiblock and inferior wall myocardial infarction. Vectorcardiographic features.* Amer. J. Cardiol., **29,** *1* (1972), 7—14.
2. Bensaid, J., Barrillon, A., Moreau, P., Pillard, D., Lenègre, J., *Étude de l'électrocardiogramme de 110 sujets âgés de plus de 90 ans.* Arch. mal. cœur, **67,** *2* (1974), 133—145.
3. Bhat, P.K., Watanabe, K., Rao, D.B., Luisada, A.A., *Conduction defects in the aging heart.* J. Amer. geriat. Soc., **22,** *11* (1974), 317—520.
4. Blackburn, H., Taylor, H.L., Keys, A., *The electrocardiogram in prediction of five-year coronary heart disease. Incidence among men aged forthy through fifty-nine.* Circulation, **61,** *1* (1970), 154—161.
5. Blackburn, H., Vasquez, C., Keys, A., *The aging electrocardiogram. A common aging process or latent coronary artery disease?* Amer. J. Cardiol., **20,** *6* (1967), 618—627.
6. Burch, G.E., *Interesting aspects in geriatric cardiology.* Amer. Heart J. **89,** *1* (1975), 99—114.
7. Caird, F.I., Campbell, A., Jackson, T.F.M., *Significance of abnormalities of electrocardiogram in old people.* Brit. Heart J., **36,** *6* (1974), 1012—1018.
8. Campbell, A., Caird, F.I., Jackson, T.F.M., *Prevalence of abnormalities of electrocardiogram in old people.* Brit. Heart J., **36,** *6* (1974), 1005—1011.
9. Castellanos, A., Chachine, R.A., Chapunoff, E., Gomez, J., Portillo, B., *Diagnosis of left anterior hemiblock in the presence of inferior wall myocardial infarction.* Chest, **60,** *6* (1971), 543—549.
10. Chou, T.C., Helm, R.A., Kaplan, S., *Clinical Vectorcardiography.* Grune and Stratton, New York, 1974.
11. Fernandez, F., *Les « hémiblocs » ventriculaires gauches.* Revue praticien, **23,** *33* (1973), 2995—3022.

12. FRIEDMAN, H.H., *Diagnostic Electrocardiography and Vectorcardiography*. McGraw-Hill Book Company, New York, 1977.
13. GOLDEN, G.S., GOLDEN, L.H., *The "nona" electrocardiogram: findings in 100 patients of the 90+ age group*. J. Amer. geriat. Soc., **22**, 7 (1974), 329–332.
14. GOLDMAN, M.J., *Principles of Clinical Electrocardiography*. Lange medical Publications, Los Altos, California, 1970.
15. GORMAN, P.A., CALATAYUD, J.B., ABRAHAM, S., CACERES, A., *Effects of age and heart disease on the QRS ages having the seventh through the tenth decades*. Amer. Heart J., **67**, *1* (1964), 39–43.
16. GRANT, R.D., *Left axis deviation, an electrocardiographicpathologic correlation study*. Circulation, **14**, *2* (1956), 233–249.
17. HISS, R.G., LAMB, L.E., *Electrocardiographic findings in 122,043 individuals*. Circulation, **25**, *6* (1962), 947–969.
18. KITCHIN, A.H., LOWTHER, C.P., MILNE, J.S., *Prevalence of clinical and electrocardiographic evidence of ischemic heart disease in the older population*. Brit. Heart J., **35**, *4* (1973), 946–953.
19. KULBERTUS, H.E., *Magnitude of risk of developing complete heartblock in patients with LAD-RBBB*. Amer. Heart J., **86**, 2 (1973), 278–279.
20. KULBERTUS, H.E., COLLIGNON, P., *Association of right bundle-branch block with left superior or inferior intraventricular block. Its relation to complete heartblock and Adams-Stokes syndrome*. Brit. Heart J., **31**, *3* (1969), 435–441.
21. LASSER, R.P., HAFT, J.I., FRIEDBERG, C.K., *Relationship of right bundle-branch block with marked left axis deviation (with left parietal or perinfarction block) to complete heartblock and syncope*. Circulation, **37**, *3* (1968), 429–437.
22. MIHALICK, M.J., FISCH, C., *Electrocardiographic findings in the aged*, Amer. Heart J., **87**, *1* (1964), 117–128.
23. OSTRANDER, L.D., *Left axis deviation: prevalence, associated conditions and prognosis*. Ann. int. Med., **75**, *1* (1971), 23–28.
24. PRYOR, R., BLUNT, S.G., *The clinical significance of true left axis deviation. Left intraventricular blocks*. Amer. Heart J., **72**, (1966), 391–413.
25. ROSENBAUM, M., ELIZARI, M.V., LAZZARA, J.O., *Anatomical basis of AV conduction disturbances*. Geriatrics, **25**, *1* (1970), 132–137.
26. ROSENBAUM, M., ELIZARI, M.V., LAZZARI, J.O., *Intraventricular trifascicular blocks: review of the literature and classification*. Amer. Heart J., **78**, *3* (1969), 450–459.
27. SHETTIGAR, U.R., HULTGREN, H.N., PFEIFER, J.F., LIPTON, M.J., *Diagnostic value of Q-waves in inferior myocardial infarction*. Amer. Heart J., 88 (1974), 170–175.
28. SIMONSON, E., *The effect of age on the electrocardiogram*. Amer. J. Cardiol., **29**, *1* (1972), 65–73.
29. TAMARO, A.E., FORIN, G., *Left fascicular hemiblocks in the elderly*. J. Amer. geriat. Soc., **25**, *10* (1977), 439–442.
30. ZAMFIRESCU, N.R., HARTIA, L., *Considérations sur la signification de la déviation axiale gauche chez les âgés; la relation avec l'hypertension artérielle*. Rev. roum. morphol. embryol. physiol., **14**, *4* (1977), 231–236.

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RÉSULTATS DE LA THÉRAPIE PROPHYLACTIQUE AU GÉROVITAL H_3 DANS LA PRATIQUE DU TERRAIN (CENTRES GÉRONTOLOGIQUES). ÉTUDE LONGITUDINALE

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Résumé. On expose les résultats d'une étude longitudinale, effectuée plus de 10 ans, concernant l'application de la thérapie prophylactique au Gérovital H_3 chez les personnes du groupe d'âge de 45–60 ans.

Cette action de géronto-prophylaxie montre l'efficience de la méthode Aslan concernant le maintien ou l'amélioration du potentiel biologique, la prévention des phénomènes de vieillissement précoce et de la pathologie chronique dégénérative.

L'efficience augmente avec la *durée* du traitement; les résultats positifs sont obtenus après deux ans de traitement surtout, exprimés par l'amélioration des indices somatophysiologiques, la diminution de la morbidité par les maladies chroniques, l'augmentation de la trophicité de l'organisme et le maintien d'une bonne capacité de travail aussi longtemps que possible.

En Roumanie, dans le cadre de l'assistance prophylactique accordée aux personnes âgées, deux formes sont organisées:

a) des examens prophylactiques périodiques;

b) la dispensairisation gérontologique.

On poursuit, à l'aide des examens prophylactiques: la surveillance médicale à l'aide des consultations géronto-prophylactiques, effectuées périodiquement aussi bien aux personnes cliniquement saines (prophylaxie primaire) qu'aux personnes malades se trouvant dans la phase initiale de la maladie (prophylaxie secondaire), ainsi qu'aux malades chroniques ayant diverses affections (hypertension artérielle, athérosclérose, maladies de l'appareil ostéo-articulaire, du système nerveux, etc.), en vue de la prévention des états aigus, des aggravations, des complications (prophylaxie tertiaire).

En tant que forme supérieure de prophylaxie, pour les personnes appartenant au groupe d'âge de 45 à 60 ans spécialement, académicien Ana Aslan a pris l'initiative, dès l'année 1954, de la dispensairisation gérontologique. Le cadre d'organisation a été constitué par « le centre gérontologique » des entreprises industrielles.

L'action de dispensairisation inclut: des examens cliniques et de laboratoire, effectués de façon périodique (tous les 6 mois), l'application des mesures de géronto-hygiène et de la thérapie biotrophique au Gérovital H_3 et Aslavital, selon « la méthode Aslan », qui consiste en: 5 séries par an de 12 injections intramusculaires de 5 ml de Gérovital H_3 ou d'Aslavital, au rythme de 3 injections par semaine; 45 jours de repos entre les séries.

Le traitement au Gérovital H_3 ou à l'Aslavital peut être administré par voie orale: 2 dragées par jour, pendant 12 jours, 8 séries par an; 30 jours de repos entre les séries.

La thérapie prophylactique au Gérovital H_3 a influencé favorablement les dystrophies générales, a limité et freiné les processus dégénératifs et a amélioré la trophicité de l'organisme, ce qui a conduit à l'augmentation du potentiel biologique du travailleur âgé.

16.433 ouvriers ayant entre 45 et 62 ans ont été inclus dans cette action.

On expose, dans le présent travail, les résultats d'une *étude longitudinale* effectuée sur un lot de 450 ouvriers ayant 45 ans et plus (70,7% hommes et 29,3% femmes) qui ont suivi régulièrement la thérapie biotrophique au Gérovital, pendant plus de 10 ans. *)

Il ressort de l'application de la thérapie biotrophique de longue durée, dans la pratique du terrain: *a)* le maintien ou une amélioration du potentiel biologique; *b)* la prévention des phénomènes de vieillissement précoce et pathologique; *c)* la diminution de la morbidité par des maladies chroniques dégénératives (les indices de la morbidité à l'incapacité temporaire de travail chez les personnes traitées ont été inférieurs de plus de 40% par rapport aux personnes du lot qui n'a pas effectué la thérapie biotrophique); *d)* le maintien ou l'amélioration de la capacité de travail; *e)* la prolongation de la période de vie active.

On a poursuivi, au cours de l'étude longitudinale, la dynamique des indices somato-physiométriques ainsi que l'état de santé des personnes dispensairisées.

On a obtenu, après 10 ans de thérapie biotrophique, l'amélioration de l'état de santé chez 54,6% des hommes et 48,8% des femmes, grâce à la prévention des maladies chroniques dégénératives. Les résultats positifs ont été plus évidents dans les arthroses, dans les formes rhumatismales dégénératives, en ostéoporose. En ce qui concerne les maladies de l'appareil cardio-vasculaire, la thérapie biotrophique a amélioré ou normalisé la tension artérielle aux cas de hypertension; ainsi, chez le groupe des personnes ayant 55—59 ans, les valeurs moyennes de la tension artérielle systolique baissent de 146 mmHg (à l'examen initial) à 133 mm Hg après 10 ans de thérapie biotrophique.

La force musculaire, mesurée au dynamomètre de Smedley, a augmenté surtout après les deux premières années de traitement (de 117,0 à 124,0 chez les hommes du groupe de 50—54 ans et de 90,6 à 94,4 chez les femmes du même groupe d'âge) et s'est maintenue pendant toute la durée de la thérapie biotrophique. Ce fait démontre l'action anabolisante et biocatalytique du Gérovital H_3, le rôle de celui-ci dans le métabolisme et la régénération cellulaire ainsi que dans l'inhibition de la monoaminoxydase (MAO), ce qui contribue à augmenter la force musculaire, à rééquilibrer la fonction de l'organisme tout entier.

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*) Recherches effectuées en collaboration avec:

1. Dr. Ştefănescu Gheorghe — Entreprise « 1 Mai » Ploieşti
2. Dr. Marian Viorica — Entreprise « Metalurgică » Plopeni
3. Dr. Berezowschi Claudia — Entreprise « Ţesătura » Iaşi
4. Dr. Saller Missi — Entreprise « Letea » Bacău
5. Dr. Moldovan Maria — Entreprise « Libertatea » Sibiu
6. Dr. Opriş Lavina — Entreprise Combinatul Siderurgic Hunedoara
7. Dr. Ghiţulescu Angela — Entreprise « Independenţa » Sibiu
8. Dr. Petcu Elena — Entreprise « Rulmentul » Bîrlad
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La *capacité vitale*, exprimée par les valeurs spirométriques, présente des augmentations significatives; ainsi, chez les hommes appartenant au groupe de 50—54 ans, les valeurs moyennes de la spirométrie augmentent de 3185 ml à 3544 ml et, chez les femmes, augmentent de 2778 ml à 2940 ml, après deux ans de traitement, et se maintiennent à ces valeurs après 10 ans aussi.

L'indice de la capacité vitale, calculé à partir du rapport existant entre les valeurs moyennes de la spirométrie en fonction de la taille, présente, en général, une diminution, avec l'avancement en âge, de 18,70 à 16,00 pour les hommes et de 15,50 à 13,00 pour les femmes.

Après l'application de la thérapie biotrophique pendant 10 ans, on enregistre, chez les hommes appartenant au groupe de 50—54 ans, un indice de la capacité vitale de 20,50 par rapport à 18,70, — la valeur initiale —, tandis que chez les hommes appartenant au groupe de 55—60 ans, on enregistre l'indice de 19,77, par rapport à la valeur initiale de 16,00.

Chez les femmes aussi on constate l'amélioration et l'augmentation de la capacité respiratoire après 10 ans de traitement. L'indice augmente, de la sorte, pour les femmes appartenant au groupe de 45—49 ans, de 15,50 à 18,44, tandis que pour celles du groupe de 50—55 ans l'indice augmente de 13,00 à 18,00, ce qui démontre que la thérapie biotrophique fait accroître la capacité vitale chez tous les groupes d'âge.

En ce qui concerne *le rendement du travail*, apprécié par l'accomplissement de la norme de productivité, dans des activités précisément établies, on a constaté que l'application pendant longtemps de la thérapie biotrophique conduit à l'accomplissement de la norme, chez les hommes, à 73,4% des sujets, et au dépassement de celle-ci à 26,6%, tandis que chez les femmes, les valeurs sont de 89,7%, respectivement, 7,7%.

La thérapie a constitué aussi un moyen efficient pour prévenir et combattre l'asthénie physique et psychique, pour améliorer la mémoire, l'attention et la capacité intellectuelle.

On a constaté, au niveau des téguments, une amélioration de la trophicité de la peau, des cheveux et des ongles, du fait de la stimulation des processus de régénération.

Le traitement contribue à régler l'homéostasie endocrinienne avec le rétablissement de la balance hormonale et l'amélioration des troubles de climactérium.

CONCLUSIONS

L'application de la thérapie prophylactique au Gérovital H_3 dans le cadre de l'action de dispensairisation des personnes âgées actives (45—60 ans), pendant longtemps — 10 ans et plus — démontre l'efficience de cette méthode concernant le maintien ou l'amélioration du potentiel biologique, la prévention des phénomènes de vieillissement précoce ou pathologique et de la pathologie chronique dégénérative associée au processus de vieillissement.

Cette efficience augmente avec la durée du traitement; les résultats positifs sont obtenus surtout après deux ans de traitement, lorsque l'amélioration des indices somato-physiométriques est évidente.

La recherche longitudinale a démontré, en même temps, une amélioration de l'état de santé, révélée par des indices diminués de morbidité par des maladies chroniques dégénératives, par l'augmentation de la trophicité de l'organisme et par le maintien d'une meilleure capacité de travail aussi longtemps que possible.

Summary. The results are presented of a 10 year longitudinal study on the prophylactic therapy with Gerovital H_3 on patients aged 45 to 60. The gerontoprophylactic action aimed at pointing out the efficacy of the method Aslan in maintaining or improving the biological potential and preventing precocious aging and chronic degenerative phenomena.

The efficacy increased with the duration of the treatment; positive results have been obtained mostly after 2 years of treatment; they were pointed out by the improvement of somato-physiometric indices, decrease in morbidity due to chronic diseases, increase in organismic trophicity, a longer maintained good working capacity.

BIBLIOGRAPHIE

1. Aslan, Ana, *Novocain als eutrophischer Faktor und die Möglichkeit einer Verlängerung der Lebensdauer.* Terapeutische Umschau, 1956, **9**, p. 167–172.
2. Aslan, Ana, *Eine neue Methode zur Prophylaxe und Behandlung des Alterns mit Novocain – Stoff H_3 – eutrophische und verjüngende Wirkung.* Therapiewoche, Karlsruhe, **1–2**, p. 10–19, 1957.
3. Aslan, Ana; Ciucă, Al.; Jucovschi, Vl.; David, C.; Chira, A.; Tăpălagă, M.; Sanda, M.; Mustață, E.; Simionescu, S., *Le Centre gérontologique.* Rev. Fr. Géront. Paris, **XI**, 2, p. 135–136, 1965.
4. Aslan, Ana, *Neue Erkenntnisse in der Geriatrie aus der Sicht der Prophylaxe.* Prophylaxe, 8: 122 Heidelberg, 1967.
5. Aslan, Ana, *Recherches concernant le processus de vieillissement et sa prophylaxie. Report at the VIIIth Europ. Congr. of Clinical Geront., Neptun, Romania, 1977.*
. Aslan, Ana, *Current theoretical bases of Gerovital H_3 therapy in the prophylaxis of aging. Institute's documentary fund. Survey on Gerovital H_3.*, Bucarest, 1979.

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ASPECTS DE LA NÉVROSE D'ADAPTATION CHEZ LES TRAVAILLEURS ÂGÉS, MÉCANICIENS, AIDES-MÉCANICIENS DE LOCOMOTIVE

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Résumé. De nombreuses recherches concernant les aspects comportamentaux différents ont relevé la possibilité du maitien d'une capacité psychique globale, même si de divers sous-systèmes considérés isolés montrent des détériorations. Les problèmes de l'adaptation psychique au processus de vieillissement ont mis en évidence le rôle des processus de compensation pour le maintien d'un « optimum fonctionnel ».

Ayant comme point de départ ces données on a poursuivi la classification des mécanismes d'action des processus de compensation au niveau psychologique et la confirmation des conditions favorables dans le transport ferroviaire.

On a étudié l'apparition de la névrose d'adaptation dans le transport ferroviaire chez les mécaniciens et aides-mécaniciens de locomotive, en raison des conditions de risque du travail, les phénomènes de non-adaptation dans leurs activité ayant comme conséquence les accidents de circulation.

Ces non-adaptations, qui adviennent quelquefois, ont pour effet la sursollicitation psychique, étant une conséquence en interaction avec les facteurs socio-professionnels (malentendus, états conflictuels au lieu de travail ou familiaux, déficience d'attitude etc.).

On connaît de la littérature de spécialité une série de recherches de « psycho-prophylaxie de la non-adaptation » (J. A. Atkinson, S. A. Carson, H. Selye, P. Pichot, E. Klinger, S. P. Crossman, D. C. McClelland etc. [1].

De nombreuses recherches de gérontologie reposent sur le concept « d'adaptation » considéré critère d'évaluation des aspects positifs ou négatifs des modifications associées au processus de vieillissement (Cattell, 1942; Tréanton, 1963; Kuhlen, 1973, etc.) [2].

Dans le domaine des problèmes psychologiques du vieillissement, le problème central est le problème de l'accommodation.

Les problèmes concernant l'adaptation psychique et la diminution des conséquences des détériorations des aptitudes « présentent une importance plus grande qu'une simple appréciation du déclin des aptitudes ».

Afin d'élaborer un programme de prévenir des non-adaptations de prolonger la capacité de travail et de récupérer les non-adaptations, on a étudié la relation entre le vieillissement et l'adaptation professionnelle pour deux professions importantes du transport ferroviaire (mécanicien et aide-mécanicien de locomotive).

MÉTHODE UTILISÉE

On a investigué 212 sujets entre 25—56 ans, 180 mécaniciens de locomotive et aides-mécaniciens et 22 anciens mécaniciens, retraités pour motifs médicaux et psychologiques.

On a utilisé une méthodologie complexe, qui comprend tant des méthodes de terrain que des méthodes expérimentales à savoir:

— la méthode d'analyse du travail en vue de l'identification des sollicitations psychiques;

— l'étude des conditions de travail en vue de l'identification des facteurs de risque dans le processus de l'adaptation des travailleurs âgés;

— l'application des preuves de psychodiagnostic dans les processus cognitifs et les traits de personnalités.

— les preuves de diagnostic psychique ont été:

— les questionnaires de personnalité Eysenck, Woodworth et Guifford, Zimmerman, la preuve d'anxiété Cattell et deux preuves originales d'assumer le risque.

Pour l'investigation de la sphère de la motivation générale et des attitudes vis-à-vis des facteurs de sollicitations on a utilisé un questionnaire psycho-social appliqué sous forme d'interview.

La répartition selon l'âge est la suivante:

87 sujets	26—39 ans
59 sujets	40—44 ans
20 sujets	au-dessus de 45 ans
20 sujets	40—58 ans (chef d'équipe)

Les critères de répartition ont été les performances professionnelles et leur comportement dans le service et dans la vie privée.

Pour une meilleure classification du lot témoin on a choisi les extrêmes, tant en ce qui concerne les performances réalisées que dans le comportement.

LA DISCUSSION DES RÉSULTATS

L'analyse des sollicitations du travail montre des exigences accrues concernant l'effort neuropsychique, les processus perceptifs et l'attention, l'équilibre et l'attitude vis-à-vis du risque.

Le remplacement de la locomotive à vapeur par la locomotive Diesel électrique a déterminé le changement des caractéristiques des exigences, tant à travers la nature du travail, qu'à travers les conditions du travail.

En outre, l'augmentation de la vitesse de circulation, l'augmentation du nombre des signales à surveiller, par l'unité de temps, le grand nombre des trains à conduire, ont déterminé l'accroissement de la tension nerveuse.

Les exigences accrues du travail en conditions de stress, le régime de travail, à cause du travail de nuit, tous impliquent l'apparition de la surtension nerveuse.

En plus, du fait que le travail de nuit est très fatigant, le programme des mécaniciens de locomotive est irrégulier: heures de repos, de sommeil imposé, en fonction des nécessités du service, ce qui trouble le cycle biologique.

Les résultats de notre recherche [7] nous indique que la fatigue provoquée par «le travail de nuit» est la cause principale des difficultés survenues dans le processus de travail (42,2%); (24,1%, 33,3%), en deuxième place se trouve la «tension nerveuse» (33,8%, 20,4%, 27,8), et puis les relations interpersonnelles («les malentendus dans le collectif de travail»).

En ce qui concerne l'état de la santé, qui se trouve en fonction de la fréquence sur la 4e place, on note une augmentation du pourcentage de maladie, par rapport à l'avancement en âge (de 7,4 à 16,7) le tableau 1.

Tableau 1

La situation des sursollicitations des mécaniciens de locomotive, par groupe d'âge

	26—39 ans	40—44 ans	sur 45
Travail de nuit	41,2%	24,1%	33,3%
Tension nerveuse	33,8%	20,4%	27,8%
Malentendus dans le collectif de travail	17,6%	9,3%	—
État de la santé	7,4%	13%	16,7%
D'autres causes (déf. organis. etc.)		7,4%	16,7%

Afin de déterminer l'intensité des sollicitations psychiques, on a utilisé une batterie de preuves psychologiques. On va présenter 2 preuves classiques.

— Eysenck et Cattell, qui décèle l'apparition de la névrose d'accommodation et une preuve originale d'assumer le risque.

À l'aide du questionnaire Eysenck (9) on a suivi deux facteurs de la personnalité:

— L'introversion et l'extraversion E (aspect global de la personnalité);

— Le névrotisme (N) ou l'instabilité émotionnelle à qui s'oppose la stabilité émotionnelle;

Le questionnaire comprend aussi des reponses pour le facteur L (mensonge, pour le contrôle de la manière de repondre au questionnaire).

La figure 1 présente les résultats obtenus pour les 3 facteurs.

De la comparaison des trois facteurs il résulte: la courbe de distribution du facteur introversion-extraversion a une dispersion régulière et s'inscrit entre les valeurs 9—17, ayant la moyenne 12, tandis que le facteur névrotisme a une petite déviation à droite, et le facteur L présente une dispersion plus limitée, ce qui dénote la sincerité de la reponse.

La déviation à droite, c'est-à-dire, vers les valeurs plus grandes, constituée dans le cas du névrotisme, indique un névrotisme accentué.

La prédominance du type introverti par rapport à celui extraverti peut être considérée une conséquence du travail du mécanicien, qui, en raison de la nature de son activité, travaille presque tout seul.

En analysant le facteur N on constate l'existance des tendances névrotiques en pourcentage de 7,28, à différences assez grandes entre les dépôts: de 2% à 15%.

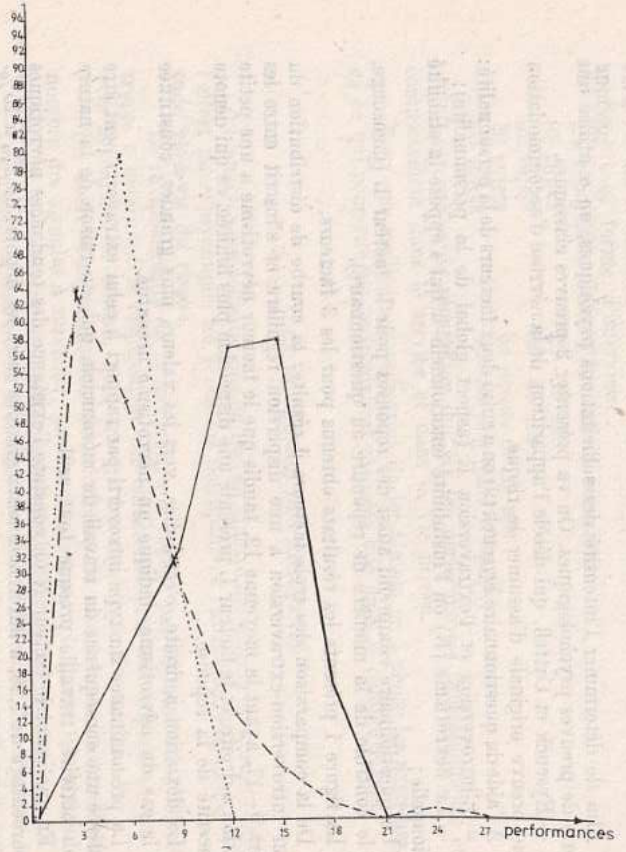

Fig. 1. — La courbe de distribution des résultats à la preuve Eysenck pour tout le lot expérimental.
——— extraversion; — — — névrotisme; ..... facteur L.

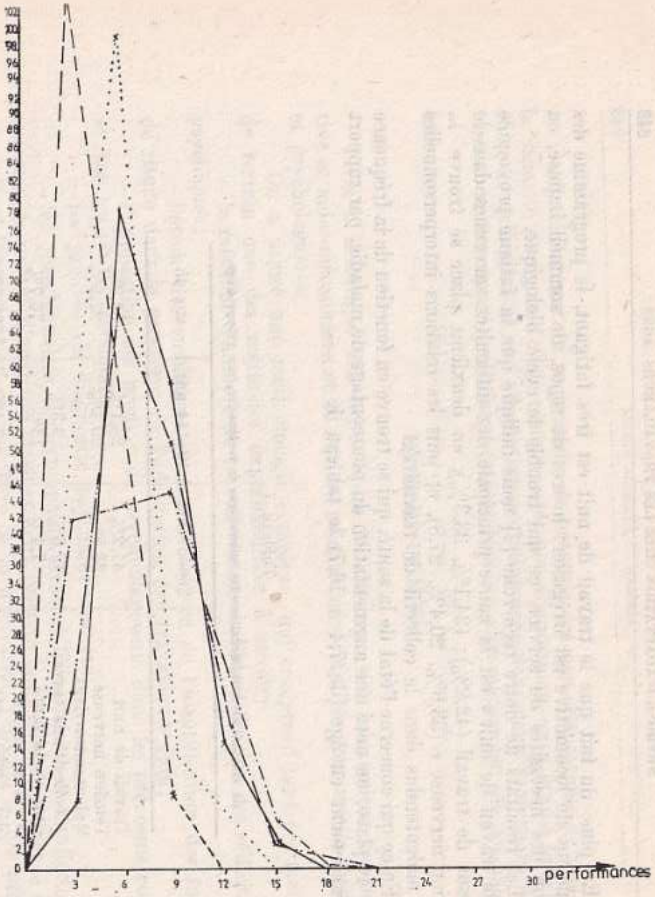

Fig. 2. — La courbe de distribution des résultats à la preuve Cattell pour tout le lot expérimental.

La constatation du névrotisme de différents degrés, aux dépôt investigués, est expliquée par la variation des sollicitations psychiques dans le processus du travail et par certaines conditions spéciales.

On a constaté l'absence des réponses névrotiques dans le groupe de bons mécaniciens et leur présence dans le groupe des mécaniciens médiocres.

Pour le facteur E-I il n'y a pas de différences de rendement entre introverti et ambiverti, et le type extraverti présente une fréquence très basse.

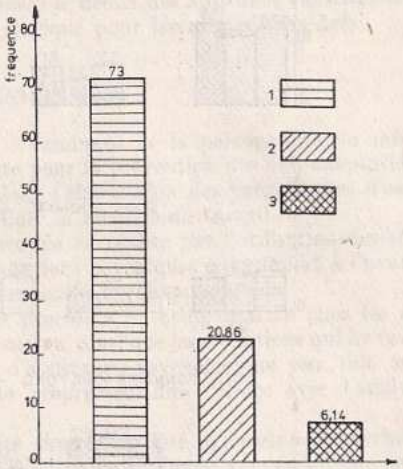

Fig. 3. — Attitude vis-à-vis du risque.
1, type prudent; 2, type intermédiaire; 3, type à inclinaison vers des situations de risque.

À l'aide du questionnaire de R. B. Cattell [11] on a analysé cinq facteurs:

Q_3 = la conscience de soi;
C = la force du moi (capacité de se contrôler);
L = la sécurité sociale
O = culpabilité
Q_4 = la tension ergique (tendances asociales).

La figure 3 présente les résultats obtenus pour les cinq facteurs.

En analysant du point de vue statistique le facteur d'anxiété selon Cattell on constate l'existence de l'anxiété dans un taux de 7,97%.

Le facteur de risque trouvé en proportion de 7,97 sur l'entier lot expérimental est rapproché des résultats du questionnaire Eysenck (un taux de 7,28%).

La preuve de l'attitude vis-à-vis du le risque montre le taux le plus élevé, 73% de sujets, à tendance abaissée d'assumer le risque.

Des tendances accentuées de penchant vers des situations dangereuses sont présentes dans un pourcentage de 6,14% des cas (Figure 3).

La fréquence des résultats indiquant l'instabilité émotive ou les attitudes d'imprudence quoique diminuée (7,28% à la preuve Eysenck 7,97% à la preuve Cattell et 6,14% à la preuve d'assumer le risque) est très importante pour la sûreté de la circulation ferroviaire, par conséquent on a effectué une analyse intensive des cas.

Il a resulté leur prédominance, chez les jeunes et les âgés, aux dépôts de triage et chez ceux qui sont dévenus mécaniciens après l'âge de 35 ans.

On a effectué l'analyse comparative par étapes d'âges des résultats des preuves de psychodiagnostic afin de révéler les modifications provoquées par l'avancement en âge.

La figure 4 présente les moyennes des résultats des preuves de personnalité par groupe d'âge.

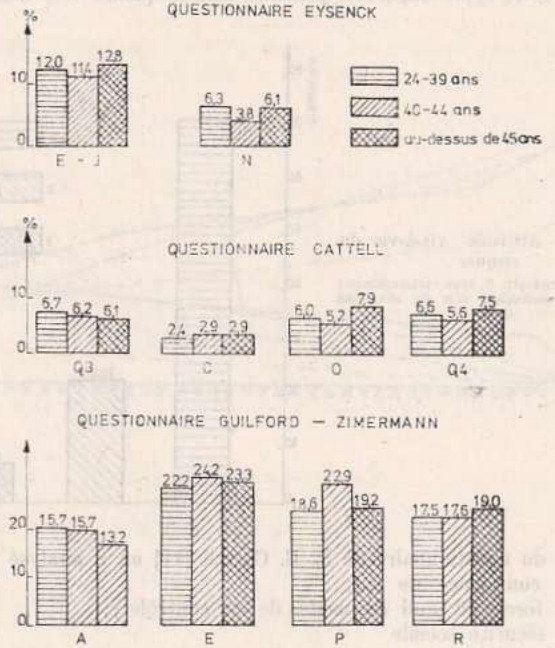

Fig. 4. — Moyennes des résultats aux preuves de personnalité par groupe d'âge.

Aux preuves Eysenck, Cattell et Guilford [12] les modifications sont significatives aux suivants indicateurs:

— Le névrotisme montre la baisse la plus importante dans la période d'âge 40—44 ans (3,8), les indicateurs O (culpabilité) et Q_4 (tension ergique augmente après 45 ans (7,9; 7,5), l'activisme (A) baisse au fur et à mesure de l'avancement en âge (de 15,7 à 13,2) et l'autocontrôle (R) augmente (de 17,5 à 18).

La stabilité émotive (E) et l'intégration sociale (P) ont les meilleures valeurs de 40 à 44 ans (24,2 et 22,3).

À la suite de l'évaluation des modifications par rapport à l'âge de divers traits de personnalité on a constaté:

— pour la majorité des indicateurs le groupe d'âge 40—44 ans présente les aspects les plus favorables.

— après l'âge de 45 ans, surviennent des modifications, certaines à aspects positifs. À savoir, en plus de certains aspects négatifs comme l'accroissement des

tendances dépressives, du sentiment de culpabilité et de la tension ergique, la baisse de l'activisme général et le ralentissement du rythme de l'exécution des mouvements, on constate aussi l'augmentation de l'introversion et la baisse de l'extraversion, de même que l'augmentation de la capacité d'autocontrôle et du contrôle de soi-même, l'augmentation de la coopération de l'intégration sociale et de la prudence.

Conformément à ces résultats il est possible l'utilisation des stratégies compensatoires, afin que le mécanicien âgé puisse s'adapter au processus de travail.

La connaissance des aspects positifs, déterminés par l'avancement en âge ainsi que la façon de pouvoir compenser le déclin des aptitudes constituent la base d'un programme d'assistance psychologique pour les mécaniciens âgés.

CONCLUSIONS

La connaissance des aspects dynamiques de la personnalité du mécanicien de locomotive âgé est très importante pour la prévention des non-adaptations dans le processus du travail, aussi que dans l'élaboration des programmes d'assistance psychologique dans le but de consolider la sécurité du travail.

L'assistance psychologique accordée se réalise par l'utilisation des stratégies de compensation de certaines détériorations psychiques par rapport à l'avancement en âge, en vue du maintien d'une capacité psychique globale.

Voire établie l'importance des processus de compensation chez les âgés, on doit analyser aussi les limites de leur action, ainsi que les conditions qui les favorisent.

Le déroulement de l'activité d'assistance psychologique sera fait selon ses principes directeurs, mais l'activité proprement-dite débute avec l'analyse profonde de chaque cas.

L'obtention de bons résultats dans l'activité d'assistance psychologique, s'appuie sur la détermination d'une relation de confiance sympathétique entre psychologue et sujet, ainsi que le sujet puisse exprimer ses sentiments et pensées et puisse extérioriser le comportement sans craindre les conséquences.

Ce cadre de protection dont a besoin l'examiné constitue « le premier pas » dans l'activité d'assistance psychologique.

Pour la prévention ou la découverte dans la phase initiale des phénomènes de vieillissement précoce, de même que les maladies chroniques qui peuvent accélérer le rythme normal de vieillissement il est nécessaire d'organiser et d'appliquer un système de gérontoprophylaxie pour les mécaniciens âgés.

L'application de la thérapie à substances biotrophiques est en cours d'expérimentation, à deux dépôts, méthode en cours de généralisation dans tout le pays.

L'effet « stimulateur » de la thérapie à substances biotrophiques va créer le cadre favorable pour l'activité d'assistance psychologique.

Summary. Many studies concerning different behavioural traits demonstrated the possibility of maintaining a certain psychic capacity, even if different subsystems considered to be isolated displayed deteriorations. The problems referring to psychic adaptation to the aging process pointed out the role played by compensation processes in maintaining a "functional optimum" state.

Starting from these data we tried to explain the action mechanisms underlining compensation processes at a psychologic level and define more accurately the favouring conditions in railway transport.

BIBLIOGRAPHIE

1. Şerban G., *Psychopathology of human adaptation*. 1976, New York, London, Plenum Press, 1976.
2. Treaton J.R., *The concept of adjustment in old age*, Williams, R.H. Tibbits, C. And Donahue Wilma (Eds).: Processes of aging, vol. I, New York, Atherton Press, 1963.
3. Kuhlen R.G., *Aging and life-adjustement*, Birren J.E.: *Hansbook of aging and the Individual*, Chicago Press, 1973.
4. Chown, Shella and Herron A., *Psychological aspects of aging in men*, Annual Review of Psychology, 1965, p. 16.
5. Welford A.T., *Vieillissement et aptitudes humaines*, P.U.F., Paris, 1964.
6. Mamali Maria, *Psycho-social aspects of aging*, Revue roumaine des sciences sociales — série de psychologie, 2, 1970, p. 181—192.
7. Mamali M. et Mamali C., *L'influence du travail sur les modifications de la personnalité des mécaniciens de locomotive, en même temps avec l'avancement en âge*. La revue des transports et télécommunications, *6*, 1979, p. 325—330.
8. Mamali M. et Mamali C., *Le rôle des facteurs de personnalité et d'attitude dans l'activité de conduite du mécanicien de locomotive*. Revue de Psychologie, *3*, 1980.
9. Eysenck H.J., Eynseck S.B.G., *Manual of the Eysenck Personality Inventory*, London, Univ. of London Press, 1964.
10. Ganansia K., *Résultats de quelques études sur l'adaptation française*, Eysenck H.J., Eysenck S.B.G., *Manuel — Inventaire de personnalité d'Eysenck*, Paris, Ed. du Centre de Psychol. Appl. 1971.
11. Cattell R.B., *La personnalité*, P.U.F., Paris, 1956.
12. Guilford J.P., *Personality*, Mc Graw-Hill, New York, 1959.

ROMANIAN J. GERONT. GERIATRICS, 1980, 1, 2, p. 249–258

LES PERFORMANCES PSYCHOLOGIQUES CHEZ LES NEURASTHÉNIQUES PENDANT LA PÉRIODE D'INVOLUTION

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Résumé. On présente les résultats de quelques investigations psychologiques (détermination du temps de réaction, l'investigation de l'attention, de la mémoire, de l'efficience opérationnelle de la pensée) effectuées sur un lot de malades neurasthéniques d'âge involutif (46–60 ans), comparé à un autre lot de malades plus jeunes (36–45 ans) ayant le même diagnostic.

L'intervalle de vie entre 46 et 60 ans (ou entre 46 et 65 ans) est appelé aujourd'hui « l'âge moyen », correspondant à de dénominations antérieures telles que, par exemple, « période d'involution » (ou l'âge involutif), période du climacterium (ou période de la ménopause), période présénile ou l'âge de la présénescence [1]. Cette dénomination fut lancée en 1963 au Séminaire de Kiev, lorsque « le troisième âge » fut divisé en trois périodes: l'âge moyen ou de transition (46–60 ans), la période âgée (61–75 ans) et la vieillesse (après 75 ans). L'âge moyen est une période marquée par de fréquentes situations critiques, par de multiples responsabilités sociales (le soin et l'éducation des enfants aussi bien que des petits-enfants – c'est à cet âge que nous devenons des grands-parents –; le soin accordé aux vieillards, etc.) et par de nombreux traumatismes psychiques provoqués par les manifestations de la ménopause, par l'apparition de certaines maladies chroniques (72% de ceux entre 45–64 ans en ont une ou deux), par le départ des enfants qui fondent leurs propres familles ou par une série de psychotraumatismes familiaux, tels que la séparation des partenaires (divorce), la mort du partenaire (veuvage), mésententes survenues entre les partenaires, la mort des parents, des proches parents ou des amis, etc. [2].

Ainsi que le souligne Butler (1976), jusqu'à présent l'âge moyen fut très peu abordé dans la littérature de spécialité (des 50 000 ouvrages de psychanalyse mentionnés dans l'index de Grinstein seulement quatre se rapportent à l'âge moyen) [3].

Dans cet ouvrage nous nous sommes proposé de mettre en évidence une série d'aspects de l'exactitude et de la rapidité, obtenus par plusieurs tests et épreuves sur un groupe de malades neurasthéniques d'âge moyen.

MATÉRIEL ET MÉTHODE

Un lot de 30 malades avec le diagnostic de neurasthénie, âgées de 46 à 60 ans (lot I) fut examiné au point de vue psychologique dans le Laboratoire de psychologie de l'Hôpital Gh. Marinescu et comparé à un autre, composé de 15 malades neurasthéniques, âgées de 36 à 45 ans. Pour les deux lots furent sélectionnées seulement des personnes ayant des études supérieures (lycée ou faculté) et l'examen psychologique se déploya selon le programme suivant: la détermination du temps de réaction (avec ou sans annonce préalable) pour obtenir des informations concernant le niveau de la réactivité basale psychomotrice, la dynamique de cette réactivité et le comportement du sujet impliqué dans la relation stimulant-réaction; l'investigation de la capacité de concentration de l'attention par l'épreuve de barrage Bourdon—Anfimov; l'investigation de la mobilité de l'attention à l'aide de l'épreuve Herwig (en deux étapes) et de l'épreuve de la recherche des chiffres 1—36 (l'épreuve de Poppelreuter en deux variantes); la recherche de la capacité de mémorisation et de reproduction de certains stimulants verbaux (par l'épreuve Rey des 15 mots) et de certains stimulants non verbaux (par l'épreuve Kim des 20 objets); l'investigation de la capacité de mémorisation et de reconnaissance spatiale (l'épreuve de la reconnaissance des stimulants géométriques 1—4); l'épreuve de vocabulaire Rey; l'investigation de l'efficience opérationnelle de la pensée par deux épreuves non verbales (test d'encastrement et test des cubes de Kohs) et 6 épreuves verbales: l'épreuve des ressemblances (Lahy, Piret), l'épreuve de l'exclusion (Lahy, Piret, Zeigarnic, Rubinstein), la classification des notions (Rubinstein), l'épreuve des analogies (Weisenburg Mc Bride), l'épreuve de l'abstraction (Shipley), l'épreuve des contes absurdes.

Les résultats obtenus par ces épreuves ont été exprimés par des indices ou des coefficients d'exactitude ou/et de rapidité qui furent calculés en rapportant les performances des sujets investigués à celles réalisées par les témoins (ayant également des études supérieures) du Laboratoire de psychologie médicale de l'Hôpital Gh. Marinescu . Les performances moyennes des témoins (ayant des études supérieures) pour les différentes épreuves ont été les suivantes: le temps de réaction 145 millisecondes pour la variante avec annonce préalable et 190 millisecondes pour la variante sans annonce préalable; le nombre moyen de signes parcourus par les témoins pour l'épreuve Bourdon—Anfimov: 2474; la note d'exactitude pour l'épreuve Herwig 8 pour la première variante et 6,6 pour la seconde; la moyenne arithmétique du temps des rangements pour l'épreuve Poppelreuter 3,46 secondes lors de la première variante (dirigée) et 3,57 secondes lors de la seconde (indépendante); le nombre des mots mémorisés lors des cinq présentations à l'épreuve Rey: 8,11, 13,13 et 14; à l'épreuve de Kim: 15 objets retenus à la première présentation et 18 objets à la cinquième; à l'épreuve de reconnaissance des stimulants géométriques: 28 des 30 groupes de modèles présentés; l'épreuve de vocabulaire Rey: 2 secondes la moyenne du temps et 110 le pointage moyen; le test d'encastrement: le temps 5 minutes; le pointage obtenu 40; l'épreuve des cubes de Kohs: le temps 8 minutes et 7 secondes tandis que l'exactitude 90%; l'épreuve des ressemblances: le temps 12 minutes, l'exactitude 80%; l'épreuve de l'exclusion: le temps 10 minutes, l'exactitude 90%; l'épreuve des analogies: le temps 10 minutes, l'exactitude 100%; l'épreuve de l'abstraction: le temps 20 minutes, le pointage obtenu 18, etc.

Le calcul des indices d'exactitude et de rapidité fut effectué selon les exemples suivants:

$$\text{Indice d'exactitude pour l'épreuve Herwig} = \frac{\text{Note du sujet} \times 100}{8 \text{ (c'est-à-dire note des témoins)}}$$

$$\text{Indice de rapidité pour le test d'encastrement} = \frac{\text{Temps des témoins (5')} \times 100}{\text{Temps du sujet}}$$

RÉSULTATS

a. Le temps de réaction. La mesure du temps de réaction (expression utilisée pour désigner l'intervalle de temps qui sépare une stimulation d'une réaction volontaire [4]) a été considérée dans le cadre de notre ouvrage comme une information sur la réactivité basale psychomotrice (la capacité du sujet de percevoir rapidement un stimulant auditif, de synchroniser en temps utile la réaction avec le stimulant et d'agir, aussi bien dirigé qu'indépendant, le degré de rythmicité de la réaction). Nous avons appliqué deux variantes, la première avec annonce, la seconde sans annonce préalable, en notant 25 réactions et en calculant ensuite la moyenne pour les 20 dernières réactions.

Ainsi que l'on peut voir dans les tableaux 1 et 2, le temps de réaction chez les malades neurasthéniques est plus long par rapport aux témoins, cette croissance étant de beaucoup plus grande chez les malades du lot I (des neurasthéniques

Tableau 1

Les valeurs du temps de réaction avec et sans annonce préalable

Temps de réaction	Avec annonce préalable				Sans annonce préalable			
	Lot I		Lot II		Lot I		Lot II	
	nº	%	nº	%	nº	%	nº	%
145–200 ms	3	10	5	33,3	—	—	—	—
200–250 ms	10	33,3	8	53,3	12	40	7	46,6
251–300 ms	10	33,3	1	6,6	7	23,3	6	40
Plus de 300	7	23,3	1	6,6	11	36,6	2	13,3
Total	30	100	15	100	30	100	15	100

âgées de 46 à 60 ans) que chez celles du lot II (des neurasthéniques entre 36 et 45 ans). Par exemple, le temps de réaction avec annonce préalable a marqué des valeurs de plus de 250 millisecondes en 56,6% des cas du lot I et seulement en 13,2% des cas du lot II (différence significative: $p < 0,01$); chez les neurasthéniques de la période d'involution, le temps de réaction a des valeurs au dessous de 0,60 par rapport aux témoins (l'indice de référence étant 1), en 66,6% des cas tandis que chez les neurasthéniques plus jeunes (lot II) le déficit au-dessous de 0,60 fut rémarqué seulement chez 26,66% des cas (différence significative: $p < 0,01$).

Tableau 2

Résultats du temps de réaction (des indices obtenus en rapportant les données à celles de témoins)

Coefficient	Avec annonce préalable				Sans annonce préalable			
	Lot I		Lot II		Lot I		Lot II	
	nº	%	nº	%	nº	%	nº	%
Jusqu'à 0,40	3	10	—	—	2	6,66	—	—
0,41—0,60	17	56,66	4	26,66	4	13,33	—	—
0,61—0,75	8	26,66	8	53,33	14	46,66	6	40
Plus de 0,75	2	6,66	3	20	10	33,33	9	60

Les courbes de réaction (de travail) ont été, en général, disrythmiques mais la disrythmie fut plus marquée chez les malades d'un âge plus avancé.

b. La capacité de concentration de l'attention fut explorée à l'aide de l'épreuve de barrage Bourdon—Anfimov. Chez le lot I le nombre des signes graphiques (lettres) parcourus a varié d'un cas à l'autre, de 760 à 2840 (en moyenne 1754 par rapport à 2474 le nombre moyen parcouru par les témoins) tandis que le nombre des omissions de 0 à 185 (la moyenne = 26). Le déficit de concentration de l'attention chez les malades du lot I comparé à celles du lot II est présenté dans le tableau nº 3: chez les deux lots on rencontre un déficit évident tant en ce qui concerne l'exactitude qu'en ce qui concerne la rapidité. Sans qu'il y ait des différences nettement significatives, le déficit de rapidité est plus grand pour le lot I que pour le lot II.

Tableau 3

Rapport exactitude-rapidité à l'épreuve de barrage Bourdon-Anfimov

Coefficient	Rapidité				Exactitude			
	Lot I		Lot II		Lot I		Lot II	
	nº	%	nº	%	nº	%	nº	%
Jusqu'à 0,50	1	3,33	—	—	14	46,6	10	66,66
0,51—0,70	15	50	5	33	8	27,7	3	20
Plus de 0,70	14	46,66	10	67	8	27,7	2	13,33

c. L'efficience de la mobilité de l'attention fut investiguée par l'épreuve Herwig (2 étapes) et l'épreuve Poppelreuter. Les résultats obtenus par l'épreuve Herwig furent normaux ou légèrement déficitaires pour les deux lots, mais quant à l'épreuve Poppelreuter on remarqua une baisse légère des performances par rapport aux témoins, aussi bien pour le lot I (coefficient au-dessous de 0,60 pour 53,3%) que pour le lot II (des résultats au-dessous de 0,60 pour 33,3% des cas) (Tableaux 4, 5).

Tableau 4

Résultats obtenus par l'épreuve Herwig

Coefficient	Etape initiale (I)				Seconde étape			
	Lot I		Lot II		Lot I		Lot II	
	nº	%	nº	%	nº	%	nº	%
Jusqu'à 0,50	3	10	2	16,66	—	—	—	—
0,51—0,70	7	23,3	4	26,66	2	6,66	3	20
Plus de 0,70	20	66,6	9	60	28	93,33	12	80

Tableau 5

Résultats obtenus par l'épreuve Poppelreuter

Coefficient	Première variante				Seconde variante			
	Lot I		Lot II		Lot I		Lot II	
	nº	%	nº	%	nº	%	nº	%
Jusqu'à 0,40	3	10	1	6,6	1	3,3	—	—
0,41—0,60	13	43,3	4	26,6	12	40,0	7	46,6
0,61—0,75	9	30	9	60,0	9	30,0	6	40,0
Plus de 0,75	5	16,6	1	6,6	8	26,6	2	13,3

d. L'investigation de la capacité de mémorisation et de reproduction. Les différents aspects de la mémoire ont été investigués à l'aide des quatre épreuves: l'épreuve Rey (15 mots, c'est-à-dire des stimulants verbaux), l'épreuve Kim (20 objets, c'est-à-dire les stimulants non verbaux), l'épreuve de la reconstruction et l'épreuve de la reconnaissance des stimulants géométriques. Par l'épreuve Rey on a poursuivi la dynamique de la mémorisation des stimulants verbaux, en effectuant 5 présentations successives et une autre après deux heures, aussi bien qu'une épreuve de reconnaissance. Les résultats sont présentés dans le tableau nº 6, d'où

Tableau 6

Résultats obtenus à l'épreuve Rey (15 mots)

Coefficient	Première présentation				5e présentation				Après 2 heures			
	Lot I		Lot II		Lot I		Lot II		Lot I		Lot II	
	nº	%	nº	%	nº	%	nº	%	nº	%	nº	%
0,75—1	4	13,3	3	20	12	40	3	20	6	20	1	6,6
0,61—0,74	10	33,3	7	47	9	30	12	80	12	40	4	27,0
0,41—0,60	15	50,0	5	33	9	30	—	—	8	27	6	40
Moins de 0,40	1	3,3	—	—	—	—	—	—	4	13,3	4	26

on remarque que le déficit est plus accentué à la première présentation et que jusqu'à la cinquième présentation les malades du lot II ont de beaucoup amélioré leurs performances, amélioration qui a lieu aussi chez les malades du lot I mais dans une mesure plus réduite.

Pour l'épreuve Kim (au lieu des mots on fait 5 présentations de 20 objets) les résultats obtenus des deux lots sont très rapprochés de ceux des témoins: au lot I le coefficient d'exactitude 0,80 à la première présentation et 0,91 à la cinquième présentation, tandis qu'au lot II 0,80 et respectivement 0,90; à cette épreuve on n'a rencontré aucun cas déficitaire au-dessous de 0,60 (tableau 7).

Tableau 7

Résultats obtenus à l'épreuve Kim

Coefficient	Première présentation				5e présentation			
	Lot I		Lot II		Lot I		Lot II	
	nº	%	nº	%	nº	%	nº	%
0,75—1	17	56,66	13	86,66	28	93,33	15	100
0,61—0,74	13	43,33	2	13,33	2	6,66	—	—
0,41—0,60	—	—	—	—	—	—	—	—
Moins de 0,41	—	—	—	—	—	—	—	—

En ce qui concerne l'épreuve de reconstruction (épreuve de mémorisation et de reproduction spatiale), les résultats ont été très variables d'un cas à l'autre. Le coefficient moyen du lot I fut de 0,46 et celui du lot II de 0,60, donc une baisse importante des performances, mais certains malades ont obtenu des résultats qui ont dépassé même la moyenne des témoins (tableau 8).

Tableau 8

Résultats à l'épreuve de reconstruction

Coefficient	Lot I		Lot II	
	nº	%	nº	%
Plus de 1	3	10	2	13,33
0,75—1	3	10	1	6,66
0,61—0,74	7	23,33	5	33,33
0,41—0,60	—	—	—	—
Moins de 0,41	17	56,66	7	46,66

Les résultats obtenus à l'épreuve de la reconnaissance des stimulants géométriques (on présente au sujet pendant 3 secondes un petit carton avec un modèle; ensuite on ajoute trois autres modèles, en notant le temps mis à recon-

naître le modèle présenté la première fois, ainsi que l'exactitude par + ou —) sont présentés dans le tableau nº 9.

Tableau 9

Les résultats à l'épreuve de reconnaissance des stimulants géométriques

Coefficient	Lot I		Lot II	
	nº	%	nº	%
0,76—1	10	33,33	1	6,66
0,61—0,75	2	6,66	6	40,0
0,41—0,60	17	56,66	7	46,66
Moins de 0,41	1	3,33	1	6,6

c. Épreuves d'efficience opérationnelle de la pensée. Aux épreuves non verbales (l'épreuve des cubes Kohs et le test d'encastrement) l'exactitude des malades des deux lots a été très rapprochée par rapport aux témoins mais on a remarqué un déficit en ce qui concerne la rapidité. Aux épreuves verbales le déficit est apparu plus évident par rapport à l'exactitude, sans qu'il y ait des différences significatives entre les deux lots (tableau 10).

DISCUSSIONS

Les sujets soumis aux différentes épreuves obtiennent certains résultats dénommés performances. La notion de performance est une entité ayant plusieurs dimensions [4], impliquant les paramètres suivants: orientation dans une situation (la compréhension de la tâche), l'organisation de l'action, l'indépendance de la solution, « l'économie » de la démarche opérationnelle, l'exactitude de la performance, la rapidité de performance, le contrôle émotionnel, la coopération et la participation affective. Le comportement d'un sujet normal est caractérisé par une compréhension rapide de la tâche, par le caractère organisé de l'action, la solution des problèmes sans solliciter aucune aide, l'utilisation de certains procédés (avec une consommation énergétique réduite non pas par des essais et des erreurs), le caractère rythmique de la performance, l'intérêt naturel en face du caractère inédit de la situation d'examen et en face de ses propres résultats, l'équilibre émotionnel [5].

Les neurasthéniques — aussi bien les jeunes que ceux plus âgés — présentent d'habitude, lors de la confrontation avec les différents tests, un comportement typique: commentaires concernant la difficulté et la longueur du test, exclamations, complaintes provoquées par la fatigue, états d'anxiété avec des tremblements, frottement des yeux ou des mains, pleurs, interruptions, abandon, demande d'aide pour résoudre le problème, sollicitation de répéter l'instruction, des manifestations de soulagement à la fin de l'épreuve, etc. (c'est-à-dire qu'en général les neurasthéniques sont caractérisés par la discontinuité dans le travail et par la diminution du contrôle émotionnel).

Chaque acte d'efficience intellectuelle implique deux paramètres se trouvant en interaction dialectique, conditionnés réciproquement, mais qui peuvent

Tableau 10

La moyenne des coefficients de rapidité et d'exactitude aux épreuves d'investigation de la réactivité basale, de l'attention, de la mémoire et de la capacité opérationnelle de la pensée

Epreuve	Lot I		Lot II	
	Exactitude	Rapidité	Exactitude	Rapidité
Temps de réaction avec annonce	—	0,55	—	0,67
Temps de réaction sans annonce	—	0,73	—	0,78
Bourdon-Anfimov	0,56	0,70	0,43	0,76
Herwig I	0,85	—	0,72	—
Herwig II	1,01	—	0,99	—
Poppelreuter I	0,58	—	0,61	—
Poppelreuter II	0,67	—	0,64	—
Rey-première présentation	0,61	—	0,66	—
Rey-cinquième présentation	0,73	—	0,81	—
Rey-deux heures après	0,62	—	0,53	—
Rey-reconnaissance	0,82	—	0,82	—
Kim — première présentation	0,80	—	0,80	—
Kim — cinquième présentation	0,90	—	0,92	—
Reconstruction	0,46	—	0,60	—
Reconnaissance des stimulants géométriques	0,64	—	0,56	—
Cubes Kohs	0,89	0,41	0,71	0,45
Encastrement	0,80	0,48	0,85	0,48
Classifications des notions	0,64	0,86	0,51	0,76
Analogies	0,63	0,69	0,65	0,76
Exclusion	0,64	0,83	0,57	0,95
Ressemblance	0,45	1,05	0,52	1,0
Contes absurdes	0,79	0,82	0,80	0,85
Abstractions	0,49	1,11	0,35	1,16

préssenter aussi des particularités individuelles: l'exactitude de l'épreuve effectuée et le temps (la rapidité) mis à effectuer l'épreuve. Au sujet de l'interaction entre les deux facteurs on peut décrire les situations suivantes: exactitude réduite et rapidité réduite d'où il résulte un échec global; rapidité accrue et exactitude réduite, impliquant la difficulté de concentration, le manque de stabilité dans l'analyse des données du problème; la rapidité réduite et l'exactitude adéquate, impliquant la difficulté d'organiser le matériel, une dépense d'énergie disproportionnée quant aux résultats; rapidité et exactitude normales impliquant une fonction psychique adéquate [5], [6], [7].

Chez les neurasténiques caractérisés par une discontinuité du travail, par un intérêt différent manifesté pour une épreuve ou l'autre, on rencontre des rapports divers entre l'exactitude et la rapidité. Par exemple, chez les neurasthéniques du lot I (d'âge moyen) à l'épreuve Bourdon—Anfimov, l'exactitude de même que la rapidité ont été réduites, déficitaires; à l'épreuve des cubes de Kohs et au test d'encastrement la rapidité a été réduite (0,41 respectivement 0,48), mais l'exactitude a été peu modifiée (0,89 et 0,80); à l'épreuve d'abstraction (Shipley) la rapidité a été accrue (1,11) tandis que l'exactitude bien réduite (0,49), etc. Butler mentionne que, pendant la période de l'âge moyen, le vocabulaire, les connaissances, l'information continuent à croître, l'âge affectant seulement la vitesse, la rapidité de l'exécution des épreuves (c'est-à-dire que, chez les sujets ayant une santé relativement bonne, les performances demeurent élevées si le temps accordé est suffisant). De même, Babcock (cité après Eysenck) soutenait que les névrotiques ne sont pas déficitaires en ce qui concerne leurs aptitudes principales mesurées par des tests qui ne limitent pas le temps, mais dans l'efficience, dans la faculté d'utiliser ces aptitudes, c'est-à-dire en déficit aux tests de rapidité qui limitent le temps. Eysenck n'a pas confirmé ces constatations, observant que lorsqu'une tâche dépend surtout de l'intelligence, la rapidité est en relation directe avec l'exactitude, tandis que lorsqu'une tâche est peu dépendante de l'intelligence (des tâches normales), la rapidité et la précision sont en relation inverse [8].

CONCLUSIONS

1. Le lot de neurasthéniques d'âge moyen (ou l'âge involutif) présente d'habitude, en comparaison des témoins, une baisse des performances, aussi bien en ce qui concerne la rapidité que l'exactitude, des baisses qui n'arrivent toutefois pas à de déteriorisations graves, le déficit ayant un caractère fonctionnel.

2. Chez les malades des deux lots, dans l'interaction exactitude — rapidité on a observé les situations différentes suivantes: une baisse de rapidité aussi bien que d'exactitude (par exemple, à l'épreuve Bourdon—Anfimov); rapidité réduite et exactitude peu modifiée (à l'épreuve des cubes de Kohs et au test d'encastrement); rapidité accrue et exactitude de beaucoup réduite (à l'épreuve d'abstraction Shipley), etc. Entre le lot I (neurasthéniques âgées de 46 à 60 ans) et le lot II (36 à 45 ans) on n'a pas rencontré de différences nettement significatives.

Summary. The paper presents the results of some psychological investigations (reaction time, attention, memory, operational efficacy of thinking ability) conducted on a group of neurasthenic patients aged 46—60, compared to a group of younger patients (35—45 years) with the same diagnosis.

BIBLIOGRAPHIE

1. Postelnicu, D., Chira, Al., Săhleanu, V., *Introduction à la Gérontologie*. Ed. Academiei, Bucarest, 1969 (en roumain).
2. Nica-Udangiu, St., *Aspects cliniques-catamnestiques en neurasthénie et les états neurasthéniformes à l'âge avancé*. Thèse. Bucarest, 1978 (en roumain).
3. Butler, R., *Psychiatry and Psychology of the Middle Age*, in "Comprehensive textbook of psychiatry" (Freedman, A., Kaplan, H., Sadock, E. ed.), Williams and Wilkins Comp., Baltimore, second edition, 1976.
4. Pieron, H., *Vocabulaire de la psychologie*. Presses Univ. de France, Paris, 1968.
5. Alexandru, S., *Laboratoire de psychologie clinique*. Ed. ştiinţifică şi enciclopedică, Bucarest, 1975 (en roumain).
6. Gavini, Hélène, *Les temps de réaction simple chez les hommes et les femmes de 55 à 85 ans*. Colloque interne. « Le vieillissement des fonctions psychologiques et psychophysiologiques », Paris, 1960, Ed. du centre national de la recherche scientifique, 1961.
7. Weckowicz, T.E., Nutter, R., Cruise, D., Yonge, K., *Speed in test performance in relation to depressive illness and age*. Canad. Psychiat. Ass. J., 17, 1972, 241—249.
8. Eysenck, H.J., *Les dimensions de la personnalité*. Presses Univ. de France, Paris, 1950.

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NEUROMORPHOLOGICAL ASPECTS OF AGING THALAMUS

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Summary. The studies were conducted on human brains from 31 subjects aged 71 to 97 years, deceased at the National Institute of Gerontology and Geriatrics during the last 20 years and 2 control brains aged 40 and 57 years, supplied by the Institute of Legal Medicine, Bucharest.

The macroscopic and microscopic aspects pointed out age-induced changes in the thalamic nuclei.

Macroscopically, the decrement in volume of the thalamic nuclei was noticed, sometimes accompanied by capillary thrombosis.

Microscopically, vascular lesions were found, as thrombotic micro-softenings, underlined by abiotrophic neuronal degeneration which finally results in neuronal loss. The last lesions occur particularly in neothalamic structures, mostly in the cortex-dependent nuclei and Luys' median centre.

The morphological changes of the nervous system in the course of aging are qualitatively and quantitatively different depending on the neuraxial area taken into consideration.

As the ontogenetic evolution (the maturation of various subsystems) is differently achieved, senile involution is not synchronous in all compartments of the nervous system.

In a previous paper the authors studied some neuromorphological aspects of cerebellous aging; the major detectable phenomenon was neuronal loss involving Purkinje cells (the largest neurons) and granular cells (the smallest neurons of the nervous system).

The present paper aims at analysing certain aspects of the aging thalamus.

As known, the thalamus is made up of different structures (nuclei) which belong to various neurophysiological subsystems with more or less sofisticated organization and distinct phylogenetic oldness, which makes its study quite difficult.

Lately, thalamic degeneration has been attributed an important role in the onset of some psychic disturbances and the concept of "thalamic dementia" has been advanced. Hence, the importance of thalamic "aging" in generating senile psychic involution.

The present paper has a twofold interest: biological, involving the asynchronous aging of different cerebral structures, and medical, involving the understanding of the various aspects of neuropsychic involution.

MATERIAL AND METHOD

The investigated brain material originated from 31 subjects aged 71 to 97 years, deceased during the last 20 years because of acute cerebral diseases. The group included 23 women and 8 men: 5 belonged to the 8th decade, 18 to the 9th decade, 8 to the 10th decade.

No subject had overt neurological pattern and none had ever suffered of nervous diseases.

Two control brains were used for comparison (aged 40 and 57 years).

The brains were embedded in formol 10%. Subsequently, the brains were photographed, then cut in verticofrontal sections. The sections were also photographed.

The fragments with thalamus were embedded in celoidine, then serially cut in 20-micron blocks.

The sections were stained with toluidine blue (Nissl method); other parts were embedded in paraffin and cut in 5-micron sections. Some were stained according to Spielmeyer method, others impregnated according to Bielschowsky method.

The basic vessels were embedded in paraffin, then cut in 5-micron sections. Hematoxylin-eosin and van Gieson stainings were used.

MACROSCOPIC DATA

The first interesting element was the enlargement of the ventricular system, particularly the third ventricle in its medial and posterior thirds (Figs 1, 2).

The enlargement corresponded to the atrophy of the basic nuclei, especially in thalamic blocks. The phenomenon occurred systematically in all cases in the 9th decade and was obvious in subjects from the 10th decade.

The second characteristic aspect noticed in 80% of the cases in the 9th decade and in all those in the 10th decade was the presence of gaps at the level of thalamic nuclei (Figs 2—5). They occur almost exclusively in laminar nuclei, Arnold's area and dorsomedial nucleus. This distribution corresponds to the most fragile vascular areas of the thalamus. They represent the vascular micropathology in the distribution of the basilar artery and do not point out any abiotrophic process.

They may be correlated with the changes in the basic vessels, particularly basilar artery (in its upper third up to the junction) and the arterial system of Willis' circle (Figs 6—8).

With one exception (woman aged 90), all cases presented atheromatous plaques at the origin of the posterior cerebral arteries and communicating vessels. In 5 cases all the components of Willis' circle were involved (Fig. 7).

No significant change in size was noticed in the anterior thalamic half (Figs 5, 9); in general, as well as dorsomedial nuclei, the anterior ones did not change.

The diminution of the thalamic "mass" was noticed in the posterior sections involving the red nucleus and locus niger. Fig. 2 shows the decrement in size of the dorsolateral and posterior dorsal nuclei, as against posterior ventral, medial and lateral ones which did not change.

A significant decrease in size of the pulvinar was noticed on the posterior sections originating from subjects in the 9th and 10th decades.

Hence, the most involved nuclear formations were dorsolateral, posterior dorsal nuclei and pulvinars.

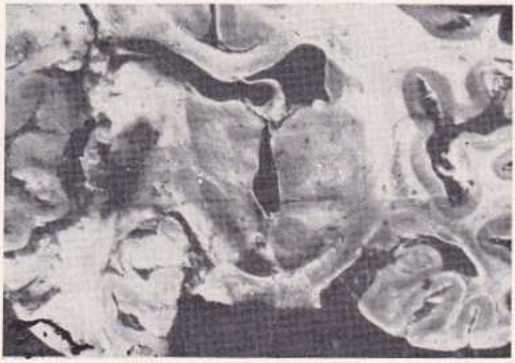

Fig. 1

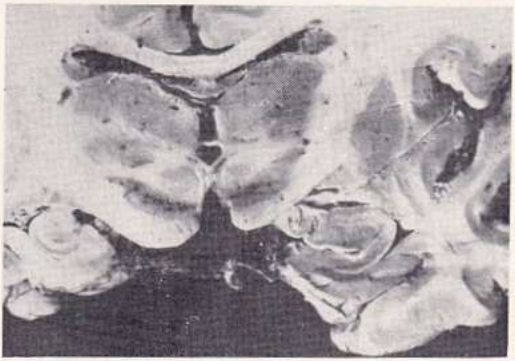

Fig. 2

Figs 1, 2. — Enlargement of the ventricular system particularly in the medial and posterior thirds.

Fig. 3. — Gaps in the laminar nuclei.

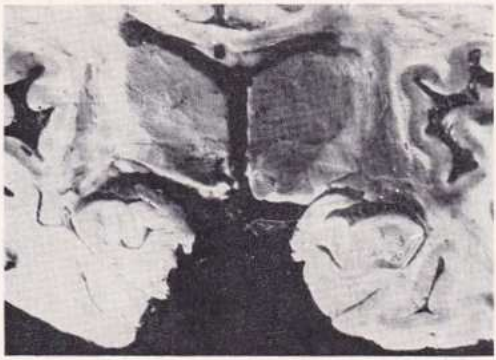

Fig. 4. — Gaps in the dorsomedial nucleus.

Fig. 5. — Gaps in the laminar nuclei and Arnold's area.

Fig. 6

Fig. 7

Fig. 8

Figs 6—8. — Atheromatous alterations as plaques at the origin of the posterior cerebral and posterior communicating arteries.

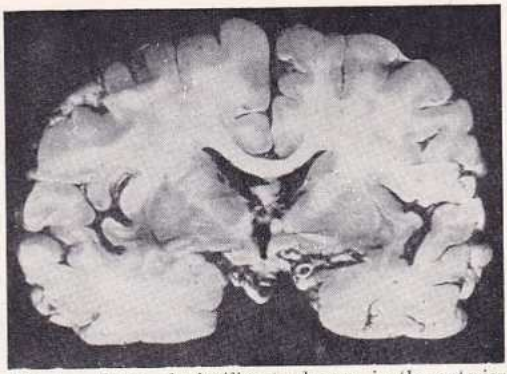

Fig. 9. — Lack of significant changes in the anterior half of the thalamus

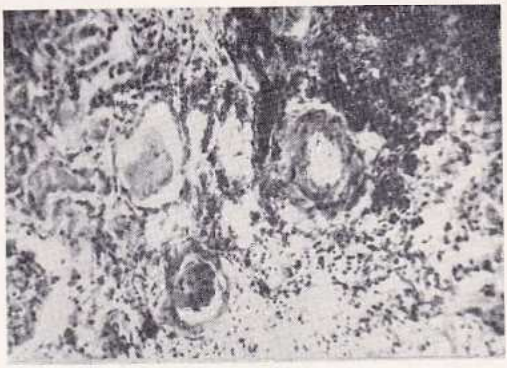

Fig. 10

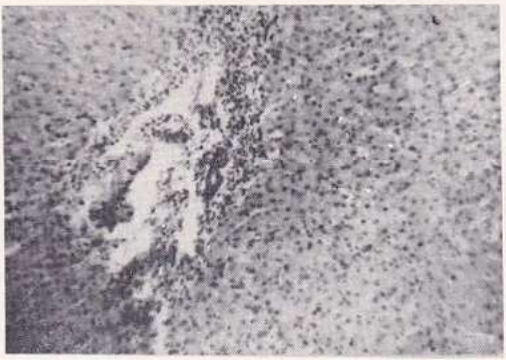

Fig. 11

Figs 10, 11. — Atheromatous lesions with perivascular necrotic areas, microthrombosis.

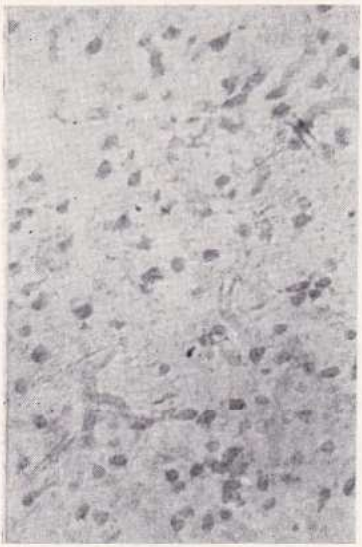

Fig. 12. — Thalamus — anterior nucleus — cell gaps. Nissl staining.

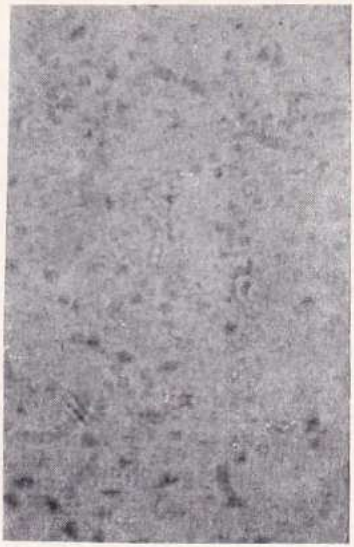

Fig. 13. — Thalamus — dorsolateral nucleus. Nissl staining.

Fig. 14. — Thalamus — centromedian nucleus. Nissl staining.

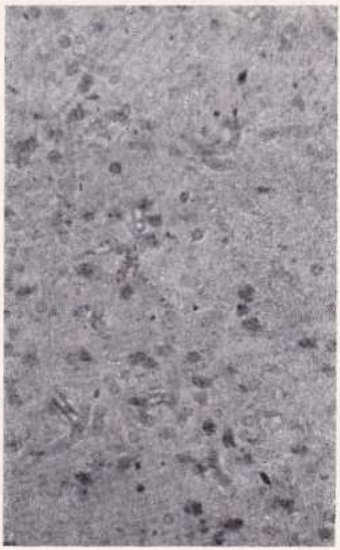

Fig. 15. — Thalamus — postero-ventral nucleus. Nissl staining.

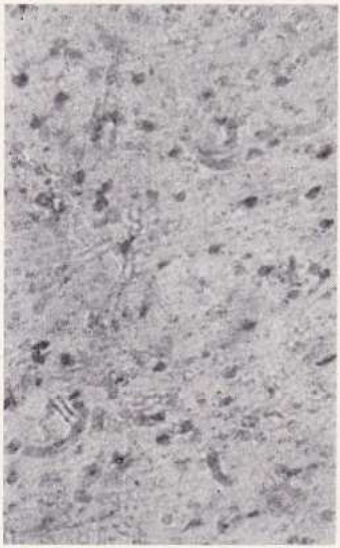

Fig. 16. — Thalamus — postero-ventral nucleus. Nissl staining.

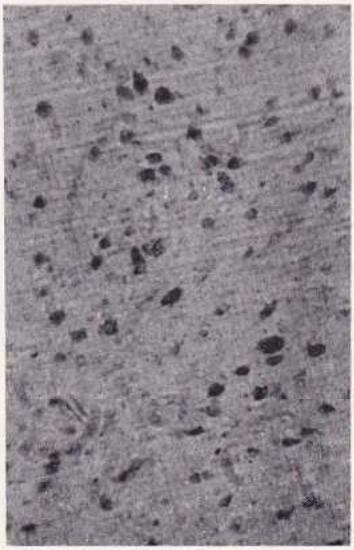

Fig. 17. — Thalamus — intralaminar nucleus, cell gaps. Nissl staining.

Fig. 18. — Thalamus — central nucleus, dispersed cells, thombotic vessel. Bielschowski staining.

MICROSCOPIC DATA

Microscopic gaps resulting from microthrombosis were frequently noticed in thalamic nuclei from 85% of the cases in the 8th decade and in all those in the 9th and 10th decades; typical atheromatous alterations and necrotic perivascular areas were also found.

They may be correlated with the significant alterations of the basilar arterial wall. Intimal and medial lipid deposits were noticed; the internal elastic lamina was disorganized (dystrophic), fragmented or replaced by collagen fibers (Figs 10–18).

Nissl-stained sections constantly displayed the characteristics of Spielmeyer's neuronal degeneration. Even the brain material originating from longevous persons (10th decade) displayed neurons with acute intumescence pointing out the still active amyotrophic process. The atrophic lesions with cell wrinkles and sclerosis were the most frequent and had the aspect of chronic cell disease described by Nissl. Lipid accumulations were found in numerous neurons. Lipo-pigmental inclusions (greenish-yellow) appeared clearly through the altered perikaryon with tigroid lysis processes and alveolus formation. Cell debris surrounded or not by neuronophagic nodular nevroglial accumulations were frequently noticed. Another characteristic consisted of the empty areas which, according to the cytoarchitectonic analysis corresponded to neuronal losses.

The above-mentioned lesions were not uniformly distributed through the thalamic nuclei.

The nuclei of the unspecific thalamic system (Foix and Niculescu's hyperchrome circular formation or Hassler's involucrum mediale), except Luys' median centre and the anterior thalamic nucleus, displayed few neuronal impairments.

Although these are fragile vascular areas, the senescent neuronal abiotrophic process was less marked than in the rest of the thalamus.

Neuronal lesions and loss were also found in dorsomedial and ventral nuclei; neuronal loss was also noticed to some extent in controls. They increased significantly from decade to decade.

The most important degenerative lesions (as relative number of neurons involved) were found in Luys' median centre, pulvinar, lateral nuclei and Arnold's area. Large areas with neuronal loss were noticed primarily in Luys' median centre.

COMMENT

The morphological impairments of the thalamus in the course of aging are the result of 2 simultaneous processes.

The first is a circulatory process. Microscopic and macroscopic vascular lesions are present, representing cerebral arteriosclerosis. In our patients none of the above-mentioned lesions was larger because the sample selecting method excluded overt neurological symptoms.

Such lesions are the result of cerebral circulatory failure, which affects neuronal aging through the biochemical changes induced.

According to the classical studies of Foix and Hilleman or Foix and Nicolescu, this process can be correlated with the structural and hemodynamic changes in the vertebro-basilar system.

The second process, abiotrophic, is the morphological expression of the nervous cell biochemical disorder resulting from the accumulation of metabolic errors in the course of aging.

Therefore, the aging process is achieved differently and the most fragile neurons belong to the cortex-dependent system. It is known that this system (the pulvinar and lateral thalamic nuclei) represents the most recent phylogenetic acquisition (C. V. Ariens Kappers). The anterior nuclei are excepted (less affected) as well as those integrated in the rhinencephalic system (Papez's circuit) and dorsomedial nuclei with important hypothalamic connections (C. Ajmone-Marsan).

In the case of lesions of the thalamic neurons of cortex-dependent nuclei, the degeneration of the nervous cell can be the transsynaptic reaction of cortical neuronal degeneration.

The most resistent neurons are cortex-independent and can be generally termed "truncothalamic" or paleothalamic. According to their connections they belong to unspecific ascending systems (Dempsey and Morrison's nonspecific recruitment systems) and extrapyramidal systems (particularly with the striated nucleus — Bălăceanu and Marcu). Curiously, Luys' median centre is an exception to this rule. Either the presence of intricated neothalamic and paleothalamic neuronal systems or the special frailty of its neuron (thoroughly studied by Martin) account for this phenomenon. Neuronal frailty is not characteristic of aging alone, but of other juvenile, adult of presenile abiotrophic processes as well.

Our cases presented involutive psychic phenomena in different stages. There was no case of dementia. Most of them (80%) had memory troubles in different stages. No correlation was established between the clinical picture and thalamic lesions found in the absence of the analysis of cortical lesions.

Memory troubles were attributed chiefly to rhinencephalic lesions.

In all our cases the system of the anterior thalamic nucleus located as a relay on the mammillo-angular route was not involved. At present we cannot specify the contribution of thalamic lesions to the involutive psychic changes of the respective lesions.

CONCLUSIONS

Based on the macroscopic and microscopic examination of the thalamus from 31 subjects aged 71 to 97 years, in comparison with 2 control subjects (aged 40 and 57 years) we may conclude:

1. The morphologic organization of the thalamus changes in the course of aging.
2. Its volume decreases.
3. Vascular lesions occur as thrombotic micro-softenings.
4. The abiotrophic neuronal degeneration leads finally to neuronal loss.
5. The abiotrophic neuronal lesions develop selectively in neothalamic structures, particularly in cortex-dependent nuclei and Luys' median centre.

Résumé. Les études ont été effectuées sur des cerveaux humains de 31 sujets âgés entre 71 et 97 ans, décédés pendant les 20 dernières années à l'Institut National de Gérontologie et Gériatrie, et deux cerveaux témoin de 40 et respectivement 57 ans fournis par l'Institut de médecine légale de Bucarest.

Tant l'aspect macroscopique que l'aspect microscopique révèlent des modifications des nucléus thalamique au cours du processus de sénescence.

Macroscopiquement une diminution du volume des nucléus thalamiques est évidente, accompagnée souvent d'une thrombose capillaire.

Microscopiquement on constate des lésions vasculaires à l'aspect de micro-ramolissements thrombotiques, accompagnés d'un processus de dégénérescence des cellules nerveuses abiotrophiques, qui détermine la dépopulation des cellules nerveuses. Ces dernières lésions se trouvent le plus souvent dans les structures néothalamiques, et surtout dans les nucléus dépendant du cortex et dans le centre médian de Luys.

REFERENCES

1. Bălăceanu C., Anghel Gabriela, *Conceptul de fiabilitate în biologie*. St. Cerc. Biotehnol., 2/1976 and 3/1977.
2. Bălăceanu C., Simion Nina, Costiniu Mira, Păunescu Margareta, *Neuromorphological aspects of aging thalamus and cerebellum* (in Romanian). 8th Congr. Clin. Geront. Neptun, Sept. 1977, p. 218–227.
3. Bondareff W., Narotzky R., *Change in the microenvironment*. Science, 1972, **176,** 1135.
4. Comfort A., *Neuromythology*. Nature, 1971, **229,** 289.
5. Crémieux A., Alliez Y., *Démences thalamiques*. Am. Med. Psychol., 1959, **2,** *5*, 833–846.
6. Daniels A.C., Chokroverti S., Barrou K.D., *Thalamic degeneration, dementia and seizures*. Arch. Neurol., Chicago, 1969, **21,** 15–24.
7. Delay J., Brion S., *Les démences tardives*. Masson et C-ie, Paris, 1962.
8. Delay J., Brion S., Escouralle R., Marques J.M., *Démences artériopathiques. Lésion du système hippocampo-mammillo-thalamique dans le déterminisme des troubles mnésiques*. Rev. Neurol., 1969, **105,** *1*, 22–23.
9. Franks L.M., *Aging in differentiated cells*. Gerontologia, 1974, **20,** 51–62.
10. Hassin C.B., *Histopathology of Peripheral and Central Nervous Systems*. Hassin C.B., Chicago, 1948.
11. Hollander J., Barrows C.H., *Enzymatic studies in senescent rodent brain*. J. Geront., 1968, **23,** 174–179.
12. Königsmark B.W., Murphy E.A., *Neuronal population in the human brain*. **228,** 1335–1336, 1970, Nature.
13. Kent S., *Solving the riddle of lipofuscin's origin may uncover clues to the aging process*. Geriatrics, May, 1976, 128–138.
14. Martin J.J., *Sémiologie et neuropathologie thalamiques humaines*. Acta Neurol. Belg., 1970, **70,** 771–794.
15. Monagle R.D., Brody H., *The effects of age upon the main nucleus of the inferior olive in the human*. J. Comp. Neurol., 1974, **155,** 66–67.
16. Samorajsky T., *How the human brain responds to aging*. J. Amer. Ger. Soc., 1976, **1,** 4–11.

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EXPERIMENTAL METHODS TO INDUCE LONGEVITY

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Summary. Several experimental researches are exposed, aimed at studying the influences of certain environmental factors, hormones, vitamins, chemical substances, on life-span.

The authors studied the effect of Gerovital H_3 on 1840 Wistar rats, half injected since 2 months old, with 4 mg/kg body weight Gerovital H_3 three times a week, for four weeks, followed by one month break, in 6 series a year. The remaining animals were injected saline solution. A 21.2% prolongation of the life span in males and 8.0% in females was noticed. The functional, biochemical and morphological investigations pointed out the better biological condition of the treated animals in late life, as against controls. The longevity of 5 successive generations was studied in a research on 3,681 Wistar rats. Administration of Gerovital H_3 since early ages resulted in the prolongation of the life span in both the treated animals and the untreated offspring belonging to the first generation issued from treated parents. The action of Aslavital was also studied. The results pointed out that this product affects the rhythm of aging and results in a 20.3% prolongation of the life span.

On the basis of Hayflick's researches on cell cultures, Officer found that the administration of Gerovital H_3 to the cell cultures resulted in the prolongation of the doubling time with another two generations; culture longevity thus increased.

The authors' researches pointed out a 16% prolongation of the life span in secondary cultures of monkey kidney cells, subsequent to Gerovital H_3 administration. The experimental methods of inducing longevity bring about useful information for evaluating the efficacy of the geriatric treatment.

Researches are well known on the role of genetic factors in longevity [1], the relationship between nutrition and life span [2, 3, 4], the use of antioxidants [5] for studying the role of free radicals in the process of aging, the effect of irradiation on the life span [6], etc.

Less numerous researches have been carried out on the therapeutic factors capable of prolonging the life span.

In the course of a 25-year longitudinal study conducted on Gerovital H_3 treated aged subjects, Ana Aslan [7] found that their life span exceeded the life expectancy calculated at the start.

The action of the biotrophic substances on life span required verification on experimental models. The accomplishment of such studies and their results are worth discussing.

The first study [8] was carried out on 1840 rats supplied by the animal farm of the institute. The animals belonged to a closed colony of French Wistar rats, resulted from a pair of rats brought from France in 1956. When 1 month old, the animals were marked by a finger-amputation system which allowed combinations of figures from 1 to 2,000. The biological evolution of each animal was followed throughout the life span; all the data interesting for the experiment were recorded in a special file.

All animals were kept under similar environmental conditions: temperature 21±1°C, humidity 60±10%. The animals' diet included 20% vegetal and animal proteins, 5% fats, carbohydrates and roughage. The basic food contained oats, whole wheat bread, milk, red meat (once a week). Carrots, beet, cabbage were added in spring. Until 6 months old the animals were fed on germinated oats seeds. Calcium salts were added periodically.

In order to study the action of Gerovital H_3 on their life span, the animals were divided into 2 equal groups. Half of the animals were administered i.m. shots with 4 mg/kg body weight Gerovital H_3, in series of 12 shots, 3 per week for 4 weeks, according to the treatment schedule indicated by Ana Aslan.

The treatment was applied with 1 month breaks since 6 months of age throughout the life time. The remaining animals received i.m. shots with saline solution in similar amounts and at the same rate; this was the control group.

Biological, physiological and biochemical investigations were performed at certain ages and a number of animals were sacrificed for the histologic examination of some organs. Obvious differences were found in morbidity, fur and weight, the treated animals displaying a far better trophic condition than the controls.

The electrocardiographic examination performed at 24 months of age (Table 1) pointed out the lower incidence of coronary irrigation disturbances (28.3±9.8%) as against controls (80±8.9%); sequelae of myocardial infarction were found only in controls (20±8.9%). The histologic examination of the heart, performed at 24

Table 1

Electrocardiogram of rats 24 months of age

	Control	Gerovital H_3
No. cases	20	20
Heart rate (per min.)	316±501	390±40.2
	R 60±10.95	R 75± 9.72
	N 35±10.67	R 15± 7.96
	L 5± 4.84	L 10± 6.70
A-V conduction (%)	35±10.63	0
Intra-V conduction disorders (%)	10± 6.70	10± 6.70
Arrhythmia (%)	5± 4.80	5± 4.81
Blood supply disorders (%)	80± 8.94	30±10.24
Infarction (%)	20± 8.94	0
QRS/T discordance (%)	35±10.63	25± 9.67

R = Right deflection
N = Normal
L = Left deflection

$\frac{PQ}{N}$ P = % alive
Q = 100 − P
N = Number in group

months of age pointed out marked myocardial sclerosis in controls and a markedly reduced invasion of connective tissue in treated animals (Figs 1, 2). The histologic examination of the kidney pointed out lesions with both groups; nevertheless, tubular degenerative nephrosis was more marked in controls as against treated rats (Figs 3, 4).

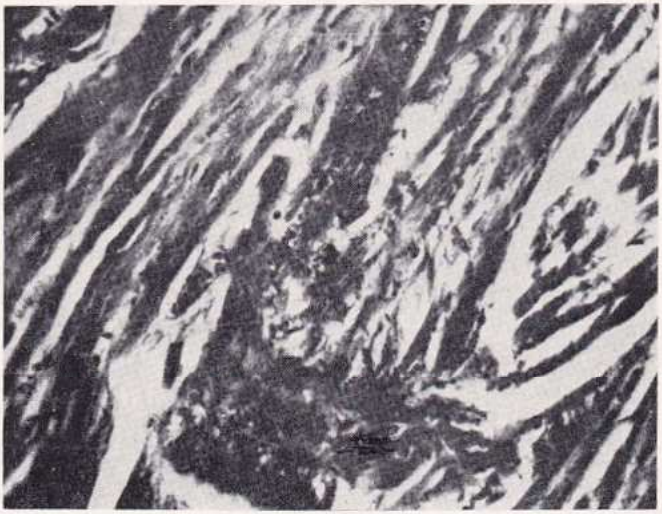

Fig. 1. — Section through the left ventricle of a 24-month-old control male rat. Rich in connective tissue between muscular fibres. PAS staining. 240×.

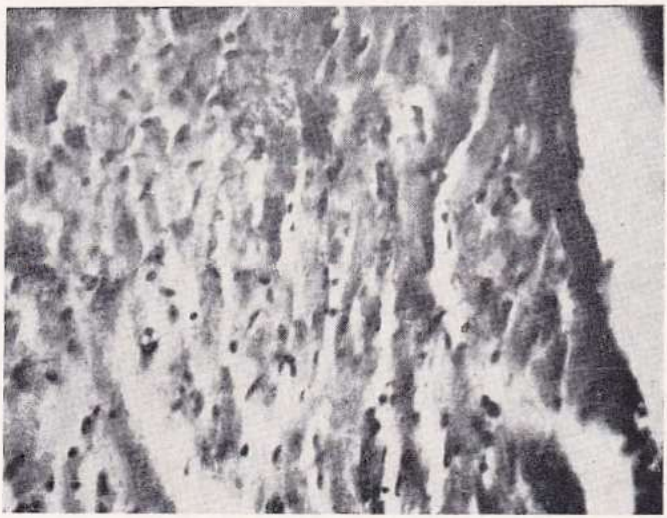

Fig. 2. — Section through the left ventricle of a 24-month-old male rat treated with Gerovital H_3. Poor cell interstitial infiltration with normal myoblasts. PAS staining. 240×.

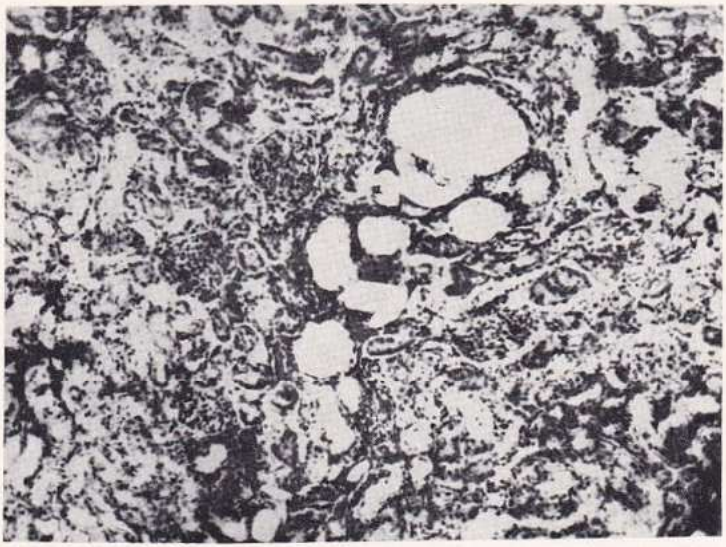

Fig. 3. — Section through the kidney of a 24-month-old control rat. Tubulonephritic lesions. PAS staining. 160×.

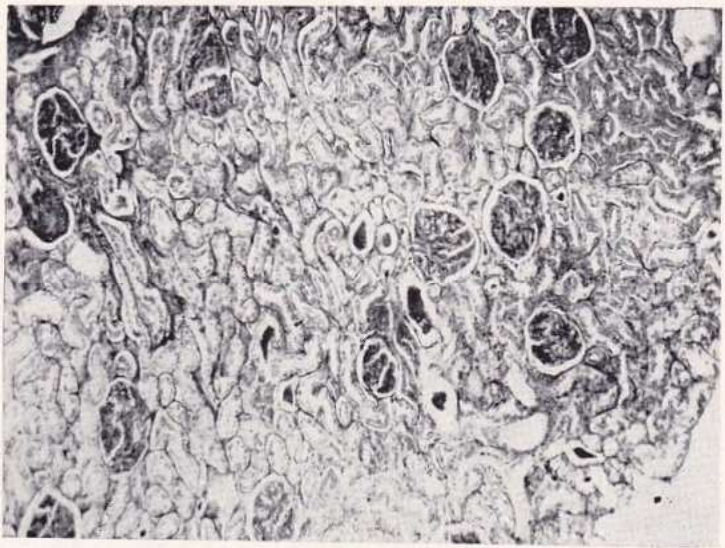

Fig. 4. — Section through the kidney of a 24-month-old rat treated with Gerovital H_3. Discrete tubulonephritic lesions. PAS staining. 150×.

The statistical analysis at the end of the study showed the average life span of Gerovital H_3 treated animals to be 651 ± 13.1 days, as compared to 537 ± 8.2 days in controls; this means a 21.2% prolongation ($p < 0.01$).

The percentage of survivors by months outlived (Table 2) as well as the survival curve (Fig. 5) show statistically and graphically the prolongation of the life span as an effect of Gerovital H_3.

Table 2

Survival curve of male rats

Age (Mo)	Control N = 460	Gerovital H_3	Age (Mo)	Control N = 460	Gerovital H_3
2	97.6±0.70 C	—	18	47.2±2.32	75.8±2.76
3	97.2±0.75	—	19	37.2±2.25	72.9±2.87
4	97.2±0.75	—	20	30.4±2.14	66.9±3.04
5	96.4±0.86	—	21	21.2±1.90	60.3±3.16
6	96.0±0.91	98.8±0.70	22	14.4±1.63	49.8±3.23
7	95.6±0.95	98.8±0.70	23	6.8±1.26	36.5±3.23
8	94.8±1.03	98.8±0.70	24	2.8±0.76	28.9±2.93
9	93.3±1.17	98.0±0.90	25	1.6±0.58	24.3±2.77
10	91.2±1.32	97.5±1.00	26	0.4±0.28	15.1±2.31
11	87.2±1.55	97.5±1.00	27	0	8.8±1.83
12	82.4±1.77	97.5±1.00	28	—	2.1±0.92
13	78.4±1.91	97.5±1.00	29	—	0.9±0.60
14	70.4±2.12	92.1±1.74	30	—	0.5±0.44
15	66.8±2.19	89.2±2.00	31	—	0.5
16	60.4±2.27	86.2±2.22	32	—	0
17	52.4±2.32	81.2±2.52	33	—	—

C = Standard deviation calculated as $\sigma = \pm \sqrt{\frac{PQ}{N}}$, where P = % alive, Q = 100 − P, N = number in group.

The analysis of mortality rates by cause of death and age pointed out the maximum incidence between 19 and 32 months of age in the treated groups as against 13 and 24 months in controls. The most frequent causes of death were acute and chronic pulmonary infections and parenchymatous degenerative processes. The incidence of tumors was lower in treated animals.

Another experiment envisaged Aslavital effect on the life span of French Wistar rats [9]. This experiment followed the same directions as the preceding one. Aslavital was administered intramuscularly and orally. In addition to i.m. shots, given according to a schedule similar to that used for Gerovital H_3, the treatment included sugar coated Aslavital pills, administered three times per week between the shots, in amounts of 10 mg/kg body weight.

The average life span was 609.6 ± 14.4 days in controls and 733.5 ± 14.1 in Aslavital treated subjects (Fig. 6). Thus, the treatment yielded in a 20.3% prolongation of the life span.

As far as morbidity is concerned, the increased resistance of the treated animals should be mentioned, which delayed the onset of infections and degenerative diseases, the most frequent causes of death.

The rats subjected to this experiment were investigated electroencephalographically in order to study the effect of Aslavital on the central nervous system. Chronic electrodes were implanted under the scalp, above the bone. The recordings at

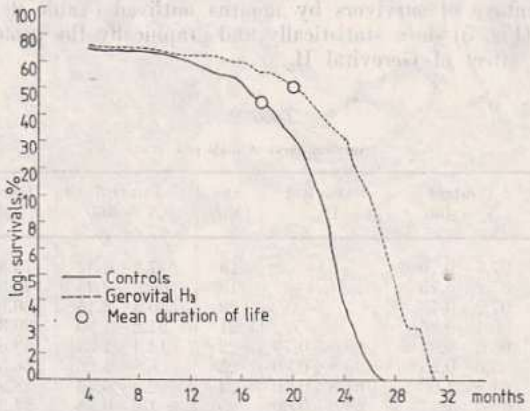

Fig. 5. — Survival curve in control and Gerovital H_3 treated rats.

9, 15 and 21 months of age pointed out the less marked slowing down of the basic rhythm in the treated animals, as against controls. The amplitude of tracings was

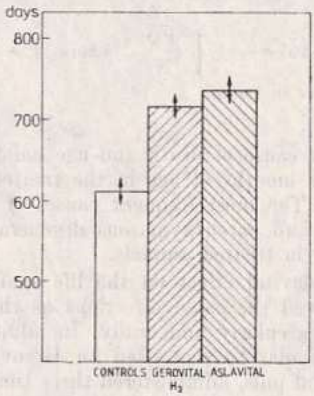

Fig. 6. — Mean life span in control, Aslavital and Gerovital H_3 treated rats.

less reduced with advanced ages in the treated rats and the slow waves were signaled only with the control group.

Another research focused on life span was carried out in collaboration with G. Acălugăriţei (this volume, p. 273—279 on 3,681 French Wistar rats from 5 successive generations. The results pointed out that Gerovital H_3 administered at younger ages induced the prolongation of life span not only in treated animals but also

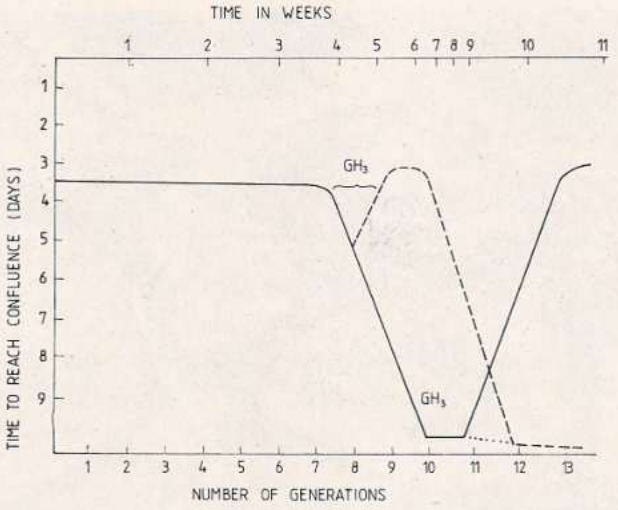

Fig. 7. — Effect of Gerovital H_3 on mouse embryo cell cultures (Officer's experiment).

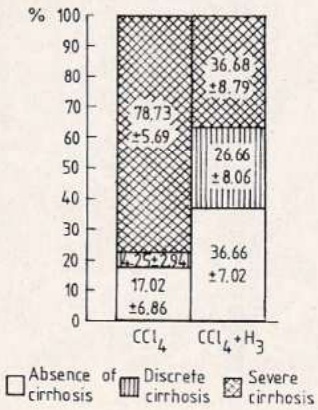

Fig. 8. — Incidence and severity of liver cirrhosis in Gerovital H_3 treated rats.

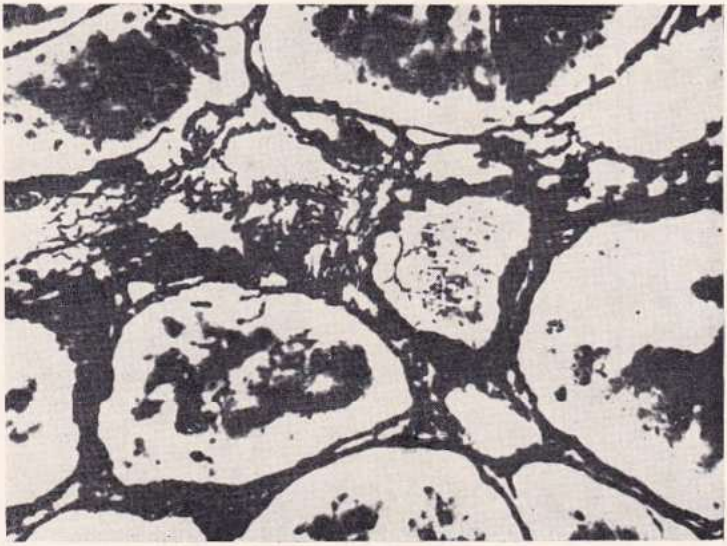

Fig. 9. — Section through the liver of a rat injected with carbon tetrachloride. (Liver cirrhosis). Liver globes surrounded by thick reticulin streaks. Gomori embedding. 240×.

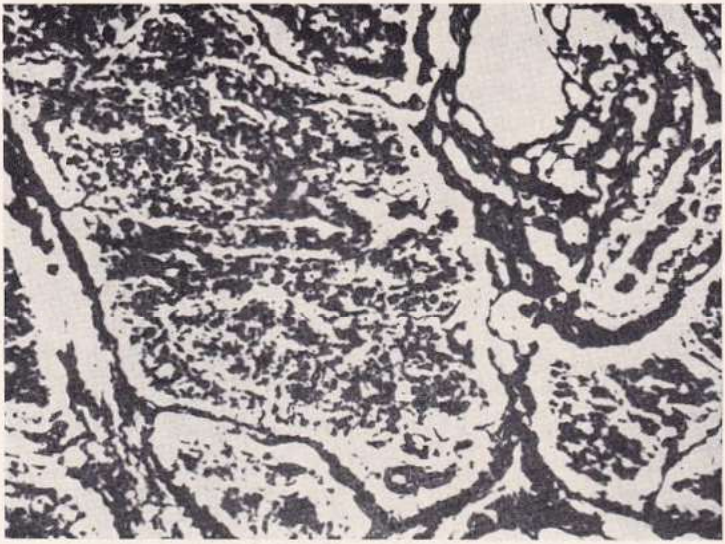

Fig. 10. — Section through the liver of a rat injected with carbon tetrachloride and treated with Gerovital H_3. Thin reticulin fibres around liber globes. Gomori embedding. 240×.

in their untreated offspring belonging to the first generation issued from treated parents.

Related to this study, mention should be made of Raskova and coll's experiment [10]. At first, the authors evidenced the increase in nonspecific resistance to *Shigella shigae* resulting from low procaine amounts injected in rats according to the Aslan method. The increase was transient, but it persisted as a result of periodical procaine injections. Subsequently, the authors noticed that nonspecific resistance to *Shigella shigae* could be passively transferred; when pregnant female rats were injected with procaine, the increased resistance was passed on to the offspring in which it persisted until the 27th day.

It has been accepted that the procaine-based biotrophic treatment which prolongs life span is mainly the result of a complex mechanism which stimulates cell regeneration and has a metabolically energizing effect.

Researches on cell cultures. As known, the cultures of cells from embryos or different organs have been used to study the process of aging or the effect of certain substances vehicled in geriatric clinics.

The researches carried out by Ana Aslan and coll. [11] pointed out that the effect of Gerovital H_3 (concentration 0.4%) on secondary monkey kidney cell cultures was the prolongation of life span by 16% in the treated cells as against controls (Table 3). A 48.3% stimulation of cell proliferative ability was also noticed in treated cultures [12] (Table 4).

Table 3

Postmitotic life span of primary tissue cultures of monkey kidney under the influence of Gerovital H_3 concentration: 0.4%

Average life span (days)		Difference in % in comparison with the control	p
Control	Gerovital H_3		
62.3	72.4	16	<0.01

Table 4

Gerovital H_3 effect on the density of monkey renal cells

Age of culture (days)	Cellular density (thousands of cells/ml medium)		Difference as compared to the control	p
	Control	Gerovital H_3		
2	163.5	218.9	33.8	<0.01
3	463.0	671.5	45.0	<0.01
4	480.3	712.3	48.3	<0.01
5	418.0	610.6	46.0	<0.01
7	363.6	529.7	45.6	<0.01

Starting from Hayflick's observations [13] which stated the limited life span of cell cultures, Officer [14] experimented the effect of Gerovital H_3 in concentration of 0.5%. The cells continued to multiply during 2—3 more generations as compared to controls.

When a similar concentration of Gerovital H_3 was added to the culture after the cells had ceased to divide, they survived longer than the controls (Fig. 7). Gerovital H_3 also prevented the cells from becoming spontaneously tumor-like, continuous lines.

Researches on the stimulation of regenerative ability. One of the experimental methods used to investigate cell regeneration *in vivo* is based on studying the reversibility of carbon tetrachloride induced cirrhotic lesions. The liver regenerating as a normal organ, cirrhosis is gradually and slowly healed. Ana Aslan and coll. [15] investigated the reversibility of cirrhotic lesions under the action of Gerovital H_3 in Wistar rats. The experiment was conducted on 162 male Wistar rats, aged 12 months, mean weight 260 g. Carbon tetrachloride was injected subcutaneously, twice a week for 8 months; 4 mg/kg body weight Gerovital H_3, i.m., 3 times per week was administered during the intoxication and 45 days after it had ceased, ring-shaped ascitic cirrohosis was detected in 82.8% of carbon tetrachloride injected animals and in only 63.3% of Gerovital H_3 treated animals. The proportion of severe hepatic lesions was 78.7% in cirrhotic controls and 36.6% in Gerovital H_3 treated group (Figs. 8—10). The oxygen uptake of liver homogenate pointed out the significant decrease in the respiratory ability of the cirrhotic liver tissue; the oxygen uptake was much higher in Gerovital H_3 treated animals.

Researches on the survival of isolated organs. Mention should be also made of the experiments conducted by Teitel and coll. [16] which proved that amounts of 10^{-10} Gerovital H_3 increase the reactivity of isolated organs and allow longer survival times, by 28% for frog right abdominal muscle and 40% for rabbit terminal ileon.

In conclusion, the availability of experimental methods which induce longevity provides useful information concerning the efficacy of the gerontological treatment.

Zusammenfassung. Es sind mehrere experimentelle Versuche erwähnt, in welchen die Lebensdauer unter der Wirkung der Umgebungsfaktoren, einiger bestimmter Hormone, Vitamine, verschiedener chemischen Substanzen beobachtet wurde. In den von den Verfassern durchgeführten Versuchen wurde die Wirkung des Gerovital H_3 auf 1840 Wistar-Ratten ersucht, aus denen die Hälfte vom Alter von 2 Monaten an mit Gerovital H_3 in Gaben von 4 mg/kg-Körper, 3 Injektionen wöchentlich, 6 Serien jährlich, injiziert wurden. Die anderen Tiere wurden mit Salzlösung injiziert. Es wurde eine Verlängerung der Lebensdauer von 20,2% bei den Männchen und von 8,0% bei den Weibchen festgestellt. Eine Reihe von funktionellen, biochemischen und morphologischen Nachforschungen hat einen besseren biologischen Status bei den betaten behandelten Tieren, im Vergleich zu den Kontrolltieren, hervorgehoben. In einem anderen Versuch auf 3681 Wistar-Ratten wurde die Langlebigkeit von 5 aufeinanderfolgenden Generationen untersucht. Die Anwendung von Gerovital H_3 von einem frühzeitigen Alter an hat die Folgen gehabt, dass die Lebensdauer bei den behandelten Tieren, sowie bei den nicht behandelten Nachkömmlingen, die der ersten Generation aus der behandelten Tieren gehörten, verlängert wurde. Es wurde auch die Wirkung des Aslavital untersucht. Die Ergebnisse haben bewiesen, dass dieses Präparat den Alternsrhythmus beeinflusst, indem es die Lebensdauer um 20,3% verlängert. Indem er die Versuche von Hayflick auf Zellkulturen fortgesetzt hat, hat Officer festgestellt, dass die Einführung von Gerovital H_3 in das Kulturmilieu die Vermehrungszeitspanne mit 2 Generationen verlängert, indem es derart die Langlebigkeit der Kulturen erhöht. Die Versuche der Verfasser haben hervorgehoben, dass das Gerovital H_3 mit 16% die Lebensdauer der sekundären Zellkulturen von Affennieren verlängert. Es wurde geschätzt, dass die Anwendung der experimenteller Verfahren von Induktion der Langlebigkeit nutzbare Indikationen für die Schätzung der Wirksamkeit der in der geriatrischen Behandlung angewandten Massnahmen, bietet.

REFERENCES

1. LANSING A.I., in *Handbook of Aging and the Individual* (J.E. BIRREN, ed.), University of Chicago Press, Chicago, 1959, p. 119–135.
2. MCCAY C.M., SPERLING G., BARNES L.L., *Growth, ageing, chronic diseases and life span in rats.* Arch. Biochem., 1943, **2**, 468–479.
3. ROSS M.H., *Life expectancy modification by change in dietary regimen of the mature rat.* In: Proceedings of the International Congress of Nutrition, 1966, **5**, p. 35–38.
4. BERG B.N., SIMMS H.S., *Nutrition and longevity in the rat. I. Food intake in relation to size, health and fertility.* J. Nutr., 1960, **71**, 242–255.
5. HARMAN D., *Free radical theory of aging. Effect of free radical reaction inhibitors on the mortality rate of male LAF mice.* J. Geront., 1968, **23**, 476.
6. CURTIS H.J., TILLEY J., CROWLEY C., *The cellular differences between acute and chronic neutron and gamma ray irradiated mice.* In: *Biological Effects of Neutron and Proton Irradiations*, 1964, Vol. 3, p. 143–155.
7. ASLAN ANA, *Longitudinal study in the National Institute of Gerontology and Geriatrics of Romania.* International Congress Series, 1978, No. 469, Recent Advances in Gerontology, Excerpta Medica.
8. ASLAN ANA, VRĂBIESCU AL., DOMILESCU C., CÎMPEANU I., COSTINIU MIRA, STĂNESCU ST., *Long-term treatment with procaine (Gerovital H_3) in Albino rats.* J. Geront., 1965, **20**, *1*, 1–8.
9. ASLAN ANA, VRĂBIESCU AL., POLOVRĂGEANU EL., *Aslavital.* Institut National de Gérontologie et de Gériatrie et Ministère de l'Industrie Chimique, Bucarest, 1975, p. 124–132.
10. RASKOVA H., VANECEK J., SEDA M., HELINEK J., *Some pharmacological properties of procaine.* Arch. int. Pharmac., 1962, **140**, *1–2*, 319–326.
11. ASLAN ANA, BĂLAN L., IEREMIA G., *Aspects of the action of Gerovital H_3 in tissue and cell cultures* (in Romanian). Fiziol. Norm. Patol., 1972, **18**, *1*, 81–88.
12. ASLAN ANA, BĂLAN L., VRĂBIESCU AL., *Behaviour of renal cells in long-term cultures. Influence of chemotherapy with Gerovital H_3.* 10th Intern. Congr. of Geront., Jerusalem, June, 1975.
13. HAYFLICK L., *The limited "in vitro" lifetime of human diploid cell strains.* Exp. Cell. Res., 1965, **37**, 614–636.
14. OFFICER J.E., *Theoretical Aspects of Aging.* MORRIS ROCKSTEIN (ed.), Academic Press, New York, 1974, p. 167–175.
15. ASLAN ANA, CÎMPEANU S., VRĂBIESCU AL., DOMILESCU C., *Über die experimentelle Leberzirrhose der weissen Wistar-Ratten unter Einfluss der Behandlung mit Gerovital H_3*, Intern. Conf. on Geront., Akadémiai Kiadó, Budapest, 1965, p. 833–844.
16. TEITEL A., STROESCU V., ȘTEFLEA D., *Investigations on the trophic and stimulating action of procaine upon isolated organs* (in Romanian). Fiziol. Norm. Patol., 1965, **11**, *1*, 67–70.

ROMANIAN J. GERONT. GERIATRICS, 1980, 1, 2, p. 273–279

NEW DATA CONCERNING THE ACTION OF GEROVITAL H_3 ON THE LIFE SPAN OF WISTAR RATS

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Summary. In a group of 3681 French Wistar rats (males and females) from a closed colony belonging to 5 successive generations, treatment with Gerovital H_3 was applied from the 2nd to the 25th month of life. Half the animals served as controls. The mean life span of the treated rats was significantly greater than in controls: in males 643.8 days as against 583.6 days, in females 704.6 days as against 630.4 days. The first generation of non-treated offspring of the treated animals exhibits a significant increase in life span in comparison to the offspring of the control group (657.9 days against 597.1 in males and 718.6 days against 658.2 days in females). No significant difference was noted in the second generation of the non-treated animals. The increased life span of the first generation of non-treated offspring of the treated animals was ascribed to the better somatic conditions of the rats treated with Gerovital H_3.

INTRODUCTION

Rats treated parenterally with Gerovital H_3 since the 2nd or 6th month of life live longer than controls [1]. Treated animals also did better than the controls in maze tests for learning capacity and memory, and there was a lower incidence of pathological changes in the electrocardiogram. In the treated animals, there was less connective tissue invasion in the myocardium and striated muscle and degenerative tubular lesions were less evident in the kidneys.

The extension of life span is connected to decrease of morbidity in animals treated with Gerovital H_3.

After administration of Gerovital H_3 treatment in humans, significant psychical and somatic improvements have been noted [2–7]. In the treated subjects — despite their advanced age — no complications (arteritis, infarction, ictus, etc.) of the age-related pre-existing pathology was noted during a treatment of 18 yrs. Increased resistance to intercurrent diseases was recorded and morbidity and mortality incidences were 75 per cent lower than in non-treated subjects.

In rats, experiments with Gerovital H_3 created an increased resistance to experimental arthritis induced by formaldehyde [8] and to the appearance of lesions after injection of croton oil in the sciatic nerve [9].

Cheymol et al. [10] found that procaine exerted a protective effect against irradiation with ^{60}CO. Similar data concerning the effects of procaine in irradiation were reported by Smith et al. [11].

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Raskova et al. [12] pointed out the increase of non-specific resistance to the *Shigella shigae* toxin by injecting small doses of procaine in mice according to the method of A. Aslan. This increased resistance could be passively transferred. When procaine was injected in pregnant mice, the increased resistance was transmitted to the offspring. This fact was checked until the 27th day of life.

Starting from the above mentioned clinical and experimental results we proposed to investigate the effects of Gerovital H_3 on the biological condition of the offspring. Morbidity (through intercurrent and chronic diseases) and life span were used as indexes.

MATERIAL AND METHOD

Investigations were carried out with 3681 French Wistar rats (2047 male and 1634 female) pertaining to 5 successive generations, maintained in a closed colony for a period of 6 yrs. The animals were divided into 4 groups (Fig. 1).

Group I. Male and female rats treated with Gerovital H_3 and male and female rats injected with saline solution (controls) (F_0 generation).

Group II. Male and female offspring of group I over 4 successive generations (F_{1-4} generations). Among these, a group of rats (male and female) were treated with Gerovital H_3, and another group served as control, being injected with saline solution.

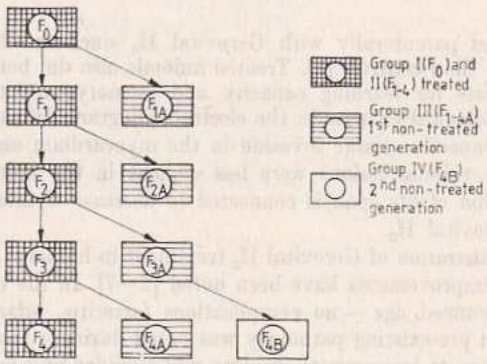

Fig. 1. — Schedule of the experiment on offspring longevity.

Group III. Offspring of animals from group I, over 4 successive generations (F_{1-4A} generations) but neither treated with Gerovital H_3 nor injected with saline solution (First non-treated generation).

Group IV. Male and female offspring of animals from group III (F_{1-4B} generations), likewise non-treated with Gerovital H_3 or saline solution (Second non-treated generation).

Gerovital H_3 was administered from the 2nd to the 24th month of life, by intramuscular injections, three times a week, in doses of 4 mg/body weight, courses of 12 injections with intermissions of two weeks. The controls of groups I and II received intramuscular injections of saline solution in the same quantity and schedule as used in the treatment with Gerovital H_3.

Mating occurred in the 8th month of life and during pregnancy the females were not injected.

In each animal, individualized by a label, the progress of body weight and of biological status was followed up by monthly observations. After decease, the cause of death and the life span were determined after calculating the mean life span and standard error for each group.

RESULTS AND DISCUSSION

Average life span of male rats from group I and II was 643.8 ± 6.4 days in treated animals and 583.6 ± 7.3 days in controls (Figs. 2 and 3). Average life span of the female rats was 704.6 ± 7.6 days in treated animals and 630.4 ± 8.6 days in controls (Table 1). Increase of average life span in treated animals was 10.3 per cent in males and 11.7 per cent in females, the difference being statistically significant ($p < 0.01$) in comparison to controls.

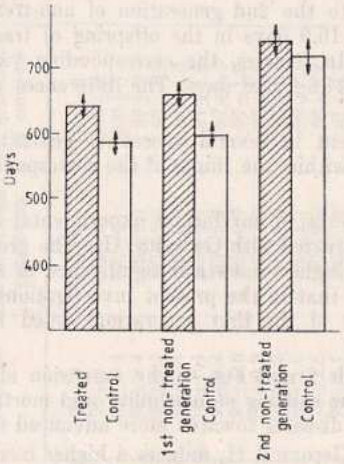

Fig. 2. — Life-span of male rats, by generation.

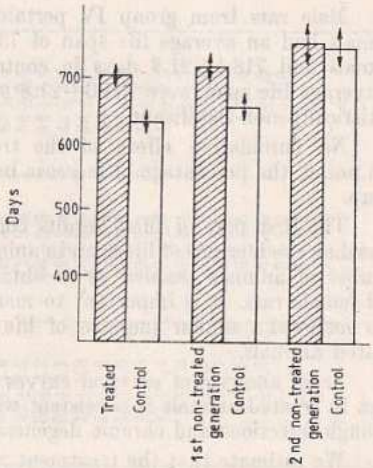

Fig. 3. — Life-span of female rats, by generation.

Male rats from group III, from the first generation of non-treated animals, had an average life span of 657.9 ± 10.5 days in the offspring of treated animals and 597.1 ± 12.8 days in controls. In females, the corresponding values of average life span were 718.6 ± 12.3 and 658.2 ± 12.9 days. The increase of average life span was thus 10.1 per cent in males and 9.1 per cent in females, a difference statistically significant ($p < 0.01$) in comparison to controls.

Table 1

Mean life span (days)

Group	Male rats					Female rats				
	Treated		Controls		Statistical significance	Treated		Controls		Statistical significance
	Number of animals	Mean life span	Number of animals	Mean life span		Number of animals	Mean life span	Number of animals	Mean life span	
I and II Treated with Gerovital H_3	649	643.8 ±6.4	649	583.6 ±7.3	$p<0.01$	467	704.6 ±7.6	436	630.4 ±8.6	$p<0.01$
III First non-treated generation	295	657.9 ±10.5	294	597.1 ±12.8	$p<0.01$	289	718.6 ±12.3	282	658.2 ±12.9	$p<0.01$
IV Second non-treated generation	80	735.3 ±16.9	80	718.1 ±21.3	$p>0.10$	80	754.0 ±21.8	80	747.6 ±20.8	$p>0.10$

Male rats from group IV pertaining to the 2nd generation of non-treated animals had an average life span of 735.3±16.9 days in the offspring of treated animals and 718.1±21.3 days in controls. In females, the corresponding values of average life span were 754.0±21.8 and 747.6±20.8 days. The differences were statistically non-significant.

No cumulative effect of the treatment in several successive generations was noted, the percentage of increase being within the limits of the corresponding group.

The first part of these results corresponds to our former experimental data recording the increase of life span in animals treated with Gerovital H_3. The greater number of animals enabled us to obtain a higher statistical significance in male and female rats. It is important to mention that in the present investigations we also observed a similar increase of life span of the first generation issued from treated animals.

From analysis of survival curves (Table 2 and Fig. 4) the extension of life span in treated animals is consistent with the shifting of morbidity and mortality through infectious and chronic degenerative diseases towards more advanced ages.

We estimate that the treatment with Gerovital H_3 induces a higher increase of non-specific resistance to noxious agents of the type described by Raskova et al. with *Shigella shigae* toxin. David and Enăchescu [13] have recorded an increase of immunological isoantibodies as well as of alexin titer, in patients undergoing a long-term treatment with Gerovital H_3 and actively immunised with group antigens.

We regard the effects of Gerovital H_3 as being due to its action at the cell level. Investigations have shown that Gerovital H_3 is a stabilizer of the cell membrane, acting on ion exchanges [14]. In cell metabolism, the substance plays a role by stimulating enzymatic activity and intervenes in the redox processes [15].

Table 2

Survival curve in percentage

Age in months	Male rats treated with Gerovital H_3	Male rats (controls)	Male rats 1st non-treated generation	Male rats 1st generation of controls	Female rats treated with Gerovital H_3	Female rats (controls)	Female rats 1st non-treated generation	Female rats 1st generation of controls
2	100±0	100±0	100±0	100±0	100±0	100±0	100±0	100±0
3	100±0	100±0	100±0	100±0	100±0	100±0	100±0	100±0
4	100±0	99±0.4	100±0	100±0	100±0	99±0.4	100±0	100±0
5	100±0	99±0.4	99±0.7	99±0.7	100±0	99±0.4	100±0	100±0
6	100±0	99±0.4	99±0.7	97±1.0	100±0	99±0.4	100±0	100±0
7	100±0	99±0.4	99±0.7	97±1.0	100±0	99±0.4	100±0	99±0.2
8	100±0	99±0.4	99±0.7	97±1.0	100±0	99±0.4	100±0	97±1.0
9	99±0.4	99±0.4	99±0.7	97±1.0	100±0	99±0.4	98±1	96±1.4
10	99±0.4	98±0.6	99±0.7	97±1.0	99±0.4	98±0.6	96±1.4	96±1.4
11	98±0.6	96±0.9	98±1.0	96±1.0	98±0.6	96±0.9	96±1.4	96±1.4
12	96±0.9	92±1.2	98±1.0	95±1.4	96±0.9	92±1.2	96±1.4	92±1.8
13	94±1.0	87±1.5	95±1.7	90±2.1	96±0.9	87±1.5	96±1.4	92±1.8
14	90±1.3	79±1.8	92±2.0	86±2.3	93±1.1	79±1.8	93±1.7	86±2.4
15	87±1.5	70±2.1	90±2.1	81±2.7	92±1.2	70±2.1	93±1.7	80±2.8
16	82±1.7	65±2.2	87±2.3	76±3.0	89±1.4	65±2.2	85±2.4	77±3.0
17	78±1.8	57±2.2	83±2.6	67±3.3	86±1.6	57±2.2	78±2.9	68±3.3
18	68±2.1	49±2.3	75±3.1	62±3.4	82±1.7	49±2.3	71±3.2	64±3.4
19	63±2.2	42±2.2	71±3.2	56±3.5	81±1.8	42±2.2	64±3.4	52±3.6
20	61±2.2	38±2.2	66±3.3	52±3.6	78±1.9	38±2.2	59±3.5	46±3.5
21	52±2.3	30±2.1	62±3.4	43±3.4	75±2.0	30±2.1	54±3.6	39±3.5
22	44±2.2	19±1.8	48±3.5	34±3.3	70±2.1	19±1.8	45±3.5	36±3.4
23	33±2.1	16±1.6	39±3.4	30±3.3	63±2.2	16±1.6	41±3.4	25±3.1
24	26±2.0	12±1.5	33±3.3	24±3.0	58±2.2	12±1.5	34±3.3	16±2.7
25	20±1.8	12±1.5	29±3.1	18±2.7	51±2.3	12±1.5	29±3.2	12±2.3
26	13±1.5	11±1.4	19±2.7	11±2.3	45±2.3	11±1.4	23±3.0	6±1.7
27	10±1.3	8±1.2	14±2.4	7±1.7	41±2.2	8±1.2	18±2.6	6±1.7
28	9±1.3	7±1.2	7±1.7	4±1.4	31±2.1	7±1.2	9±2.0	4±1.5
29	5±1.0	3±0.7	6±1.5	4±1.4	26±2.0	3±0.7	7±1.7	3±1.3
30	4±0.9	2±0.6	6±1.5	4±1.4	21±1.8	2±0.6	4±1.4	3±1.3
31	2±0.6	1±0.4	3±1.0	2±1.0	11±1.4	1±0.4	3±1.2	2±1.0
32	—	—	3±1.0	2±1.0	7±1.1	—	3±1.2	6
33	—	—	1±0.7	—	4±0.9	—	3±1.2	—
34	—	—	1±0.7	—	3±0.7	—	—	—
35	—	—	—	—	2±0.6	—	—	—
36	—	—	—	—	2±0.6	—	—	—
37	—	—	—	—	1±0.4	—	—	—

Standard deviation calculated as $\sigma = \pm \sqrt{\frac{PQ}{N}}$, where P = % alive; Q = 100 − P; N = number in group.

Teitel et al. [14] demonstrated that procaine in certain doses increased the reactivity of isolated organs and promoted longer survival. Aslan et al. [16] obtained an increase of cell survival in cell cultures of monkey kidney treated with Gerovital H_3.

Our results revealed that treatment with Gerovital H_3 induced an extended life span in the first generation of offspring issued from the treated groups. This can probably be explained by the better somatic conditions induced in the parents by treatment with Gerovital H_3.

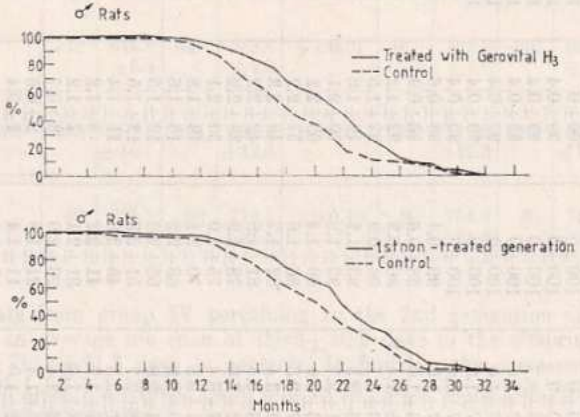

Fig. 4. — Survival curve.

CONCLUSION

Gerovital H_3 treatment in rats produced a significant extension of average life span in the treated animals as well as in the first following generation.

This effect was ascribed to the higher metabolic conditions due to treatment with the biotrophic substance Gerovital H_3.

Résumé. Un groupe de 3 681 rats Wistar français (mâles et femelles), provenant de 5 générations successives d'une colonie fermée, a été traité au Gérovital H_3, à partir du 2e jusqu'au 25e mois de vie. La moitié d'entre eux ont été témoins. La durée moyenne de vie des animaux traités a été considérablement plus grande que celle des témoins; pour les mâles 643,8 jours par rapport à 583,6 jours, et pour les femelles 704,6 jours par rapport à 630,4 jours. La première génération d'animaux non traités provenus de parents traités ont présenté un accroissement significatif de la durée de vie vis-à-vis de la génération correspondante provenue des témoins; pour les mâles 657,9 jours par rapport à 597,1 jours, pour les femelles 718,6 jours par rapport à 658,2 jours. À la 2e génération d'animaux non traités, on ne constate pas de différences significatives. L'accroissement de la durée de vie de la première génération d'animaux non traités provenus de parents traités a été attribué aux conditions somatiques supérieures des rats traités au Gérovital H_3.

REFERENCES

1. ASLAN, A., VRĂBIESCU, AL., DOMILESCU, C., CÎMPEANU, L., COSTINIU, M., STĂNESCU, S. (1965) *Long-term treatment with Procaine (Gerovital H_3) in Albino rats.* J. Geront., **20**, *1*, 1–8.
2. ASLAN, A. (1960) *Procaine therapy in old age and other disorders (Novocaine-factor H_3).* Geront. Clin., **2**,, *3*, 148–176.
3. ASLAN, A. (1962) *The therapeutics of old age. The action of procaine – clinical and experimental conclusions.* In *Medical and Clinical Aspects of Ageing* (ed. N.T. BLUMENTHAL), Columbia Univ. Press, New York.
4. ASLAN, A., CÎMPEANU, S. (1958) *Die Wirkung von Novocain und p-Amino-Benzoesäure auf Sauerstoff-Verbrauch der Bierhefe.* Arzneimittelforsch., **8**, *3*, 116–120.
5. ASLAN, A., COSMOVICI, N., LALU, P., BUNESCU, G. (1965) *Development of the influenza virus epidemic in the Bucharest Institute of Geriatrics (February–March, 1959).* Int. Conf. Geront., Akadémiai Kiadó, Budapest, 409–413.
6. ASLAN, A., CÎRJE, M., NICOLAE, D. (1969) *Die Wirkung des Gerovital H_3 auf die Folazidämie bei Menschen.* Prophylaxe, **8**, *2*, 25–29.
7. ASLAN, A., DAVID, C. (1960) *Prophylaxe der Arteriosklerose.* Arzneimittelforsch., *11*, 869–876.
8. ASLAN, A., NEDLER, M., TUDEA, L. (1951) *The effects of procaine on experimental arthritis induced in white rats* (in Romanian). Com. Acad. R.P.R., **1**, 1111–1116.
9. ASLAN, A., VRĂBIESCU, AL., CÎMPEANU, L. (1962) *Morphological changes in neurodystrophy provoked in rats. Influence of Gerovital H_3 treatment* (in Romanian). Fiziol. Norm. Patol., *1*, 21–27.
10. CHEYMOL, J., CHABRIER, P., ADOLPHE, M., SELIM, M. (1952) Ref. by RASKOVA in *Some pharmacological properties of procaine.*
11. SMITH, W.W., ALDERMAN, I.M., GILLESPIE, R.E. (1952) Ref. by RASKOVA in *Some pharmacological properties of procaine.*
12. RASKOVA, H., VANECEK, J., SEDA, M., JELINEK, J. (1952) *Some pharmacological properties of procaine.* Archs. Int. Pharmacodyn., **CXL**, *1–2*.
13. DAVID, C., ENĂCHESCU, G. (1968) *Immunologische Untersuchungen bei Bejahrten. Dynamische Aspekte der Reaktivität bei antigenen Stimuli aus dem 0AB Blutgruppensystem.* "Therapeutische Stimulierungsmöglichkeiten der immunologischen Reaktivität". Kongressband 7, Wiesbaden, I.F. Bergmann.
14. TEITEL, A., STROESCU, V., ŞTEFLEA, D. (1965) *Researches concerning the trophic and stimulating actions of procaine on isolated organs* (in Romanian). Fiziol. Norm. Patol., **11**, *1*, 67–70.
15. ASLAN, A., IRIMESCU, I., CÎMPEANU, L. ET AL. (1960, 1961) *Die Wirkung von p-Aminobenzoyldiäthylaminoäthand auf das Leber-Homogenat weisser Raten.* Agressologie, *1*, 381–388; Arzneimittelforsch, *11*, 36–37.
16. ASLAN, A., BĂLAN, L., IEREMIA, G. (1972) *Aspects of Gerovital H_3 action on tissue and cell cultures.* Fiziol. Norm. Patol., **18**, *1*, 81–88.

ROMANIAN J. GERONT. GERIATRICS, 1980, 1, 2, p. 281–289

LEARNING ABILITY, MEMORY AND PASSIVE AVOIDANCE BEHAVIOUR IN RATS ACCORDING TO AGE AND UNDER THE INFLUENCE OF ASLAVITAL CHEMOTHERAPY

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Summary. The research was conducted on 150 male Wistar rats of different ages.

The behaviour in the maze was studied on a number of 60 rats aged 14 to 20 months (a group of treated rats and a control group). The treated rats aged 14 months crossed the maze in a mean time of 25.5±0.8 sec. and made a mean number of errors of 1.2±0.1; the controls of the same age had a mean time of 44.4±2.2 sec. and a mean number of errors of 2.5±0.1.

The treated 20-month-old rats covered the distance in a mean time of 73.2+6.4 sec., making on average 3.5±0.2 errors; for the control rats of the same age the corresponding figures were 143.1±6.7 sec. and 5.5±0.4. The results obtained show significant differences between the 14-month-old rats belonging to the control group and those subjected to the treatment with Aslavital.

The passive avoidance behaviour was studied in 90 rats, 4, 14 and 20 months old.

The research concerning the short- and long-term memory showed significant differences in relation to age.

The treatment improved the results obtained: 80% of the 4-month-old rats treated with Aslavital maintained the reaction of avoiding the noxious environment as against 46.6% of the control rats. At the age of 14 months the proportion was 86.6% in treated rats and 53.5% in controls.

The results obtained prove the decreased learning ability and memory in old age and the obvious improvement due to Aslavital chemotherapy.

To test rats' learning ability and memory with advancing age, the complex maze induced the most conclusive results, although it is not clear when do the changes occur [1–5].

Other data were found by studying the way in which the ability to avoid a noxious factor is developed and maintained [4, 6–9].

In previous researches we pointed out the better solving of the complex maze in rats treated with Gerovital H_3 as compared to controls. The time in which the distance was covered was shorter and the number of errors smaller [10, 11].

We started again a series of similar researches using the new procaine-based product – Aslavital – [12] in both tests: the maze and the passive avoidance behaviour.

I. THE MAZE

MATERIAL AND METHOD

The experiments were carried out on 60 Wistar male rats aged 14 and 20 months. Each age group was made up of 15 controls and 15 Aslavital-treated rats. The dose of Aslavital was 4 mg/kg body weight. The treatment started at

4 months and consisted of series of 12 intramuscular injections — 3 injections weekly —, alternating with 15-day breaks. The controls were injected with saline.

For the maze we used Verzár-McDougall's model. The experiment consisted of 3 stages, each of them including 10 trials. The motivation was search of food, the rats having been previously starved.

During the first stage of the experiment, the food was placed progressively at 30 cm distance from the maze entrance. The maze ways were learned by the rat during these 10 trials of the first stage.

During the second stage, the food was placed at the exit and the knowledge acquired during the first stage was reinforced.

During the third stage the rat had to solve certain problems making use of what he had learned in previous situations, without any food stimulus.

The time in which the distance was covered and the errors made were recorded.

RESULTS

(1) The mean time in which the distance was covered was 44.4 ± 2.2 sec. in the second stage and 119.9 ± 9 sec. in the third stage for the 14-month-old controls. The corresponding figures for the rats treated with Aslavital were 25.5 ± 0.8 sec. and 82.2 ± 6.4 sec. respectively (Table 1, Fig. 1).

Table 1

Mean running time and mean errors*

Age	Stage	Mean running time (seconds)			Mean errors		
		Control	Aslavital-treated	Statistical significance between controls and treated	Control	Aslavital-treated	Statistical significance between controls and treated
14-month-old rats	2nd stage	44.43 ±2.19	25.46 ±0.76	$p<0.01$	2.42 ±0.12	1.18 ±0.01	$p<0.01$
	3rd stage	119.97 ±9.68	82.22 ±6.44	$p<0.01$	4.55 ±0.33	3.10 ±0.26	$p<0.01$
20-month-old rats	2nd stage	113.15 ±6.66	73.24 ±6.44	$p<0.01$	5.52 ±0.41	3.54 ±0.19	$p<0.01$
	3rd stage	148.95 ±10.95	114.81 ±9.48	$p<0.01$	4.78 ±0.36	2.50 ±0.14	$p<0.01$
Statistical significance between 14- and 20-month-old rats	2nd stage	$p<0.01$	$p<0.01$	—	$p<0.01$	$p<0.01$	—
	3rd stage	$p<0.10$ <0.05	$p<0.10$	—	$p>0.50$	$p=0.05$	—

* The results obtained were comparatively analysed using Student's "t" test.

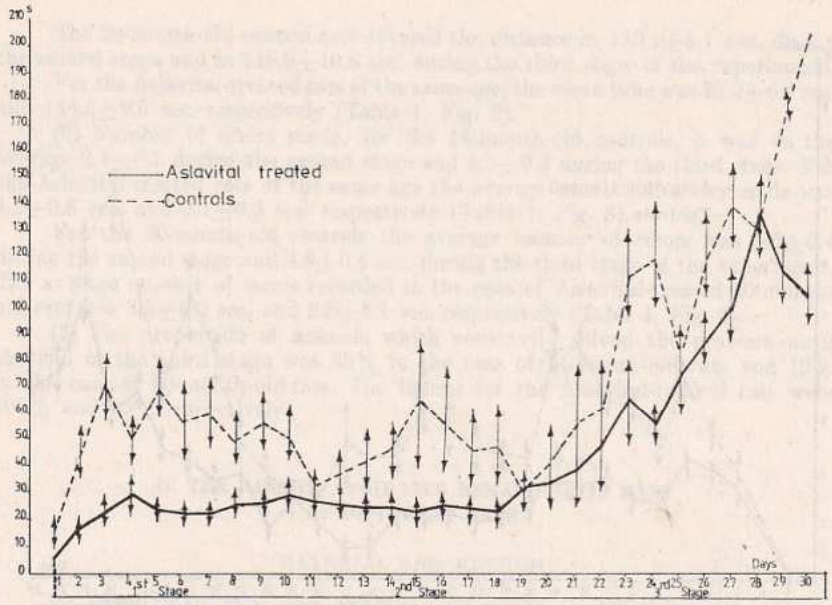

Fig. 1. — Mean running time — 14-month-old rats.

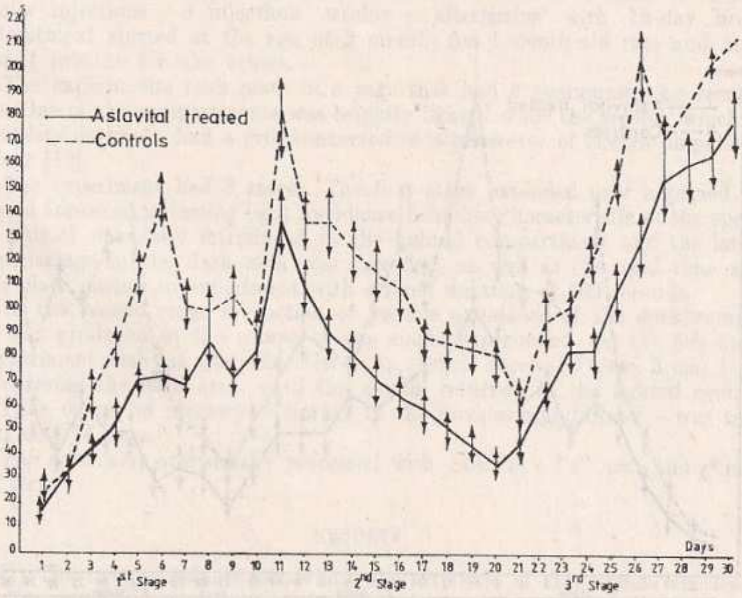

Fig. 2. — Mean running time — 20-month-old rats.

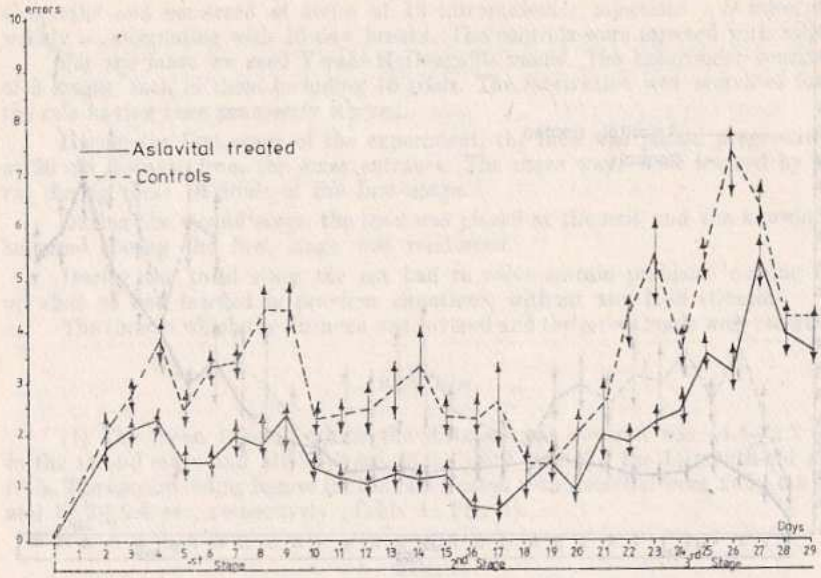

Fig. 3. — Mean errors — 14-month-old rats.

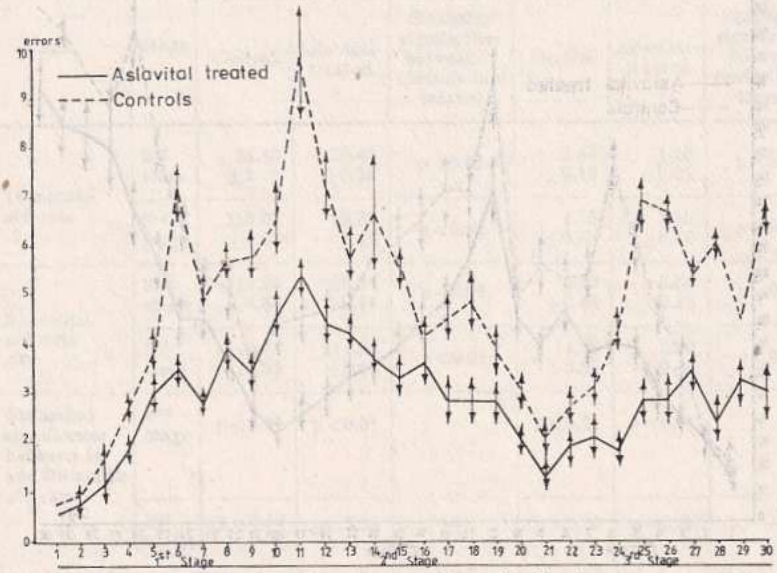

Fig. 4. — Mean errors — 20-month-old rats.

The 20-month-old control rats covered the distance in 113.1±6.7 sec. during the second stage and in 148.9±10.8 sec. during the third stage of the experiments. For the Aslavital-treated rats of the same age, the mean time was 73.2±6.4 sec. and 144.8±9.5 sec. respectively (Table 1, Fig. 2).

(2) Number of errors made: for the 14-month-old controls, it was on the average 2.4±0.1 during the second stage and 4.5±0.3 during the third stage. For the Aslavital-treated rats of the same age the average number of errors made was 1.2±0.8 sec. and 3.1±0.3 sec. respectively (Table 1, Fig. 3).

For the 20-month-old controls the average number of errors was 5.5±0.4 during the second stage and 4.8±0.4 sec. during the third stage of the experiment. The average number of errors recorded in the case of Aslavital-treated 20-month-old rats was 3.5±0.2 sec. and 2.5±0.1 sec. respectively (Table 1, Fig. 4).

(3) The proportion of animals which constantly solved the problem until the end of the third stage was 33% in the case of 14-month-old rats and 13% in the case of 20-month-old rats. The figures for the Aslavital-treated rats were 100% and 80% respectively.

II. THE PASSIVE AVOIDANCE BEHAVIOUR IN RATS OF DIFFERENT AGES

MATERIAL AND METHOD

90 Wistar male rats aged 4, 14 and 20 months were used in this experiment. Each group was made up of 15 controls and 15 rats treated with Aslavital in a dose of 4 mg/kg body weight. The treatment consisted of series of 12 intramuscular injections — 3 injections weekly —, alternating with 15-day breaks. The treatment started at the age of 2 months for 4-month-old rats and at the age of 4 months for the others.

The experiments took place in a cage that had 2 communicating compartments. One of the compartments was brightly lighted while the second, which was in complete darkness, had a grill connected to a generator of electric impulses on the floor [13].

The experiment had 2 stages. The first stage extended over a period of 7 days and consisted in testing light avoidance behavior characteristic of the species. Each animal was daily introduced in the lighted compartment and the latency of the passage in the dark area was recorded, as well as the total time spent in this place during an experiment with a fixed duration of 300 seconds.

In the second stage a reaction of passive avoidance of the dark compartment was produced in the course of one single experiment. On the 8th day of the experiment each rat was subjected to an electric shock (50 c/sec, 5 ms, 1 mA) after entering the dark area, until the animal returned to the lighted compartment. The degree of memory — storage of the noxious significance — was tested in the next 14 days.

The data were statistically processed with Student's "t" test and χ^2 correlation test.

RESULTS

(1) The light avoidance behaviour characteristic of this animal species did not suffer significant modifications in point of age and treatment (Table 2).

Table 2

Light avoidance behaviour*

Age	Mean value of latency of passage to dark room (seconds)			Mean value of total time spent in the dark room (seconds)		
	Controls	Aslavital-treated	Statistical significance	Controls	Aslavital-treated	Statistical significance
4-month-old rats	8.03 ±1.04	7.45 ±1.20	$p>0.50$	273.55 ±7.66	260.15 ±4.18	$p<0.50$ >0.10
14-month-old rats	8.77 ±0.53	10.85 ±1.57	$p<0.50$ >0.10	274.53 ±3.60	265.53 ±4.58	$p<0.50$ >0.10
20-month-old rats	13.03 ±1.72	13.25 ±1.47	$p>0.50$	257.43 ±7.99	261.76 ±6.60	$p>0.50$

* The results were statistically analysed with Student's "t" test.

(2) Short-term memory. After the electric shock was applied, during the same trial the 4-, 14- and 20-month-old controls avoided the dark compartment in a proportion of 80%, 86.7% and 60% respectively. The differences between the 4-, 14- and 20-month-old rats were significant.

100% of the Aslavital-treated rats aged 4 months avoided a noxious environment and so did 100% of those aged 14 months as well as 73.3% of the rats aged 20 months. The differences were significant for the 4-month-old rats and at the limit of statistical significance for the 14-month-old rats (Table 3, Fig. 5).

Table 3

Recall capacity of painful meaning*

		Short-term memory			Long-term memory		
		4-month-old rats	14-month-old rats	20-month-old rats	4-month-old rats	14-month-old rats	20-month-old rats
Controls	Maintained avoidance reaction %	80 ±2.66	86.67 ±2.26	60 ±3.26	46.66 ±3.32	53.33 ±3.32	33.34 ±3.14
	Constant extinction %	20 ±2.66	13.33 ±2.26	40 ±3.26	20 ±2.66	13.33 ±2.26	46.66 ±3.32
	Inconstant extinction %	—	—	—	33.34 ±3.14	33.34 ±3.14	20 ±2.66
Aslavital-treated	Maintained avoidance reaction %	100	100	73.33 ±2.95	80 ±2.66	86.66 ±2.26	40 ±3.27
	Constant extinction %	—	—	26.67 ±2.95	—	—	26.66 ±2.94
	Inconstant extinction %	—	—	—	20 ±2.66	13.34 ±2.26	33.34 ±3.14
	Statistical significance	$p<0.02$ >0.01	$p<0.10$ >0.05	$p<0.30$ >0.20	$p<0.02$ >0.01	$p<0.01$ >0.001	$p<0.20$ >0.10

* The results were statistically analysed with the χ^2 correlation test.

(3) For long-term memory, significant changes were reported in the controls in point of age. The best results were obtained with the 14-month-old rats, much better in the case of the treated rats. In the 4-month-old rats the proportion of rats in which the avoidance reaction was maintained was 80% as compared with the controls; for the 14-month-old rats it was 86.6% in the treated animals and 53.3% in the controls. The differences were statistically significant (Table 3, Fig. 6).

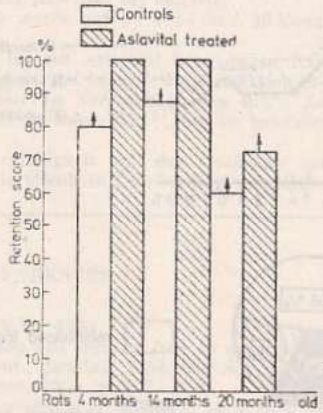

Fig. 5. — Short-term memory. Painful meaning retention score immediately after the electric shock.

(4) The latency of escape response to electric shock showed statistically significant differences between the 20-month-old (7.6±0.3 sec.), 4-month-old (3.8±0.2 sec.) and 14-month-old rats (4.0±0.3 sec.). No significant differences were noticed between the control and treated rats within the age groups.

DISCUSSION

The decrease in learning ability and memory with aging is explained by the structural and metabolical modifications at the level of the central nervous system. An important part is played by the decrease of the RNA content as well as by the frequency of errors in the transcription and transduction of information on the neuronal RNA molecule with advanced age [14, 15].

Aslavital treatment induced better results both in solving the maze and in developing and maintaining the avoidance behaviour.

The similar effect produced by Gerovital H_3 was attributed to procaine which acts not only as an entire molecule but through its hydrolysis products diethylaminoethanol (DEAE) and paraaminobenzoic acid (PABA). Researches with ^{14}C carried out by Groth et al. [16] proved that dimethylaminoethanol (DMAE) crosses the blood-brain barrier, penetrates into the nervous cell and is transformed into choline and acetylcholine. Results obtained by administration of procaine ascertain that DEAE, resulted from procaine hydrolysis, is a precursor of acetylcholine. Thus, Gerovital H_3 supplies through DEAE the metabolic pathway which determines the increase in acetylcholine production.

Aslavital influences the production of acetylcholine by the action of procaine, of the larger quantity of potassium ions and of the glutamic acid included

in its content. Due to the important part played in the intermediate metabolism, glutamic acid bridges the gap between glucides, lipids and proteins. By changing into alpha-ketoglutamic acid it may interfere in the energy metabolism of the nervous tissue [17, 18].

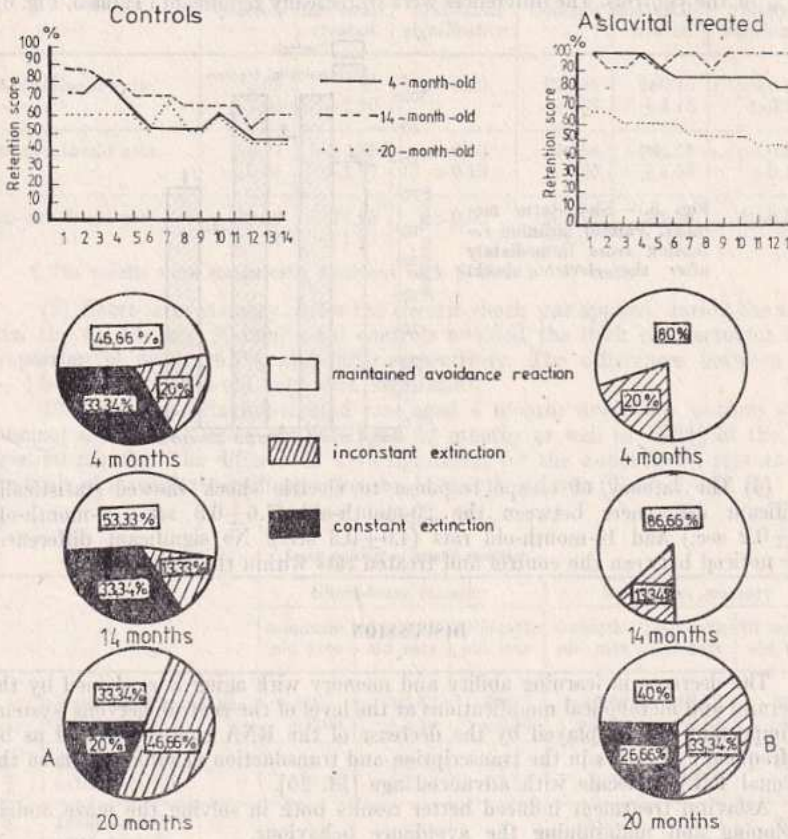

Fig. 6. — Long-term memory.
A = dynamics of long-term memory over 14 days subsequent to the single trial with painful stimulus learning.
B = recall capacity over the 14 days of observation.

CONCLUSIONS

The treatment with Aslavital can improve the involutive changes which occur during the process of aging in the central nervous system. This was evidenced during the study on memory and learning ability of rats of different ages.

The role of procaine, potassium ions and glutamic acid in restoring the nervous cell's metabolism and functionality accounts for this action.

Zusammenfassung. Die Forschung hat 150 Wistar Männchen Ratten erforscht.

Das Benehmen hatte man bei 60 14 und 20 Monate alten Ratten studiert (behandelte und Zeugen).

Die 14 monatigen Ratten haben durchschnittlich in 25,5±0,8 sec. Die kleine Zahl von Rechenfehlern war 1.2±0.1. Die zeugen in demselben Alter.

Die Ergebnisse die man erhalten hat, zeigen im Benehmen, durchschnittlich, seinen kennzeichnenden Unterschied zu der Gruppe mit Aslavital br, handelt.

Das passive Vermeidung Benehmen wurde auf 90 4, 14 und 20 Monate alten Ratten studiert.

Wir haben bessere Ergebnisse bei den mit Aslavital behandelten Ratten.

Bei 80% 4 Monate alten Ratten mit Aslavital behandelt die Reaktion in der Vermeidung der schädlichen Umgebung wurde erleichtert, im Vergleich zu den 46,6% Zeuge.

Die Zahl für die 14 Monate alte Ratten waren 86,6% für die behandelte Gruppe und 53,3% für die Zeugen.

Die Experimente zeigen daß die Lernfähigkeit und das Gedächnis nehmen mit dem Alter ab und daß die Aslavital Chemotherapie offenbare Verbesserung veranlaßt.

REFERENCES

1. Brody, S., *Biogenetics and Growth*, N.Y., 1945.
2. Verzar, F., McDougall, F.J., *Learning and memory tests in young and old rats.* Third Congress Intern. Assoc. Geront., London, 1954, *Old Age in the Modern World.* E. & Livingstone Ltd., London, 1955, p. 247–259.
3. Goodrick, C., *Learning, retention and extinction of a complex maze habit for mature, young and senescent Wistar albino rats.* J. Geront., 1968, **23**, 298–304.
4. Goodrick, C., *Error goal-gradients of mature, young and aged rats during training in a 14-unit spatial maze.* Psychol. Rep., 1973, **32**, 359–362.
5. Goodrick, C., *Maze learning of mature, young and aged rats as a function of distribution of practice.* J. Exp. Psychol., 1973, **98**, 344–349.
6. Mělka, J., *Conditioning in rats of different age.* Activ. nerv. sup. (Praha), 1965, **7**, *2*, 121.
7. Doty, B., *The effects of cage environment upon avoidance responding of aged rats.* J. Geront., 1972, **27**, *3*, 358–360.
8. Chown, S., *Aged and the rigidities.* J. Geront., 1961, **16**, 353–362.
9. Goodrick, C., *Behavioural rigidity as a mechanism for facilitation of problem solving for aged rats.* J. Geront., 1975, **30**, *2*, 181–184.
10. Aslan, A., Vrăbiescu, Al., Domilescu, C., Cîmpeanu, L., Costiniu, M., Stănescu, S., *Longterm treatment with procaine (Gerovital H_3) in albino rats.* J. Geront., 1965, **20**, *1*, 1–8.
11. Aslan, A., Vrăbiescu, Al., David, C., *Gerovital H_3*, ed. by the National Institute of Gerontology and Geriatrics and the Ministry of Chemical Industry, Bucharest, 1977.
12. Aslan, A., *Bases théoriques actuelles de la thérapie à la procaïne dans la prévention de la sénescence.* In: Aslavital, ed. by the National Institute of Gerontology and Geriatrics and the Ministry of Chemical Industry, Bucharest, 1977, p. 5–26.
13. Sterescu-Volanschi, M., Tău, H.G., Pascalov-Stoenescu, L., Sterescu, N., *Decrease of acquisition and retention of passive avoidance behaviour in adult rats following single neonatal hydrocortisone administration.* Rev. Roum. Physiol., 1973, **10**, *3*, 251–259.
14. Hyden, H., *The Neuron.* Elsevier, Amsterdam, 1967.
15. Oja, S.S., *Protein and nucleic acid metabolism of aging brain. Chemical and methodological aspects.* 4th European Symp. on Basic Research in Gerontology, Varberg, 1973, p. 16.
16. Groth, D.P., Bain, J.A., Pfeiffer, C.C., *The comparative distribution of ^{14}C labeled DEAE and choline in the mouse.* J. Pharm. Exp. Therap., 1950, **1**, *28 A*, 122.
17. Tower, D.B., *Glutamic acid-metabolism in the mammalian central nervous system.* 3rd Symp. Biochem. of the Central Nervous System. F. Brücke, Pergamon Press, 1959, p. 213–250.
18. Boulanger, P., *Traité de biochimie générale*, Masson, Paris, 1959, p. 1368–1370.

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MACROPHAGES MIGRATION INHIBITION AS EVALUATING PARAMETER OF CELL IMMUNITY IN THE AGING PROCESS. THE INFLUENCE OF ASLAVITAL TREATMENT

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Summary. The present paper aims at studying the macrophage behaviour under the influence of the migration inhibition factor secreted by sensitized lymphocytes, in relation to age and under the action of Aslavital treatment. The experiments were made on young and old male Wistar rats in several experimental types.

The results obtained underline the following points of view:

— Inhibition in the migration of peritoneal macrophages decreases as Wistar male rats grow old.

— Aslavital treatment maintains in old animals' macrophages a response to the migration inhibition factor comparable with that in young animals.

Lymphocytes, activated by a series of soluble or particled antigens, elaborate substances known under the name of lymphokynes, which are lymphocytary effectors having different biological effects.

The lymphokynes system represents an important step expressing cell sensitiveness.

Lymphocytes and macrophages agglomeration in the area where the antigen has been introduced is the result of chemotactic lymphokynes release by the first lymphocytes which come into contact with the antigen, as well as of the migration inhibition factor that hampers subsequent dispersion of immunologically implicated cells [1].

Macrophages play an important role in a series of immunological reactions: they are involved in the cooperation between T and B lymphocytes, can secrete a number of active substances, some of which are involved in the genesis of inflammatory processes and participate in the rejection phenomena of grafts and tumours. At present, they are considered to be responsible for an immunoregulatory action demonstrated by a suppressive effect on T lymphocytes.

Our present paper aims at studying the peritoneal macrophages behaviour in Wistar rats under the influence of the migration inhibition factor secreted by sensitized lymphocytes, as an evaluating parameter of cell immunity at different ages and under the influence of Aslavital treatment.

MATERIAL AND METHOD

The experiments were made on 120 Wister rats, aged 4–6 and 24–28 months. The old rats were divided into two groups: control and treated with Aslavital. Aslavital treatment was administered as follows:

(1) Intensively two months before sacrification, according to the following procedure: two weeks daily 4 mg/kg body weight, two weeks pause.

(2) Three times a week 4 mg/kg body weight in series of 12 injections, with a month pause between the series, the treatment beginning when the animals are 14 months old.

ANIMALS IMMUNIZATION

The animals were sensitized by intradermic inoculation of BCG vaccine (produced by "Dr. I. Cantacuzino" Institute) with 5×10^{-4} g BCG/kg body weight, chosen as a dose which produces maximum inhibition of peritoneal macrophages migration in young animals. The skin test was made using 10^{-5} ovalbumin and PPD (a protein purified from *Mycobacterium tuberculosis*, without phenol, in "Dr. I. Cantacuzino" Institute).

LYMPHOCYTES CULTIVATION FOR THE MIGRATION INHIBITION FACTOR (MIF) PRODUCTION

Cells were obtained by lymph nodes dissociation 21 days after the animals' immunization in RPMI-1640 (Gibco Bio-Cult) medium enriched with autologous serum (inactivated at 56°C for 30 minutes) in which 100 U.I./ml penicillin, pH = 7.2—7.4 was added. Viability was determined by colouring with trypan blue. Cellular suspension having a density of 10^7 cells/ml medium was cultivated for 24 h at 37°C in double samples, with antigen (100 g BCG/ml) and without antigen (control). After centrifugation for 15 minutes at 2500 g the supernatant was obtained and dialysed in RPMI-1640 medium. It was tested to control MIF [2].

OBTAINING PERITONEAL MACROPHAGES

The peritoneal exudate cells were obtained from non-immunized animals by washing the peritoneal cavity with PBS (phosphate buffered isotonic saline). After centrifugation they were reduced to a concentration of 10^8 cells/ml and were resuspended in RPMI-1640 medium in which 10% autologous serum was added.

Cell migration inhibition was carried out using the capillary tube method [3]. It was noticed in the presence of non-related BSA (bovine serum albumin) antigen, PPD 100 μg/ml medium and BCG 50 μg/ml culture medium.

The migration areas were microscopically delimited, copied on Whatman paper, cut up and weighed [2].

Each experiment was carried out in 6 samples, standard deviation (SD) and the migration index were calculated (Im = Area × / Control area × 100) [4].

RESULTS AND DISCUSSION

In order to observe the level at which changes in the aging process take place (lymphocyte or macrophage), we examined the inhibition in the peritoneal macrophage migration under the following experimental conditions:

(A) Peritoneal macrophages of young animals (4—6 months) in the presence of lymphokynes produced by old animals' lymphocytes (24—28 months).

(B) Macrophages of young animals under the action of lymphokynes produced by old animals' lymphocytes treated intensively with Aslavital.

(C) Macrophages of young animals under the action of lymphokynes produced by old animals' lymphocytes treated with Aslavital for a long time.

(D) Macrophages of old animals and lymphokynes of young animals.

(E) Macrophages of old animals treated intensively with Aslavital and lymphokynes of young animals.

(F) Macrophages of old animals treated with Aslavital for a long time and lymphokynes of young animals.

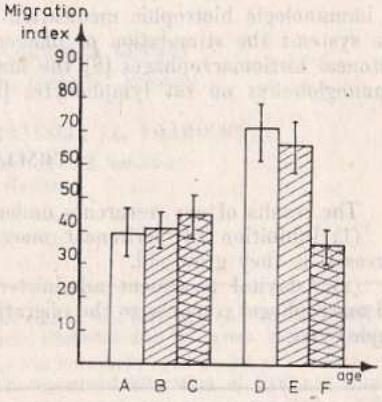

Fig. 1. — Peritoneal macrophages migration in male Wistar rats depending on age and Aslavital treatment.

A, Macrophages of young animals (4—6 months) + lymphocytes of old animals (24—28 months); *B*, macrophages of young animals + lymphocytes of old animals treated intensively with Aslavital; *C*, macrophages of young animals + lymphocytes of old animals treated with Aslavital for a long time; *D*, macrophages of old animals + lymphocytes of young animals; *E*, macrophages of old animals treated intensively with Aslavital + lymphocytes of animals aged 6 months; *F*, macrophages of old animals treated for a long time with Aslavital + lymphocytes of young animals.

Our results point to the fact that macrophages are affected by the aging process. When we observed the reaction of young animals' macrophages to lymphokynes produced by old animals' lymphocytes, the migration index had a considerably lower value in comparison with the old macrophage — young lymphocyte system (Im = 39.81 as against 70.88), which means that in the first case a significant inhibition takes place in the macrophages migration.

Similar values were obtained when old lymphocyte donors were treated with Aslavital in the two variants (Im = 45.35 and 41.21; Fig. 1, *B* and *C*).

When Aslavital treatment was administered to old macrophage donors, the migration index reached the values obtained for young animals, being more obvious in the cases when Aslavital treatment was administered for a long time starting with 14-month-old animals (Fig. 1, *F*).

The fact is known that the interaction between the migration inhibition factor and the macrophage takes place at the level of specific receptors in the cell membrane. These are glycoproteic receptors, the glucidic part being represented by L-fucose, and have the ability of re-forming after having been experimentally eliminated [5].

Our results might be explained by reduction of either the receptors for MIF on the membrane of old animals' macrophages or of the number of cells that carry these receptors.

Peritoneal macrophages represent a heterogeneous population from the morphologic and functional points of view. By centrifugation in the gradient we obtained subpopulations that differed from each other according to their ability to bind antigens, to induce antibody synthesis by B lymphocytes through intracellular identification of the antigen and its metabolization, resulting in the formation of ARNi antigen complexes [6].

The extent to which a macrophage population becomes implicated in the immune response depends on the activity and relation existing at a certain

time between different subpopulations. The decrease in the population carrying receptors for MIF may be the result of the differentiation and maturation of these cellular traits occuring with age.

Czlovkowska and Korlak [7] showed a decrease of cell mediated immunity with persons over 60, expressed by the inhibitive test of blood leucocyte migration.

Researches carried out in our Institute pointed out a decreased action of the immunologic biotrophic medication upon some components of the immunologic system: the stimulation of phagocytosis capacity of blood leucocytes and peritoneal histiomacrophages [8], the maintenance of a high rate of receptors for immunoglobulins on rat lymphocytes [9].

CONCLUSIONS

The results of our researches underline the following points of view:

(1) Inhibition of peritoneal macrophages migration in Wistar male rats decreases as they grow old.

(2) Aslavital treatment administered to old animals re-establishes peritoneal macrophages response to the migration inhibition factor secreted by sensitized lymphocytes.

Résumé. Ce travail repose sur l'étude du comportement du macrophage sous l'influence du facteur d'inhibition de la migration, sécrété par les lymphocytes sensibilisés, en fonction de l'âge et sous l'action du traitement à l'Aslavital. Les expériences ont été effectuées sur des rats Wistar mâles jeunes et âgés, en plusieurs variantes expérimentales.

Les résultats des recherches ont révélé les aspects suivants:

— L'inhibition de la migration des macrophages du péritoine décroit avec l'âge chez les rats Wistar mâles.

— Le traitement à l'Aslavital maintient chez les macrophages des animaux âgés une réponse au facteur d'inhibition de la migration comparable à celui des animaux jeunes.

REFERENCES

1. Robert T. McCluskey, Paul D. Leber, *Mechanisms of Cell-Mediated Immunity*. Robert T. McCluskey (Ed.), Stanley Cohen, 1974, p. 1—25.
2. G. Şandru, *A leukocyte migration inhibition assay technique using blood clot fragments in vitro*. Europ. J. Immunol., 1975, *5*, *10*.
3. J.R. David, R.A. David, *In Vitro Methods in Cell-Mediated Immunity*. B.R. Bloom and P.R. Glad (Eds.), Academic Press, New York, 1971, p. 249.
4. Heinz G. Remold, Anne B. Katz, Edgar Haler, John R. David, *Studies on MIF: Recovery of MIF activity after purification by gel filtration and disc electrophoresis*. Cell. Immunol., 1970, *1*, 133—145.
5. John R. David, Heinz G. Remold, *Immunobiology of the Macrophage*. David S. Nelson (Ed.), Academic Press, New York, 1976, p. 401—423.
6. Howard J.G., *Mononuclear Phagocytes*. R. Van Furth (Ed.), Blackwell, Oxford, 1970, p. 178—199.
7. Anna Czlovkowska, Janina Korlak, *The immune response during aging*. J. Immunol., 1979, **34**, *1*, 9—13.
8. A. Aslan, L. Bălan, S. Brătianu, A. Vrăbiescu, *Investigations on the endocytosis function of peritoneal histiomacrophages in cultures under the influence of Gerovital H_3 and Aslavital*. Proceedings Basic Gerontology, Varberg, 1973, p. 53.
9. M. Manciulea, V. Gheţie, T. Ionescu, *Variation of Fc receptor bearing spleen lymphocytes in rats of different ages following Gerovital H_3 and Aslavital treatment*. VII-th European Congress of Clinical Gerontology, Neptun (Mangalia), Romania, 1977.

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ANTIALBUMIN ANTIBODIES IN OLD AGERS AND THE INFLUENCE OF BIOTROPHIC TREATMENT WITH GEROVITAL H_3

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Summary. The presence of antialbumin antibodies (AAA) was investigated by immunodiffusion in the sera of 415 subjects aged 40 to 90 years, clinically free of overt hepatic diseases.

An increased incidence of AAA (30—40%) was noticed in aged people as compared with healthy young adults (9—16%) suggesting an age-dependent alteration of liver cell function.

The AAA incidence was significantly reduced by Gerovital H_3 treatment, i.e. 22% in the 116 treated individuals comparatively with 32% in the 299 untreated ones.

INTRODUCTION

In 1974 a new category of antibiodies was demonstrated in sera of patients with hepatic diseases [1]. This observation was due to the reaction obtained in immunodiffusion between sera from normal animals and sera from hepatic patients. It was demonstrated that the reaction takes place between the albumin polymers of high molecular weight in the animals' sera and immunoglobulins (especially IgM) in the patients' sera. These antibodies were denominated antialbumin antibodies (AAA) and their presence in the serum was specifically associated with the presence of liver cell dysfunction. Considering the important role played by the hepatocyte in albumin metabolism, the liver specificity of AAA suggested that liver cell disturbances of most different etiology induce AAA synthesis [2, 3].

The correlation found between presence of AAA and alteration of the biochemical and immunological parameters reflecting liver cell membrane injury allowed the localization of the pathogenic mechanism at this cellular level [4]. Liver cell receptors specific to the binding of modified albumin molecules (polymerized by aging or glutaraldehyde treatment) and not of the monomeric, native ones, were demonstrated in rabbits and it was assumed that these receptors have a role in the catabolism of serum albumin [5]. Thus, a dysfunction of these receptors or thier numeric reduction leads to a decreased albumin catabolism and to an increased concentration of circulating aged serum albumin molecules. These molecules bearing specific new antigenic determinants [6] are recognized as non-self and elicit AAA synthesis.

In this paper, considering the hepatic substrate of the occurrence of autoantibodies in aged individuals [7—10], we attempted an estimation of the hepatocellular function in this population using the AAA test.

MATERIAL AND METHODS

The study was carried out in 415 sera obtained from subjects aged 40 to 90 years, subsequently grouped by decade of age and sex. These subjects were clinically free of any sign of hepatic disease. Of these, a total of 116 had previously received a prophylactic treatment with Gerovital H_3: 1 ampoule in intramuscular injections 3 times a week (12 injections in 4 weeks). The cure had been repeated after intervals of 1—2 months.

The sera obtained from both groups of subjects (treated and untreated) were stored at —20°C prior to examination.

The AAA, respectively the antialbumin precipitins (AA-P) were detected by immunodiffusion, according to the method described by Lenkei and Gheţie [11].

RESULTS AND DISCUSSION

An increased incidence of AA-P (30 to 40%) was noticed in the untreated subjects investigated (40—90 years) compared with that previously recorded in young healthy adults [12]. Previous results regarding the distribution of AA-P incidence by sex and age showed that in women the incidence increased with age, whereas in men the level remained approximately constant [13].

As many studies confirmed the diagnostic value of AA-P for liver cell dysfunction [3, 4, 12], the increase with age of these antibodies reflects subclinical hepatocyte injury which probably appears in time as a result of complex infectious, metabolic and toxic aggressive factors.

It should be noted that the incidence of hepatitis B surface antigen (HBsAg) was low, no correlations being noticed between AA-P and HBsAg presence in untreated as well as in Gerovital H_3 treated individuals [13]. These results seem to contradict previous data obtained in young adults in whom highly significant correlations have been registered between AAA and HBsAg [14, 15]. A recent investigation carried out in 1063 apparently healthy persons aged 1 to 90 years showed that the significant correlations registered between HBsAg and AAA in subjects under the age of 40 years gradually disappear after this age [16]. In the same study it was also observed that while lower in men than in women, AA-P incidence increased steadily with age. Thus, it is highly probable that while in children and young adults hepatitis B virus is the main etiologic agent leading to liver cell lesions, in aged subjects the factors inducing liver cell dysfunction are different and seem to be more active in rural than in urban areas, especially for men.

Other studies supporting a slow process, in time, of liver fibrosis refer to another liver cell receptor specific to IgA polymerized molecules (not recognizing the monomeric ones) which was assumed to play a role in IgA catabolism [17]. It is well known that IgA concentration increases with age and also in liver cirrhosis [18]. Therefore presence of AA-P and of raised IgA concentration both in aged subjects and in young cirrhotics may reflect alterations of hepatocyte membrane receptors induced by a process of fibrosis.

Gerovital H_3 treatment decreased the AA-P incidence in both sexes. Thus, the AA-P incidence was 32.2% in the 299 untreated subjects and 22.6% in the 116 subjects prophylactically treated with Gerovital H_3, the mean age being similar in both groups (Table 1).

Age and sex distribution of the Gerovital H_3 treated subjects as well as AA-P incidence are presented in Table 2.

Table 1

Incidence of antialbumin-precipitins (AA-P)

Sex	No. cases	Mean age	AA-P (%)
A. Males	120	66.6	31.09
Females	179	62.9	32.9
TOTAL:	299	64.75	32.1
B. Males	39	65.32	23
Females	77	64.85	22.7
TOTAL:	166	65.–	22.6

A — Untreated
B — Treated with Gerovital H_3

Table 2

Age and sex distribution of 116 clinically healthy subjects, treated with Gerovital H_3. AA-P presence according to sex and age

Sex	Age (years)	Number of cases				
		41–50	51–60	61–70	71–80	81–90
Females		10(0)*	15(3)	20(6)	18(5)	14(3)
Males		8(0)	6(2)	9(4)	8(3)	8(0)
	TOTAL:	18(0)	21(5)	29(10)	36(8)	12(3)

* In brackets number of AA-P positive cases.

As may be seen in Table 2, the long-term treatment with Gerovital H_3 clearly decreases AA-P incidence with age in both sexes and particularly in men. The number of cases is small, so that other studies are necessary to confirm the present observations. Mention must be made of the fact that our research work still continues.

This reduced AA-P incidence in Gerovital H_3 treated subjects reflects an improvement of liver cell function probably associated with the general eutrophic effect of this drug noticed by Aslan in the aged organisms [19]. The anabolic action of Gerovital H_3 was demonstrated in clinical studies in which the nitrous balance was proved to become positive in treated aged people [19]. The treatment also corrected the dysproteinemia of old individuals [20, 21].

Experimentally it was found that the regeneration of the hepatic tissue was stimulated in old animals by treatment with Gerovital H_3. Stimulation of tissular

regeneration was also clearly shown in studies estimating the quantitative variations of nucleic acids during hepatic regeneration [22]. Gerovital H_3 has also a favourable effect on the connective tissue as revealed by experimental studies regarding the collagen fibers in hepatic cirrhosis and rat tail [23, 24]. A decrease of the connective invasion in the liver has been described in the cases treated with Gerovital H_3 over long periods of time.

An improvement in cell membrane function was recently shown in studies carried out in old rats in which the proportion of Fc receptor bearing lymphocytes was 44% in animals treated with Gerovital H_3 as compared with the untreated ones in whom it was only 20% [25].

Based on these data it may be assumed that long-term treatment with Gerovital H_3 decreases the deterioration of cell structures and prevents fibrosis, concomitantly maintaining a high percentage of receptors on cell membranes.

CONCLUSIONS

The incidence of AA-P increases with age.

The long-term treatment with the biotrophic product Gerovital H_3 has a beneficial effect by lowering the AA-P incidence, thus maintaining homeostasis in old agers.

Riassunto. Allo scopo di stabilire l'incidenza degli anticorpi antialbumina polimerizzata (AAA), abbiamo fatto delle ricerche su 415 soggetti gruppati secondo il sesso e l'età — per decenni — avendo fra 40 e 90 anni.

Abbiamo costatato un'alta frequenza degli AAA (30—40%) ai detti soggetti in relazione agle adulti giovani (9—16%). Per quanto riguardano le donne, abbiamo osservato una tendenza di aumentare dell'incidenza degli AAA coll'avanzare dell'età, mentre per gli uomini il livello si mantiene pressappoco costante.

Paragonando i dati riguardanti i fenomeni autoimmunitari messi in evidenza sul gruppo testimone con i dati ottenuti sul gruppo trattato con Gerovital H_3 abbiamo costatato una differente incidenza dei fenomeni auto-immunitari per i soggetti che hanno seguito il tratamento biotrofico di lungo periodo.

L'incidenza degli AAA viene ridotta in modo significativo per i soggetti del gruppo trattato con Gerovital H_3 (22% in relazione al 32% per il gruppo testimone).

REFERENCES

1. Lenkei R., Mota G., Dan M.E., Laky M. (1974), *The polymerized albumin and anti-albumin autoantibodies in patients with hepatic diseases.* Rev. Roum. Biochim., **11,** 271—276.
2. Lenkei R. (1978), *Anti-albumin antibodies in chronic hepatitis and cirrhosis.* Thesis, Bucharest.
3. Cheta D., Lenkei R., Mihăescu S., Mihalache N., Ionescu-Tîrgoviște C., Popescu E. (1979), *Immunological study of liver diseases in diabetics.* Rev. Roum. Méd. — Méd. Int., **17,** 59—66.
4. Lenkei R., Buligescu L., Belaşcu I., Pospai D., Dobre I. (1980), *Anti-albumin antibodies in chronic liver diseases. Diagnostic significance of these antibodies in patients with conventional or immunosuppressive therapy.* Clin. Exp. Immunol. In press.
5. Lenkei R., Onică D., Gheție V. (1977), *Receptors for polymerized albumin on liver cells.* Experientia, **33,** 1046—1047.
6. Onică D., Lenkei R., Gheție V. Immunochemistry, **15,** *of glutaraldehyde-treated homologous albumin in rabbits.* (1978), *Immunogenicity* 687—693.

7. Rowley M.J., Buchanan H., Mackay I.R. (1968), *Reciprocal change with age in antibody to extrinsic and intrinsic antigens.* Lancet, **2**, 24–26.
8. Waldorf D.S., Willkens R.F., Decker J.L. (1968), *Impaired delayed hypersensitivity in an aging population. Association with antinuclear reactivity and rheumathoid factor.* J. Amer. Med. Ass., **203**, 831–834.
9. Mackay I.R. (1972), *Ageing and immunological function in man.* Gerontologia, **18**, 285–304.
10. Roberts-Thompson I.C., Whittingham S., Younghaiyud V., Mackay I.R. (1974), *Ageing, immune response, and mortality.* Lancet, **2**, 368–370.
11. Lenkei R., Gheţie V. (1977), *Methods for detection of anti-albumin autoantibodies in hepatic disorders.* J. Immunol. Methods, **16**, 23–30.
12. Lenkei R., Babeş V.T., Buligescu L., Dobre I. (1976), *Antipolymerized albumin antibodies — a test for the evaluation of hepatic function in HBsAg-positive subjects.* Rev. Roum. Méd. – Virol., **27**, 246–252.
13. Aslan Ana, Ionescu Theodora, Manciulea Mioara, Lenkei Rodica (1980), *Autoimmune phenomena in the elderly.* Rom. J. Geront. Geriatrics, **1**, 133–141.
14. Lenkei R., Babeş V.T., Dan M.E., Mustea A., Dobre I. (1977), *Correlations between antialbumin antibodies and HBsAg in hepatic patients.* J. Med. Virol., **1**, 29–34.
15. Lenkei R., Babeş V.T., Mustea A., Dobre I. (1979), *Deeper insight into HBsAg-antialbumin antibody correlations.* J. Med. Virol., **4**, 137–145.
16. Lenkei R. (1980) *A new antigen/antibody system — the polymerized albumin and antialbumin antibodies.* Rev. Roum. Méd. – Méd. Int., **18**, 129–147.
17. Hopf U., Brandtzaeg P., Hütteroth T.H., Meyer zum Büschenfelde K. H. (1978), *In vivo and in vitro binding of IgA to the plasma membrane of hepatocytes.* Scand. J. Immunol., **8**, 543–549.
18. Feizi T. (1968), *Immunoglobulins in chronic liver disease.* Gut, **9**, 193–211.
19. Aslan A. (1956), *Eine neue Methode zur Prophylaxe und Behandlung des Alterns mit Novokain-Stoff H_3 — eutrophische und verjüngernde Wirkung.* Therapiewoche, 1/2, 14–22.
20. Aslan A. (1962), *The therapeutics of old age. The action of procaine — clinical and experimental conclusions,* in *Medical and Clinical Aspects of Ageing,* Ed. H.T. Blumenthal, vol. 4, p. 272–292.
21. Kurth H. (1961), *Klinische Studien über die Novokaintherapie arteriosklerotischer Patienten.* Z. Ges. Inn. Med., **20**, 879–885.
22. Naum M., Rusu C. (1973), *Variation of nucleic acid and histones in hepatic regeneration of the Wistar white rat in relation to age and the biotrophic treatment with Aslavital.* 4th Intern. Sympos. of Basic Res. in Geront. Varberg, Sweden.
23. Aslan A., Cîmpeanu Ş., Vrăbiescu Al., Domilescu C. (1965). *Über die experimentelle Leber-Zirrhose der weißen Wistar-Ratten unter Einfluß der Behandlung mit Gerovital H_3.* Intern. Conf. on Geront., Akadémiai Kiadó, Budapest, p. 88–92.
24. Aslan A., Vrăbiescu Al. (1965), *A study of the evolution in regard to age of certain physical constants of collagen.* Gerontologia, **11**, *1–2*, 34.
25. Manciulea M., Gheţie V., Ionescu Th. (1977), *Fc receptors from rat spleen lymphocytes in correlation with age and Gerovital H_3 or Aslavital treatment.* Comm. 8th Europ. Congr. Clinical Gerontology, Neptun, Romania, p. 186–191.

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ENZYMOLOGICAL FINDINGS CONCERNING THE ACTION OF GEROVITAL H_3 ON MONKEY KIDNEY CELL CULTURES

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Summary. The activity of acid phosphatase was determined according to Fiske-Subbarow method. The Gerovital H_3-treated cultures had a significantly lower activity than the non-treated controls. In senescent cells this difference is more obvious and proves the biostimulation of the metabolic function as well as the stabilization of the lysosomal membrane induced by Gerovital H_3.

In this experimental model Gerovital H_3 inhibits the activity of acid phosphatase, or prevents the release of this lysosomal hydrolase maintaining the integrity of cell membranes.

Much information has accumulated over the years on the aging of the human being; the proggressive development of researches in this field is due to the accumulation of new data and improved technique. Although the changes of parenchymatous cells in different tissues, the result of advancing age, have been thoroughly studied, it is still difficult to distinguish between the physiological and pathological aging processes.

The concept of aging has recently gained a new meaning, because it partly reflects the effects of stress on cells and tissues. The process of aging seems to result from impairment of the normal morpho-functional balance by metabolic biochemical and bioelectrical disturbances consisting in either lack or excess of enzymes, ions or free radicals, imbalanced colloidal phenomena which may occur even before the overt structural changes.

At present, cell cultures are used on an ever larger scale in researches aimed at solving the major problems of cell biology; however, the mechanisms which produce aging of the cell are not yet perfectly understood.

The basic processes insuring the viability of the cell are identical *in vivo* and *in vitro*, including the energy and biosynthetical processes. Macromorphology is entirely based on constitutional micromorphology, which in turn is determined by the enzymatic systems conditioned by the nucleic acids, DNA and RNA. Biochemical factors, strictly controlled by the genetic information furnished by the DNA molecule, are involved in the anatomoclinical processes.

We investigated the enzymatic activity of acid phosphatase and lactic dehydrogenase in kidney cell cultures obtained from *Cercopithecus* monkeys and followed up concomitantly the *in vitro* influence of the biotrophic treatment with Gerovital H_3, on the activity of these enzymes of particular importance for cell metabolism.

MATERIAL AND METHOD

Cell cultures. The study was performed on *Cercopithecus* kidney cells supplied by the "Cantacuzino" Institute. The cells were cultured in neutral glass flasks of the Roux type.

The suspension used was an average concentration of 2.5×10^5 cells/ml of IC^{65} culture medium supplemented with 10% calf serum and 0.08% Gerovital H_3.

BIOCHEMICAL DETERMINATION OF ACID PHOSPHATASE

The activity of acid phosphatase was determined according to the Fiske-Subbarow method, based on the quantitative determination of inorganic phosphorus released during the phosphorylation reaction catalysed by the enzyme.

The cells were detached from the glass at 7, 14 and 21 days by means of a 0.25% trypsin solution which was used for 15 minutes at 37°C. After detaching the cells, trypsin was washed off with normal saline. The suspension was centrifuged for 10 minutes at 1000 rpm and the cells were washed twice more with normal saline. After washing, the medium used for the extraction of the enzyme was added in a ratio of one part suspension to ten parts extraction medium. Extraction was done with acetic acid-acetate buffer, pH 5.2. Triton × 100 was then added and the mixture homogenized mechanically in the cold. In order to obtain complete extraction of the proteins soluble in the buffer solution, the mixture was allowed to stand for one hour at 4°C. The supernate representing the total protein extract, in which phosphatase activity was determined, was obtained by centrifugation of the homogenate for 20 minutes at 7000 rpm at 4°C.

The enzyme solution, together with the beta-glycerophosphate substrate, in the presence of acetic acid-acetate buffer, was incubated for 30 minutes at 37°C. The enzymatic reaction was arrested with trichloroacetic acid. A solution of 2.5% ammonium molybdate in 5 N sulphuric acid and a reducing solution of eiconogen was then added. The inorganic phosphorus released in the reaction was measured colorimetrically at 660 nm. Enzymatic activity was expressed as Pi released in the reaction.

BIOCHEMICAL DETERMINATION OF LACTIC DEHYDROGENASE

The activity of lactic dehydrogenase was determined by assessing the concentration of $NADH_2$ and its variation in time, permitting direct measurement of the reduction of pyruvate to lactate.

Proteins were extracted with 0.01 M NaCl at 4°C. Enzymatic activity was determined in the supernate obtained by centrifugation for 30 minutes at 7000 rpm. The reaction mixture consisting of 0.01 M sodium pyruvate pH 7.3 and the enzymatic solution was prepared in the spectrophotometer cuvette. Readings were taken every 30 seconds for 3 minutes at 340 mm with a Zeiss spectrophotometer.

The specific activity was expressed in units per mg of protein.

Protein concentration was determined according to the Lowry method.

One enzyme unit is defined as the quantity of enzyme protein capable of furnishing an oxidation rate of one micromole $NADH_2$ per minute.

RESULTS AND DISCUSSION

Since 1945, Ana Aslan has applied her procaine-based therapy against the aging phenomenon because "the process of aging can be influenced not only by hygienic steps but also by substances that influence cell anabolism" [1]. Research work concerning the effect of procaine on cells showed that it is involved in the synthesis of nucleic acids and in cell metabolism. In 1948 Richterich [2] pointed out the influence of procaine on glycolysis in the Krebs cycle, as well as on oxidative phosphorylation.

Researches carried out by Aslan et al. [3] on cell cultures demonstrated a 16% increase of postmitotic life span in monkey kidney cells, as well as a 22.4% increase in tritium thymidine uptake.

Biochemical determination of acid phosphatase and lactic dehydrogenase activity as well as electron microscopic studies [4] of *Cercopithecus* kidney cell cultures furnished new data on the mechanism of action of Gerovital H_3.

Investigations on enzymatic activity were performed at various intervals, testing the activity at 7, 14 and 21 days both on control cultures and on Gerovital H_3-treated cultures.

Fig. 1 shows the low value of acid phosphatase activity in 7-day-old cultures, an increased activity at 14 days, followed by a decrease at 21 days, although the value at this time is higher than that at 7 days.

The curve showed a similar aspect both in the controls and in the Gerovital H_3-treated cultures, although the treated cultures had a significantly lower activity ($p < 0.01$) than the non-treated control. The more advanced the age of the cells, the more significant the difference.

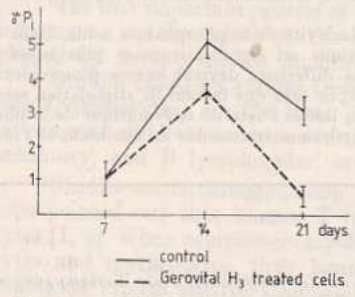

Fig. 1. — Acid phosphatase activity in monkey kidney cells.

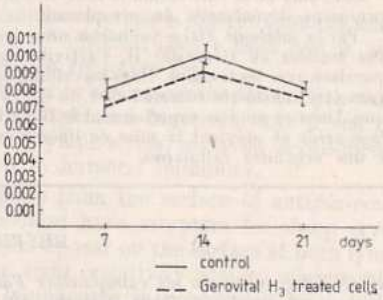

Fig. 2. — LDH activity in monkey kidney cells.

The results of our research tally with Officer's data [5], according to which cultured Gerovital H_3-treated mouse fibroblasts last longer than the controls; they also agree with Baker's finding that Gerovital H_3 maintains the elasticity of the erythrocyte membrane [6].

At present, enzymological techniques are used in investigating cellular metabolic activity. Acid phosphatase and lactic dehydrogenase have been chosen because they are involved in glucide and phosphorus metabolism. Another reason for studying acid phosphatase was its lysosomal localization.

Recent studies [7] confirmed the increased number of lysosomes and autophagic vacuoles in the senescent cell.

The results of our research are consistent with the data which point out the increased activity of lysosomal enzymes in senescent diploid cells. It was demonstrated the accumulation of lysosomal enzymes within the human WI-38 strain of foetal diploid cells, which can produce breakage of the genetic pool [7].

The increased acid phosphatase activity in senescent cells can be explained like that of beta-glucuronidase, by a series of mechanisms, such as the increased permeability of lysosomal membrane with advancing age, which allows a rapid release of large amounts of enzymes in the cytoplasm.

The activity of LDH was studied at the same time intervals (7, 14 and 21 days). At 14 days an increase in the specific activity of this enzyme was noted, followed by a decrease at 21 days. The differences noted between the control (non-treated) cultures and the cultures treated with Gerovital H_3 were non-significant (Fig. 2).

CONCLUSIONS

Gerovital H_3 acts on the cell membrane, particularly on the lysosomal membrane and stabilizes its physiological potential.

Gerovital H_3 inhibits the acid phosphatase activity and/or prevents the release of this lysosomal enzyme into the cytoplasm.

The biochemical data are consistent with the electron microscopic findings obtained in researches on *Cercopithecus* kidney cell cultures.

Résumé. En vue d'expliquer le mécanisme par lequel le Gérovital H_3 agit au niveau cellulaire, les auteurs ont entrepris des recherches enzymatiques.

Au cours de la cultivation la mise en liberté des hydrolases lysosomales pourrait précéder les processus dégénératifs du cytoplasme.

Par la méthode Fiske-Subbarow on a évalué l'activité de la phosphatase acide. Dans les cellules traitées au Gérovital H_3 l'activité enzymatique est significativement plus basse en comparaison avec les témoins. Dans les cellules âgées la différence devient encore plus évidente, pouvant être considérée comme l'effet du Gérovital H_3 en tant que facteur de stimulation métabolique. Dans ce modèle expérimental le Gérovital H_3 inhibe l'activité enzymatique de la phosphatase acide et prévient la mise en liberté de la hydrolase lysosomale en maintenant l'intégrité des organites cellulaires.

REFERENCES

1. Aslan Ana, *Novokain als eutrophischer Faktor und die Möglichkeit einer Verlängerung der Lebensdauer.* Ther. Umsch., 1956, *9*, 167–172.
2. Richterich R., *Enzymopathologie, Enzyme in Klinik und Forschung.* Springer, Berlin, 1958, p. 504.
3. Aslan Ana, Bălan L., Ieremia G., *Aspects of the action of Gerovital H_3 in tissue and cell cultures* (in Romanian). Fiziol. Norm. Patol., 1972, **18**, *1*, 81–88.
4. Aslan Ana, Ionescu Theodora, Răchită Mariana, Tudor Mioara, Andrei Victoria, *Electron microscopic and biochemical findings concerning the influence of Gerovital H_3 on monkey kidney cultured cells.* Abstr. of the Fifth Internat. Congress of Histochem. and Cytochem. Bucharest, 1977, p. 29.
5. Officer J.E., *Gerovital H_3 growth enhancing effect on aged mouse embryo fibroblasts cultured in vitro.* Sympos. Intern. Geront., Bucharest, 1972, p. 547.
6. Baker R., Powars D., Haywood L.I., *Restoration of the deformability of "irreversibly" sickled cells by procaine hydrochloride.* Biochem. Biophys. Res. Commun., 1974, **59**, *2*, 548–556.
7. Cristofalo V.I., in Holecková E., Cristofalo V.I. (Eds), *Aging in Cell and Tissue Culture*, Plenum Press, N.Y., 1970, p. 83.

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ROSETTE-FORMING ABILITY OF HUMAN T LYMPHOCYTES IN RELATION TO AGE AND BIOTROPHIC TREATMENT

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Summary. Using sheep erythrocyte receptors as membrane markers for the T lymphocytes involved in cell-mediated immunity, the authors investigated age-induced changes and the effect of Gerovital H_3 treatment at the level of the T lymphocyte.

Rosette-forming T lymphocite percentage decreases in untreated subjects with advancing age, but keeps close to that of younger ages in Gerovital H_3-treated subjects, as against controls.

The specific and differentiated immune response is the result of various and complex metabolic processes which ensure acknowledgement and processing of antigenic molecules for identifying "antigenic information", its "memorization" and synthesis of effectors specifically reactive to the antigen which triggered their formation.

The first important process of the immune response is antigen immune acknowledgement; it takes place at the surface of antigen-reactive cells and is accomplished by antigen-specific immunoglobulinic receptors [1].

Studies based on various techniques led to the separation of antigen-reactive cells (lymphocytes), on the basis of their origin and functions, into 2 cell populations with different immune reactivity: T lymphocytes, involved in cell-mediated immunity, and B lymphocytes, involved in humoral immunity.

Studies on immunoglobulinic receptors from the surface of antigen-reactive cells pointed out that human T lymphocytes have receptors for sheep erythrocytes [1, 2]. When complementary molecules appear on the surface of both lymphocytes and erythrocytes, their bonds are tight, relatively stable, microscopically visible as typical rosette structures: a lymphocyte is surrounded by a variable number of erythrocytes. It is their rosette-forming ability with sheep erythrocytes that enabled the identification and isolation of human T lymphocytes.

Human B lymphocytes were identified, due to easily detectable immunoglobulins and antigen-antibody complement receptors on the surface of the cell membrane, by rosette-forming with anti-Ig antibody-covered sheep erythrocytes [1, 3].

Because there are data in the field literature which demonstrate the impairment of T and B lymphocytes in the course of aging [4] and also contradictory data on the number of human T lymphocytes [2, 4–8] the authors focused their research on the rosette-forming ability of human T lymphocytes from peripheral blood as the parameter of cell-mediated immunity, in relation to age and biotrophic treatment.

MATERIAL AND METHOD

Rosette-forming ability was tested on circulating T lymphocytes from 100 subjects distributed by age-decades — controls and subjects treated with Gerovital H_3 according to Ana Aslan's method.

ISOLATION OF LYMPHOCYTES

The lymphocytes were isolated from 15—20 ml peripheral blood samples heparinated by centrifugation in density gradient on Ficoll-Natrium metrizoate mixture, density = 1.077 [9]. Separated cells were collected and washed three times in IC_{65} medium ("Dr. I. Cantacuzino" Institute).

The resulting lymphocytes were 95±5% pure and had a 95±5% viability.

PREPARATION OF ERYTHROCYTES

Sheep erythrocytes extracted by venous puncture were kept in Alsever solution 1:2 and prepared to obtain the suspension with concentration = 3.2×10^8 erythrocytes/ml IC_{65} medium.

ROSETTE FORMATION

Rosette formation was accomplished using a mixture which contained 150:1 sheep erythrocytes and lymphocytes [9].

Rosettes were counted microscopically. The samples were embedded in formol 2% and stained with toluidine blue 0.2% in PBS (phosphate-buffered isotonic saline). We considered as rosettes the cells binding at least 4 erythrocytes on their surface.

A minimum of 300 lymphocytes were counted for each sample.

The experiments were conducted in parallel on controls and Gerovital H_3-treated subjects in order to avoid technical errors due to the quality of erythrocytes extracted from different groups.

The results were analysed statistically.

RESULTS AND COMMENTS

Using sheep erythrocyte receptors as membrane-markers for T lymphocytes, which play an important role in T and B cells cooperation in the immune response, the authors investigated the changes induced by age and Gerovital H_3 treatment at the level of T lymphocyte.

The results pointed out the obvious decrease in rosette-forming T cells with the subjects aged 60 to 80 (Table 1).

With Gerovital H_3-treated subjects, the proportion of T lymphocytes remained constantly 67% in all age groups. Our data pointed out an obvious difference in T lymphocyte percentage between controls and Gerovital H_3-treated subjects in the last age-decades (60—70, 70—80) (Fig. 1). In the control group, T lymphocyte percentage decreased, whereas it remained unchanged in the treated group.

The results of this experiment tally with the data from the field literature [2, 4, 5, 10].

As T lymphocytes have been divided into 2 distinct cell subpopulations, helper and suppressor T cells [11], the decrease in T lymphocyte population can

be correlated with either a deficiency of helper or suppressor cells or a defective interrelationship between them.

The deficiency of helper T lymphocytes can cause a decline in the differentiation of antibody-producing B lymphocytes for thymus-dependent antigens.

Table 1

Mean values of circulating T lymphocite percentage in relation to age and biotrophic treatment

Age*	50–60 years	60–70 years	70–80 years
Control	71.54±4.1	60.03±3.25	59.12±4.1
Gerovital H_3	67.90±7.7	67.30±6.7	66.25±5.9

* Each age group contained 15 subjects.

Age-related deficiency of suppressor cells may be correlated with the increase in B lymphocyte clones capable of producing autoantibodies leading to autoimmune diseases. The age-induced increase in autoantibodies was pointed out by data from the field literature and results we published in a previous paper [12].

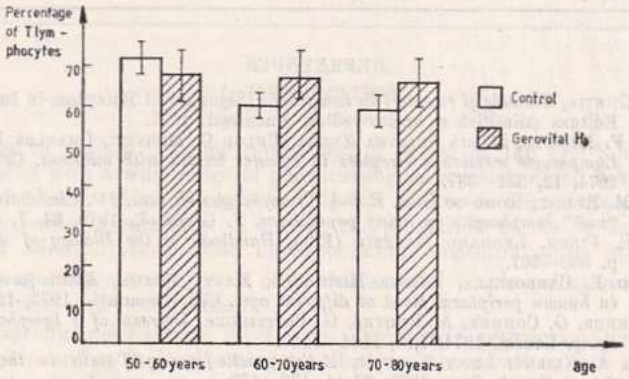

Fig. 1. — Variation of circulating T lymphocyte percentage in relation to age and biotrophic treatment.

With Gerovital H_3-treated subjects a tighter erythrocyte binding by T lymphocyte receptors was noticed, as against controls. Such results suggest the positive influence of the biotrophic treatment with Gerovital H_3 on either the functional condition of membrane receptors, or on the number of T lymphocytes which decreases, triggered by the age-induced atrophy of the thymus.

The above-mentioned data are supported by the results of a previous experiment carried out at the National Institute of Gerontology and Geriatrics, which pointed out that the biotrophic treatment with Gerovital H_3 and Aslavital helped maintaining high percentages of Fc receptor carrier lymphocytes in adult and old

treated rats, comparable to those of young control rats and corrected age-induced changes in Fc^+ lymphoid cells [13].

Taking into consideration the multiple implications of T lymphocytes in cell-mediated immune response and their cooperation with the B lymphocytes in the humoral immune response, the authors envisage a series of studies aiming to point out other lymphocyte subpopulations which could reveal new data on the age-induced modifications of the immune system.

CONCLUSIONS

The results of the present study pointed out that: (1) the percentage of T lymphocytes decreased in controls aged 60–80; (2) the treatment with Gerovital H_3 helped keeping a constant percentage of T lymphocytes in all age groups, higher than in controls.

Résumé. En utilisant les récepteurs pour les érytrocytes de mouton en tant que markers de membrane pour les lymphocytes T, responsables de l'immunité cellulaire médiate, nous nous sommes proposé dans ce travail l'investigation des modifications déterminées par l'âge et par le traitement biotrophique au Gérovital H_3, au niveau du lymphocyte T.

Les résultats obtenus chez les sujets non traités ont révélé une diminution du pourcentage des lymphocytes T porteuses de rosettes E avec l'âge. Par rapport au lot témoin, chez les sujets traités au Gérovital H_3 le pourcentage de lymphocytes formatrices de rosettes E est plus rapproché des jeunes âges.

REFERENCES

1. Victor Gheţie, *Semnale şi receptori în imunologie* (Signals and Receptors in Immunology). Editura ştiinţifică şi enciclopedică, Bucureşti, 1977.
2. Nelson F. Mendes, Maria Juliana Zenha, Chloe C. Musatti, Charles K. Naspitz, *Lymphocyte membrane receptors in cultures treated with mitogens.* Cell Immunol. 1974, **12**, 331–337.
3. Mohan M. Reddy, Kong-oo Goh, *B and T lymphocytes in man. IV. Circulating B, T and "null" lymphocytes in aging populations.* J. Gerontol., 1979, **34**, *1*, 5–8.
4. Caleb E. Finch, Leonard Hayflik (Eds), *Handbook of the Biology of Aging.* 1977, p. 380–401.
5. Edhardo E. Carrosella, Ksenia Mochanco, Marta Braun, *Rosette-forming T cells in human peripheral blood at different ages.* Cell. Immunol., 1974, **12**, 323–325.
6. W. Augener, G. Cohnen, A. Reuter, G. Brittinger, *Decrease of T lymphocytes during aging.* Lancet, 1974, **1**, *8*, 1164–1166.
7. Barbara A. Neilan, Luigi Tadeimi, *Active rosette-forming T cells in the elderly.* J. Amer. Geriat. Soc., 1979, **27**, *4*, 170–173.
8. F.R. Davey, S. Huntington, *Age-related variation in lymphocyte subpopulation.* Gerontology, 1977, **23**, *5*, 381–389.
9. C. Galatiuc, A. Sulica, M. Gherman, *Metodologia caracterizării populaţiilor de limfocite umane* (Methods for characterizing human lymphocytes populations). Timişoara medicală, 1980, *1*,36.
10. A.A. Mac Kinney jr., *Effect of aging on the peripheral blood lymphocyte count.* J. Geront., 1978, **33**, *2*, 213–216.
11. Robert T. McCluskey, Stanley Cohen (Eds), *Mechanism of Cell-Mediated Immunity.* 1974, p. 331–339.
12. Ana Aslan, Rodica Lenkei, Mioara Manciulea, Victoria Andrei, Theodora Ionescu, *Autoimmune phenomena in aged people correlated with Gerovital H_3 and Aslavital therapy.* VIIth European Congress of Clinical Gerontology, Neptun, Romania, 1977.
13. Mioara Manciulea, Victor Gheţie, Theodora Ionescu, *Variation of Fc receptor bearing spleen lymphocytes in rats of different ages following Gerovital H_3 and Aslavital treatment.* VIIth European Congress of Clinical Gerontology, Neptun, Romania, 1977.

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THE SPECIFICITY PROBLEM IN THE MECHANISM OF ACTION OF PROCAINE

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Summary. Clinical and pharmacological studies on procaine suggest different pharmacodynamic mechanisms of the specific as well as nonspecific type. Specific interactions involve a spatial and electronic fit between the drug molecule and the pharmacological receptor. This paper presents some examples of procaine specific mechanisms of action (in the anesthetic, antidepressive, sympatholytic, antiarrhythmic, antihistaminic effects of biotrophic medication) in the light of a theoretical and experimental study of physico-chemical properties of procaine molecule.

Membrane effects, largely manifesting themselves by a nonspecific mechanism are exemplified by the results of experimental studies on the interaction between procaine and erythrocyte membrane.

I. INTRODUCTION

Trying to explain procaine mechanism of action at the systemic level we are confronted with a wide range of pharmacological actions, which have a strong clinical and pharmacological support. This fact makes us accept the presence of different molecular mechanisms of action; the prevalence of one or another is a function of administration, dose, biodisponibility, organism state, etc.

There are two extreme types of mechanisms by which a drug can exert its action: specific and nonspecific.

The specific mechanisms involve an appropriate interaction between the drug molecule and a molecular target; effective concentrations are quite low ($< 10^{-5}$) and significant correlations can be established, in series of analogous drug compounds, between pharmacological actions and physico-chemical properties. In this case we are talking about pharmacological receptors — molecules or complex molecular aggregates of protein nature; despite the various names used for such receptors in pharmacological explanations (adrenergic, nicotinic, muscarinic, histaminic, etc.) their separation and physico-chemical description are far from being completed.

By contrast, nonspecific mechanisms require high drug concentrations and their efficacy generally correlates with the hydrophobicity of compounds.

There are, however, a lot of drugs (procaine included) that combine both types of mechanisms. In the following we shall exemplify by means of procaine, using original results of quantum and molecular experimental pharmacology.

II. SPECIFIC MECHANISMS

The detailed analysis of procaine specific mechanisms of action requires a comprehensive description of physico-chemical properties of the drug molecule; an important role is also played by the information given by quantitative structure-activity relationships (QSAR) on large classes of related compounds.

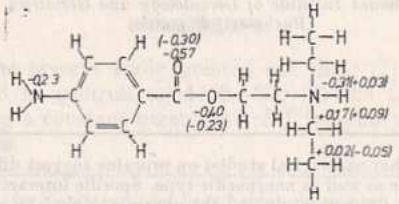

Fig. 1. — Electron charges on some atoms in procaine molecule computed with quantum-mechanical methods EHT and CNDO/2 (values in brackets). The values are in electron units(e).

For the electronic and conformational description of procaine molecule we used quantum-mechanical methods (EHT, CNDO/2) described elsewhere [1, 2] and an experimental method (nuclear magnetic resonance spectroscopy — NMR).

Quantum approximations developed by quantum biochemists describe the valence electron distribution in a molecule using some known empirical parameters; some distinct chemical groups (possible pharmacophores) are therefore pointed out as well as the relative strength of the chemical bonds. By means of an optimization procedure, based on the total electronic energy minimization relative to all dihedral angles around simple chemical bonds, the most probable conformers are obtained [1].

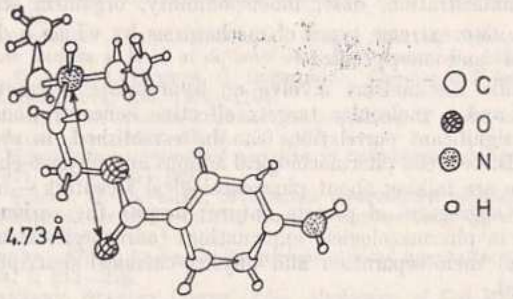

Fig. 2. — The most probable conformer of procaine molecule as determined by theoretical and experimental methods.

Fig. 1 illustrates the electronic charges at the most important atomic centers in procaine molecule, computed by quantum-mechanical methods EHT and CNDO/2 (in brackets). An interesting peculiarity of these results is the diffuse

distribution of the positive charge on the diethylamino group over all the atoms in this group. This aspect is equally described in the trimethyl group of acetylcholine [3]. Another relevant conclusion is the indication of possible pharmacophores: the nucleophilic carbonyl oxygen (which has the most negative charge) and the ester oxygen. The *para*-amino nitrogen has a negative charge; its pharmacological role may be related to the possibility of a resonance effect through the aromatic system [1]. We can postulate, therefore, the existence of three pharmacophores — the diethylamino nitrogen and carbonyl (or ester) oxygen implied in ionic interactions and the benzenic system, important because of its hydrophobic capacity.

Fig. 2 presents the most probable conformation (in water solution) of procaine molecule derived from quantum-chemical computations and a NMR study of the dihedral angle dependence of the coupling constant J. The computed distance between the two possible ionic pharmacophores (the diethylamino nitrogen and carbonyl oxygen) is 4.73 Å.

Now we can discuss some pharmacological data of the biotrophic therapy, taking into account the above electronic and conformational peculiarities.

II.A. LOCAL ANESTHESIA

There are many models of molecular mechanism of local anesthesia [4] based on the hydrophobic interaction between the anesthetic molecule and the axon membrane of the neuron. In the last years several papers were published pointing out the key role played by the specific interaction between the drug and a particular receptor, situated in the sodium channel of the axon membrane. Thus, Hille [5] advances the idea of an anesthetic receptor in the channel, that could be approached by hydrophobic drugs through the lipid phase and by hydrophilic drugs through the aqueous pore. Our most stable procaine conformer may be considered as a "mirror image" of the active site of this receptor (Fig. 3).

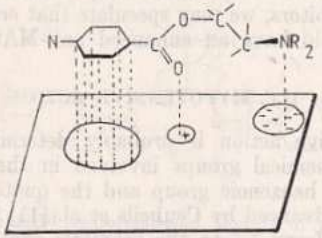

Fig. 3. — Pattern of the anesthetic receptor active site as suggested by the spatial distribution of the anesthetic pharmacophores.

II.B. ANTIDEPRESSIVE ACTION

This clinically well documented action of procaine generally involves its ability of restoring the catecholamine level by reversible, competitive inhibition of monoaminoxidase (MAO) [6]. As shown by Yau [7] and Fuller and Ronsh [8], there is a significant substrate specificity of the *in vitro* inhibition, directed to serotonin. Fig. 4, *1* represents the *trans* conformer of the serotonin molecule. Consi-

dering the competition between procaine and serotonin for the MAO site of action it is surprising to reveal a significant steric fit between the pharmacophores of both compounds. Thus, the distance between the quaternary nitrogen and indole nitrogen (negatively charged) is 4.71 Å in the *trans* conformer of serotonin; the

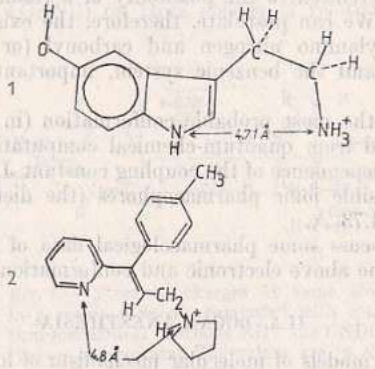

Fig. 4. — *1*, The *trans* conformer of serotonin; *2*, a potent antagonist of the H_1 receptor for histamine.

corresponding distance between the quaternary nitrogen and carbonyl oxygen in procaine is 4.73 Å. A different pattern can be observed in other MAO substrates (example: in adrenaline and noradrenaline the distance between the ternary nitrogen and hydroxyl oxygen is 2.93 Å).

According to a recent study, concerning structure-activity relationships in some series of MAO inhibitors, we may speculate that *ortho*-methyl or *ortho*-metoxi procaine derivatives could have an enhanced anti-MAO potency [9].

II.C. HYPOTENSIVE ACTION

Procaine hypotensive action is probably determined by a sympatholytic mechanism [10]. The chemical groups involved in the action of sympatholytic agents are the aromatic benzenoic group and the quaternary nitrogen (N^+). The sympatholytic pattern advanced by Coubeils et al. [11] is defined by two parameters: D — the distance from N^+ to the aromatic center, and H — the distance from N^+ to the aromatic plane (see Fig. 5), having the optimal values D = 5.42 Å and H = 1.21 Å. In the procaine conformer determined by us the corresponding values are D = 6.1 Å and H = 1.18 Å. This fitness argues for a common mechanism of action.

II.D. ANTIARRHYTHMIC ACTION

Approaching the conformational aspects of some antiarrhythmic drugs, Murphy et al. [12] established a strong correlation between the pharmacological activity of a compound and the distance between the two pharmacophores: the alkyl nitrogen and the ester oxygen. In a series of compounds formed by procaine and

four semi-ridig conformational analogs with a fixed $N^+—O$ distance (Fig. 6, *1—4*), the pharmacological activity increases as this distance increases from 2.9 Å to 4.2 Å. In the *gauche* conformation (relative to the dihedral angle around the ethylenic bond) the $N^+—O$ (ester) distance in procaine is 2.9 Å and in the *trans* confor-

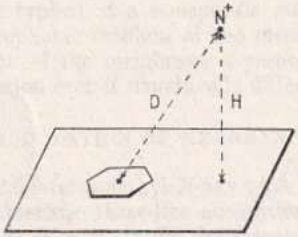

Fig. 5. — The sympatholytic pattern with the two determining parameters D and H.

mation this distance is 3.7 Å. The fact that the procaine antiarrhythmic action is lower than that of other four compounds supports our conclusion concerning the *gauche* preference.

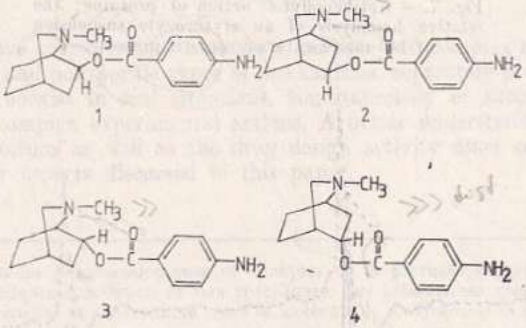

Fig. 6. — Semi-rigid conformational analogs of procaine with antiarrhythmic action.

II.E. ANTIHISTAMINIC ACTION

There are at least two histamine receptors, noted with H_1 and H_2, which differ by their distribution, function, agonist and antagonist affinity. Ganellin (quoted in [13]) showed that a strong antagonist of H_1 receptor (Fig. 4, 2) has a 4.8 Å distance between the quaternary nitrogen and the imidazole nitrogen (with negative charge). Considering that the corresponding pharmacophores in the procaine molecule are N^+ and the carbonyl oxygen, between which the computed distance is 4.73 Å, we can assert that the procaine antihistaminic action is mediated by the H_1 receptor.

III. NONSPECIFIC MECHANISMS

This type of mechanisms are involved in the interaction of local anesthetics with hydrophobic media of natural or artificial membranes. We shall illustrate them with two examples of procaine action on erythrocyte membrane studied in our laboratory.

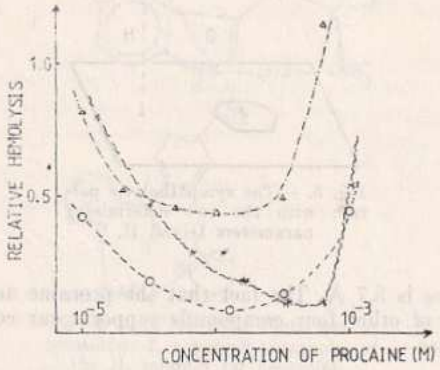

Fig. 7. — Antihemolytic action of procaine; the relative hemolysis of an erythrocyte suspension at 146 mosM external osmotic pressure.

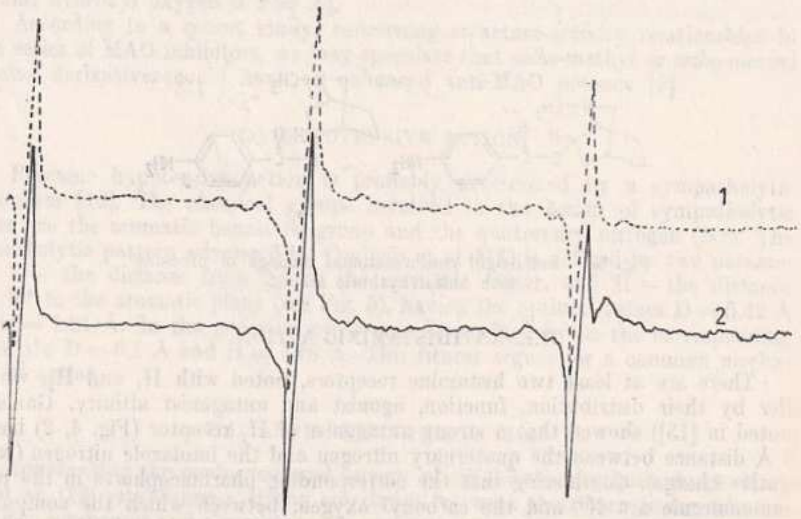

Fig. 8. — The EPR spectrum of TEMPO in an erythrocyte suspension without procaine (dotted line) and with procaine, 1.17 mM (continuous line).

III.A. ANTIHEMOLYTIC ACTION

In a study *in vitro*, using a simple methodology we found that procaine has a protective action against hypotonic lysis of human erythrocytes. In spite of individual variability, a common pattern of the dose-action relationship is observed (Fig. 7). This pattern is typical of a nonspecific mechanism including the drug intercalation in the hydrophobic medium of the membrane hydrocarbonic region. The consequent expansion of the membrane is responsible for the increased stability. Other local anesthetics, even if structurally different, have similar effects [13].

III.B. MODULATION OF MEMBRANE DYNAMICS

The spin label 2,2,6,6-tetramethyl-N-oxy-piperidine (TEMPO) is a stable free radical with a characteristic three-line absorption spectrum of electron paramagnetic resonance (RES) (Fig. 8, *1*). In the presence of erythrocyte suspension its EPR spectrum is unchanged. The presence of procaine (1.17 mM) in the medium induces a solubilization of a fraction of TEMPO molecules in the lipid matrix of the membrane (as indicated by the small shoulder of the third line in the EPR spectrum — Fig. 8, *2*), most probably by a fluidization effect (a decrease in microviscosity) on the membrane. Other anesthetics can also induce the same effect [14] by a common hydrophobic, nonspecific interaction.

IV. CONCLUSIONS

The above considerations indicate a multiple and complex action of procaine. Both specific and nonspecific types of mechanisms, separately presented for clarity reasons, can coexist in real situations, simultaneously or successively, resulting in the very complex experimental actions. A better understanding of pharmacological mechanisms as well as the drug design activity must separately consider the particular aspects discussed in this paper.

Résumé. Les études pharmacologiques et cliniques de la procaïne suggèrent des mécanismes pharmacodynamiques spécifiques et non spécifiques. Les interactions spécifiques comprennent un ajustement spatial et électronique entre la molécule de médicament et le récepteur pharmacologique.

Cet article présente quelques exemples de mécanismes d'action spécifiques de la procaïne (dans les effets anesthésiques, antidépressifs, sympatholytiques, antiarythmiques et antihistaminiques) s'étayant sur des études théoriques et expérimentales des propriétés physico-chimiques de la molécule de procaïne.

Les effets sur la membrane, qui se manifestent, en général, par des mécanismes non spécifiques, sont exemplifiés par les résultats des études expérimentales sur l'interaction de la procaïne avec la membrane érythrocytaire.

REFERENCES

1. Crăescu C.T., M.N. Ţugulea, *A molecular orbital study of the para-substituent effect in benzoic acids*, Rev. Roum. Chim., **24**, 783 (1979).
2. Pople J.A., D.L. Beveridge, *Approximate Molecular Orbital Theory*, McGraw-Hill, London, 1970.

3. Pullman A., G.H. Post, *An ab initio SCF molecular orbital study of acetylcholine*, Theoret. Chim. Acta, **32**, 77 (1973).
4. De Jong R.H., *Physiology and Pharmacology of Local Anesthesia*, Ch. C. Thomas, Springfield, 1970.
5. Hille B., *Ionic channels in nerve membranes*, Progr. Biophys. Mol. Biol. **21**, 1 (1970).
6. MacFarlane M.D., H. Bresbis, *Procaine (Gerovital H_3) therapy: mechanism of inhibition of monoamine oxidase*, J. Amer. Geriatrics Soc., **22**, 365 (1974).
7. Yau T.M., *Gerovital H_3, monoamine oxidases and brain monoamines*, Symp. Theor. Aspects Aging, Miami, Florida, 1974.
8. Fuller R.W., B.W. Ronsh, *Procaine hydrochloride as a monoamine oxidase inhibitor: implications for geriatric therapy*, J. Amer. Geriatrics Soc., **25**, 90 (1977).
9. Crăescu C.T., *Quantitative structure-activity relationships using MTD parameters in some series of MAO inhibitors*, Rev. Roum. Biochim., **18**, 11 (1980).
10. Luth P., *A review of procaine-therapy in elderly individuals*, J. Gerontol., **15**, 395 (1960).
11. Coubeils J.L., P. Courrière, B. Pullman, *Quantum-mechanical study of the conformational properties of sympatholytic compounds*, J. Med. Chem., **15**, 453 (1976).
12. Murphy J.C., E.S. Watson, P.W. Wirth, C.R. Clark, R.F. Borne, *Conformational aspects of the antifibrillatory activity of procaine*, Eur. J. Pharmacol., **40**, 359 (1976).
13. Sheetz M.D., S.J. Singer, *Biological membranes as bilayer couples. A molecular mechanism of drug-erythrocyte interactions*, Proc. Nat. Acad. Sci. USA, **71**, 4457 (1974).
14. Hubbell W.L., H.M. McConnell, *Spin-label studies of the excitable membranes of nerve and muscle*, Proc. Nat. Acad. Sci. USA, **61**, 12 (1968).

ROMANIAN J. GERONT. GERIATRICS, 1980, 1, 2, p. 317–327

THE RELATION BETWEEN AGE AND LIPID PEROXIDATION IN RAT LIVER AND BRAIN HOMOGENATE

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Summary. The rat brain and liver homogenates autoxidize spontaneously and reproducibly when incubated at 37°C. Malonyldialdehyde (MDA) concentration was used as an indicator in this process.

MDA concentration in young, adult and old rat liver and brain homogenates at zero time of incubation does not present significant changes in relation to the age of the animals under experiment.

The old rat brain homogenate susceptibility to autoxidation followed by incubation of the samples at 37°C for 30, 60 and 120 min, is significantly lower as compared with the young rat brain. Under the same conditions, the old rat liver homogenate displays a significantly increased susceptibility to autoxidation as compared with the young rat liver.

The antioxidant activity of serum obtained from young, adult and old animals on autoxidation of rat brain and liver homogenates of different ages, varies between 70% and 90% for a volume of 60 µl serum, without any age-related changes.

The ascorbic acid acts either as a pro-oxidant or as an antioxidant depending on its concentration in the reaction medium, on the homogenate (liver or brain) and on the age of the animal under experiment.

INTRODUCTION

Biological material contains a wide range of unsaturated lipids, especially in the lipoproteic structure of cellular and subcellular membranes. The oxidative deterioration process of unsaturated fatty acids of these structures (lipid peroxidation) has a considerable importance in our attempts to understand the mechanism underlying cell injury. The age pigment (lipofuscin) is derived from a lipoprotein complex such as that found in cell membranes, by the lipid peroxidation process [1].

Lipid peroxidation in isolated tissues, homogenates, cells and organelles implies the generation of free radicals in the system by enzymic and non-enzymic catalytic mechanisms. Transition metals irons are important components of non-enzymic tissue peroxidation.

The biological structures capable of peroxidation require antioxidant natural protection. The natural antioxidant system of the organism includes such coumpounds as vitamin E, β-carotene, purine bases, glutathione and vitamin C. The latter two display a pro-oxidant activity under certain conditions. Enzymes and proteins such as catalase, glutathione-peroxidase, superoxide-dismutase, caeruloplasmin and transferrin are important components of the body's antioxidant defence system [2].

In the last years efforts have been made to understand the mechanism of the aging process at the molecular level and a great number of studies have tried to

demonstrate the role played by free radicals in the aging process [3—5]. Free radicals (atoms or molecules which contain an unpaired electron) induce lipid peroxidation.

It is the purpose of this report to show the possible changes occurring with age in rat brain and liver homogenates susceptibility to autoxidation, the antioxidant action of serum obtained from rats of different ages upon these homogenates. The ascorbic acid in the presence of metal ions (e.g. Cu^{2+}, Fe^{2+}) function as a source of free radicals, activating the lipid peroxidation process. Using different concentrations of ascorbic acid (0.2, 0.4, 0.8, 1.2 and 2 mM), we studied the action of this compound upon the rat liver and brain homogenates of different ages, trying to point out the possible changes related to age in the process of lipid peroxidation. We investigated the action of DL-α-tocopherol (vitamin E) in concentrations of 0.033, 0.077 and 0.15 mM in the system upon the lipid peroxidation of liver and brain adult rat homogenates. At the same time we determined the concentrations of non-haem iron and ascorbic acid in young, adult and old brain and liver rat.

MATERIAL AND METHODS

In our experiment we used Wistar rats, at three age levels: young (1—2 months), adult (6—8 months) and old (24—26 months). The animals were decapitated. We obtained a "pool serum" from rats having the same age. The liver and brain were homogenized 10% (w/v) in 0.15 M KCl solution, then centrifuged for 15 min at 5000 g. The supernatant fluid was used to study lipid peroxidation.

Autoxidation. The reaction system used in the autoxidation process contains 0.5 ml of supernatant, stock solution (0.1 M Tris-HCl pH 7.4 — 0.15 M KCl 1:2 v/v), as well as other constituents corresponding to the work system. The total volume system was maintained at 3 ml, with adequate buffer volumes. The ascorbic acid concentration in the reaction medium was 0.2, 0.4, 0.8, 1.2 and 2 mM. DL-α-tocopherol (vitamin E) was added in the reaction medium in concentrations of 0.0033, 0.077 and 0.15 mM. In the system we used 60 µl of serum. The samples were incubated at 37°C in a water bath for 30, 60 and 120 min. After incubation, the reaction was stopped by adding 28% TCA, and the quantity of lipid peroxides was evaluated by thiobarbituric acid reaction. The results were given in nmoles malonyldialdehyde (MDA) per 100 mg protein, using an extinction coefficient of 1.56 $nmoles^{-1}$ cm^2 at 535 nm [6]. Protein estimation was done according to Lowry's method [7].

The non-haem iron content. We added an equal volume of HCl 2N to the corresponding volumes of the supernatant obtained by centrifuging the initial homogenates (0.5 ml for liver and 2 ml for brain). The samples were introduced in a water bath at 100°C for 15 min. After cooling, the mixture was centrifuged for 15 min at 8000 g. Then 2 ml of the supernatant was taken for the assay of iron by the ortho-phenanthrolin method [8]. Absorbance was measured at 510 nm and the iron concentration was given in mg per 100 g wet tissue.

The ascorbic acid content. The ascorbic acid was determined in the extract obtained by homogenizing the rat liver and brain in TCA 6%. The samples (2 ml) were used to determine the ascorbic acid by the 2,4-dinitrophenylhydrazine method [9]. The concentration was expressed as mg ascorbic acid per 100 g wet weight of tissue.

Statistical analysis of significance was established at the 5% level of significance ($p < 0.05$) using Student's "t" test for the means of two independent samples. The values presented in tables 1—3 are the mean $\pm$SD of the number of animals shown in brakets.

RESULTS

MDA production in rat brain and liver homogenates of different ages, incubated at 37°C for 30, 60 and 120 min is represented in table 1. MDA concentration in the young, adult and old rat brain homogenate at zero time of incubation does not allow significant changes in relation to the age of animals under experiment. The values given in nmoles MDA/100 mg protein are 82.6 ± 18.56 for the young rat brain homogenate and 77.44 ± 17.04 for the old rat brain homogenate.

Susceptibility to autoxidation of the old rat brain homogenate followed by incubation of the samples at 37°C for 30, 60 and 120 min, is significantly lower as compared with the young and adult rat brain, except for one value (Table 1).

Table 1

Lipid peroxide formation (nmoles of MDA/100 mg protein) in rat brain and liver homogenates incubated at 37°C for 30, 60 and 120 min

Groups of animals	Brain			
	Time of incubation			
	0	30 min	60 min	120 min
Young (1—2 months)	82.6±18.56 (10)	507.88±147.16 (10)	734.60±157.08 (10)	899.96±119.92 (10)
Adult (6—8 months)	83.96±19.36 (12)	454.88±89.36 (12)	664.32±144.80 (12)	876.12±139.48 (12)
Old (24—26 months)	77.44±17.04 (9)	340.04±86.40 (9) p<0.02(Y) p<0.01(A)	560.36±145.16 (9) p<0.05(Y) p>0.05(A)	756.24±136.84 (9) p<0.05(Y) p<0.05(A)

Groups of animals	Liver			
	Time of incubation			
	0	30 min	60 min	120 min
Young (1—2 months)	28.44±8.64 (14)	92.92±21.64 (14)	162.88±40.04 (14)	247.48±63.68 (14)
Adult (6—8 months)	30.40±6.64 (12)	99.28±24.92 (12)	193.24±36.64 (12)	308.72±40.20 (12)
Old (24—26 months)	34.68±10.04 (9)	151.92±28.88 (9) p<0.001(Y) p<0.001(A)	256.64±42.60 (9) p<0.01(Y) p<0.01(A)	307.36±45.84 (9) p<0.05(Y) n.s.(A)

MDA concentration in rat liver homogenate at zero time of incubation significantly changes in relation to the age of the animals under study. MDA con-

tent in the young, adult and old liver homogenates incubated at 37°C has increased values within the first 30 min for the old animals (151.92±28.88) as compared with young animals (92.92±21.64), $p < 0.001$. The same changes can be noticed in the samples incubated for 60 min: MDA concentration has higher values than in the young animals ($p < 0.01$).

The effect of pooled serum obtained from young, adult and old animals upon autoxidation of rat brain and liver homogenates of different ages is represented

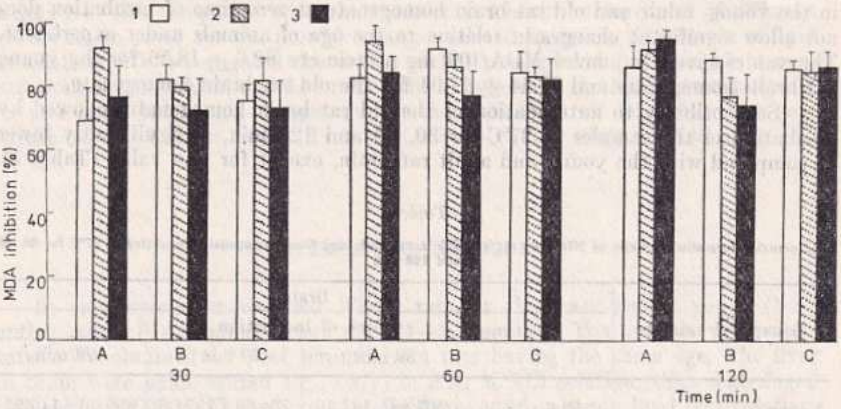

Fig. 1. — Effect of 60 µl of pooled rat serum on the autoxidation of rat brain homogenates incubated at 37°C for 30, 60 and 120 minutes.

1, young rat brain; *2*, adult rat brain; *3*, old rat brain; *A*, serum from young rats; *B*, serum from adult rats; *C*, serum from old rats.

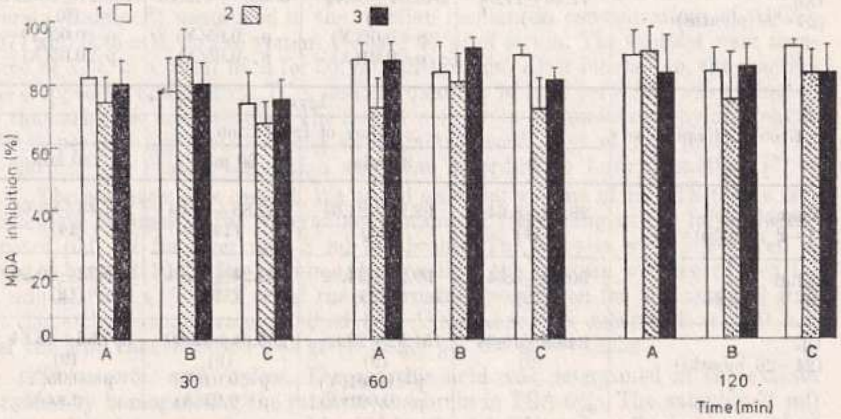

Fig. 2. — Effect of 60 µl of pooled rat serum on the autoxidation of rat liver homogenates incubated at 37°C for 30, 60 and 120 minutes.

1, young rat liver; *2*, adult rat liver; *3*, old rat liver; *A*, serum from young rats; *B*, serum from adult rats; *C*, serum from old rats.

in Figs 1 and 2. Inhibition is expressed in terms of percentages related to the values obtained in the control homogenate without serum. The presence of 60 μl serum in the reaction medium inhibits MDA production in the young, adult and old rat brain homogenates between 70% and 90%, without any significant changes dependent on age.

The ascorbic acid catalyses lipid peroxidation in the young, adult and old rat brain homogenates (Fig. 3, *A—E*). MDA production in the adult rat brain homogenate incubated with different concentrations of ascorbic acid, is quoted under the values obtained for the young and old rat brain for all the three times of incubation. The values have been compared to controls, without ascorbic acid (zero line). Usually, standard deviations are too great to allow significant differences in relation to the age groups considered in our study. High concentration of ascorbic acid in the reaction medium (2 mM) does not induce an antioxidant action in the young, adult and old rat brain homogenates.

The changes in the lipid peroxidation process caused by the ascorbic acid in five different concentrations in the young, adult and old liver homogenate incubated for 30, 60 and 120 min are represented in Fig. 4, *A — E*. The stimulation of MDA production, given in nmoles per 100 mg protein, is significantly increased in the young and old liver homogenate as compared with the adult. As the concentration of ascorbic acid increases in the reaction medium, the stimulation rate of lipid peroxidation lowers so that in the system, for a concentration of 1.2 and 2 mM ascorbic acid, MDA concentration after two hours of incubation reaches the control test value. The concentration of 2 mM ascorbic acid in the reaction medium indicates the limit to which it can induce a pro-oxidant action in the system.

The concentration of non-haem iron and ascorbic acid in the rat brain and liver is given in tables 2 and 3. We can not notice important changes in the content of non-haem iron for the three age groups under study. The ascorbic acid content is significantly lower in the old and adult rat liver and brain as compared with the young group.

Table 2

The non-haem iron content of rat brain and liver

Groups of animals	Non-haem iron (mg/100 g of tissue)	
	Brain	Liver
Young (1—2 months)	1.15±0.12 (5)	5.36±0.79 (5)
Adult (6—8 months)	1.28±0.24 (5)	6.03±1.76 (5)
Old (24—26 months)	1.22±0.18 (5)	5.91±1.15 (5)

Another experiment used DL-α-tocopherol (vitamin E) which was prepared as an emulsion with Tween 80 (2.32 mM DL-α-tocopherol in 3 mM Tween 80). The antioxidant action of vitamin E in a concentration of 0.030, 0.077 and 0.15 mM upon adult rat brain and liver homogenates, after 60 and 120 min of incu-

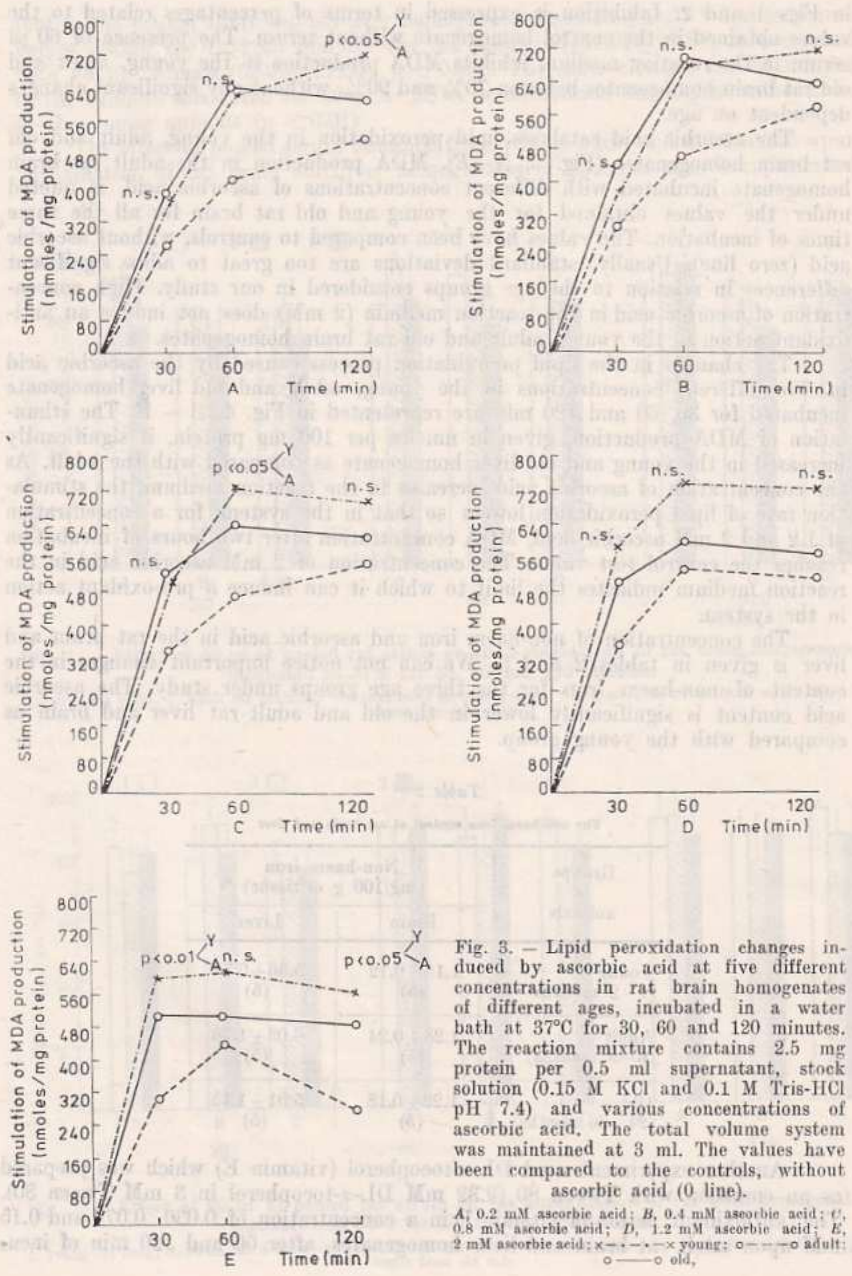

Fig. 3. — Lipid peroxidation changes induced by ascorbic acid at five different concentrations in rat brain homogenates of different ages, incubated in a water bath at 37°C for 30, 60 and 120 minutes. The reaction mixture contains 2.5 mg protein per 0.5 ml supernatant, stock solution (0.15 M KCl and 0.1 M Tris-HCl pH 7.4) and various concentrations of ascorbic acid. The total volume system was maintained at 3 ml. The values have been compared to the controls, without ascorbic acid (0 line).

A, 0.2 mM ascorbic acid; *B*, 0.4 mM ascorbic acid; *C*, 0.8 mM ascorbic acid; *D*, 1.2 mM ascorbic acid; *E*, 2 mM ascorbic acid; ×—·—·—× young; o— — —o adult; o——o old.

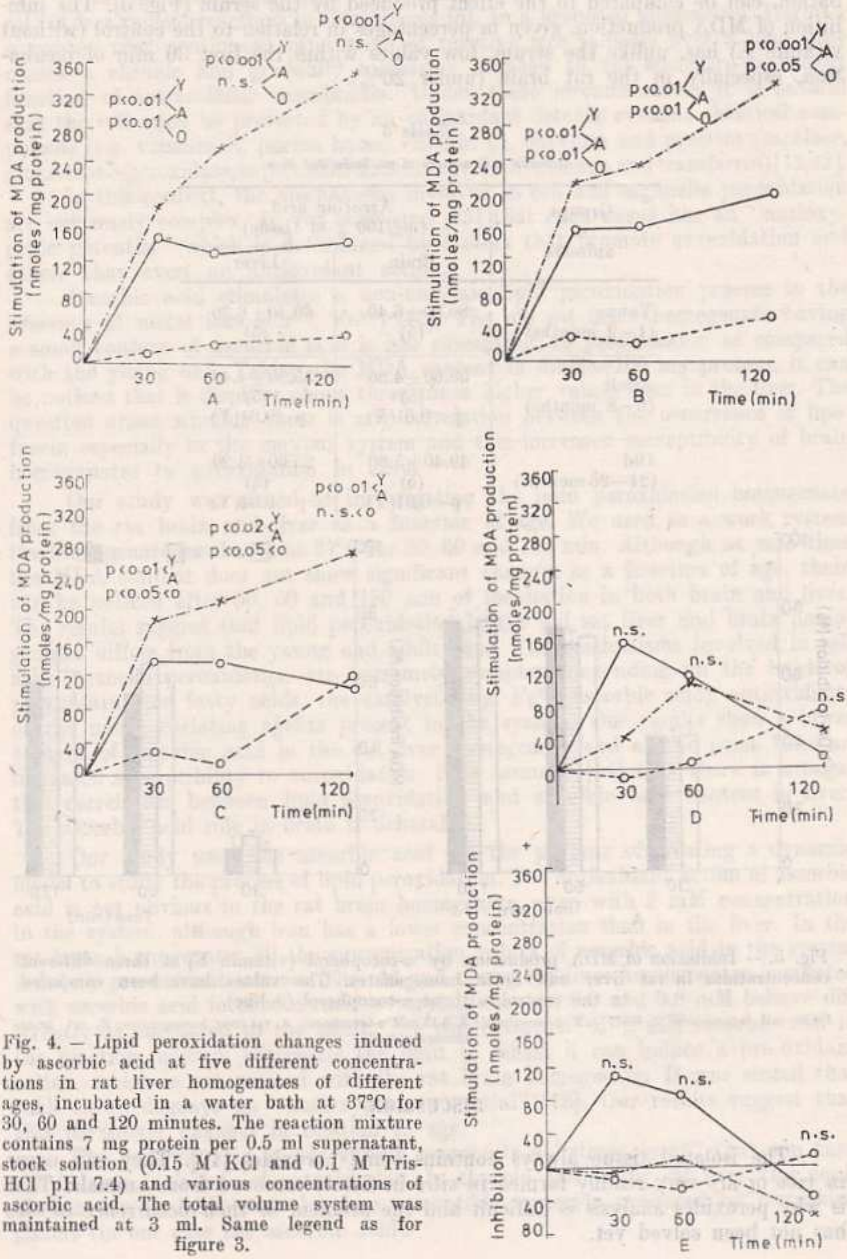

Fig. 4. — Lipid peroxidation changes induced by ascorbic acid at five different concentrations in rat liver homogenates of different ages, incubated in a water bath at 37°C for 30, 60 and 120 minutes. The reaction mixture contains 7 mg protein per 0.5 ml supernatant, stock solution (0.15 M KCl and 0.1 M Tris-HCl pH 7.4) and various concentrations of ascorbic acid. The total volume system was maintained at 3 ml. Same legend as for figure 3.

bation, can be compared to the effect produced by the serum (Fig. 5). The inhibition of MDA production, given in percentages in relation to the control (without vitamin E) has, unlike the serum, low values within the first 30 min of incubation, especially in the rat brain (under 20%).

Table 3

Ascorbic acid content of rat brain and liver

Groups of animals	Ascorbic acid (mg/100 g of tissue)	
	Brain	Liver
Young (1—2 months)	80.20±6.40 (5)	60.40±6.30 (5)
Adult (6—8 months)	58.60±4.80 (5) p<0.01(Y)	35.90±4.40 (5) p<0.01(Y)
Old (24—26 months)	49.40±5.80 (5) p<0.01(Y)	25.60±3.20 (5) p<0.01(Y)

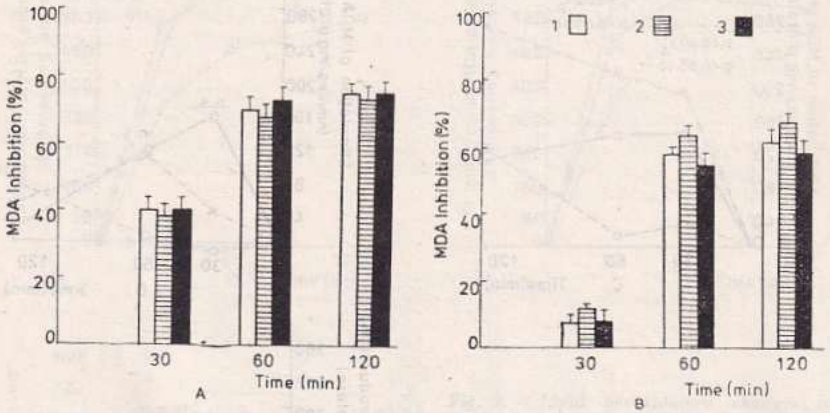

Fig. 5. — Inhibition of MDA production by α-tocopherol (vitamin E) at three different concentrations in rat liver and brain homogenates. The values have been compared to the control, without α-tocopherol (0 line).

1, 0.03 mM α-tocopherol; *2*, 0.077 mM α-tocopherol; *3*, 0.15 mM α-tocopherol; *A*, rat liver homogenates; *B*, rat brain homogenates.

DISCUSSION

The isolated tissue always contains some peroxides [10]. They can occur *in vivo* or are very readily formed *in vitro* in tissues removed from animals. That is why peroxides analysis is difficult and the problem of their occurrence *in vivo* has not been solved yet.

With regard to the aging process itself, Harman has stressed the degradative role of free radical reactions in this process [5]. In a proposed mechanism, Harman suggested that continuous production of reactive free radicals over a long time causes a chronic and gradually increasing damage to the structure-dependent function of intracellular membranes. Under these circumstances, it is natural that the cell must be protected by an antioxidant defence system: chemical compounds (e.g. vitamin E, purine bases, vitamin C), enzymes and proteins (catalase, glutathione-peroxidase, superoxide-dismutase, caeruloplasmin and transferrin) [11,12].

In this context, the mechanisms involved in cell and organelle peroxidation are extremely complex. It was suggested [13] that each tissue has an "antioxygenic potential" which is determined by factors that promote autoxidation and others that exert an antioxidant action.

Ascorbic acid stimulates a non-enzymic lipid peroxidation process in the presence of metal ions (Cu^{2+}, Fe^{2+}) [11]. The old rat brain homogenate having a small content of ascorbic acid is less susceptible to peroxidation as compared with the young one. Taking the MDA content in nmoles/100 mg protein, it can be noticed that it displays about three times higher values than in the liver. The question arises whether there is any correlation between the occurrence of lipofuscin especially in the nervous system and this increased susceptibility of brain homogenates to autoxidation *in vitro*.

Our study was aimed at investigating the lipid peroxidation homogenate from the rat brain and liver as a function of age. We used as a work system the homogenate incubated at 37°C for 30, 60 and 120 min. Although at zero time the MDA content does not show significant changes as a function of age, these can be noticed after 30, 60 and 120 min of incubation in both brain and liver. The results suggest that lipid peroxidation in the old rat liver and brain homogenates differs from the young and adult ones. The mechanisms involved in cell and organelle peroxidation are extremely complex, depending on the levels of polyunsaturated fatty acids, the catalysts (e.g. Fe^{2+}, ascorbic acid), antioxidants or the metal chelating agents present in the system. Our results show a lower content of ascorbic acid in the old liver homogenate and at the same time an increased susceptibility to autoxidation. It is assumed [14] that there is a negative correlation between lipid peroxidation and ascorbic acid content in liver. The ascorbic acid role in brain is debatable.

Our study used the ascorbic acid for the purpose of creating a dynamic model to study the process of lipid peroxidation. The antioxidant action of ascorbic acid is not obvious in the rat brain homogenate, even with 2 mM concentration in the system, although iron has a lower concentration than in the liver. In the rat brain homogenates all the concentration values of ascorbic acid in the system induce a pro-oxidant action. The old and young rat liver homogenates incubated with ascorbic acid in concentrations varying between 0.2 and 0.8 mM behave differently as compared to the adult. The concentration of 2 mM ascorbic acid in the reaction medium represents the limit to which it can induce a pro-oxidant action, which is not noticed with the rat brain homogenate. It was stated that each tissue displays an "antioxygenic potential" [13]. Our results suggest that this parameter changes in relation to age.

The ascorbic acid in our system represents a "stress agent" that can turn the balance in favour of autoxidation. In the old and young rat liver this equilibrium can be labile and therefore susceptible to action produced by disturbing factors (in our case the ascorbic acid).

The antioxidant activity of vitamin E leads to the hypothesis that this substance could represent the main protecting agent in biological systems. Vitamin E is a strong antioxidant *in vitro*, but its role *in vivo* is not yet well known [15] [16]. Using the same experimental model (the adult rat brain and liver homogenate), we followed the antioxidant action of vitamin E *in vitro*. At the same time, we tested the antioxidant action of the rat serum obtained from young, adult and old animals upon the young, adult and old rat brain and liver homogenate. The antioxidant action of the rat serum (60 µl) is strong, varying between 70% and 90%, irrespective of the animal age. The DL-α-tocopherol emulsion presents values similar to rat serum (in the MDA inhibition rate) for concentrations of about 1000 times higher in the system (the quantity of vitamin E in the rat serum has values of 3 µmoles/100 ml [7]).

It is known that the serum antioxidant action depends to a large extent on the two plasmatic fractions, caeruloplasmin and transferrin [12, 16, 18]. The organism has a complex and very strong antioxidant system which acts for maintaining the integrity of cell structure.

Résumé. Les homogénats de foie et de cerveau de rat sont spontanément et reproductiblement auto-oxydés lorsqu'ils sont incubés à 37°. La teneur en MDA a été utilisée comme indicateur pour exprimer ce processus.

La concentration de MDA dans les homogénats de cerveau et de foie de rat jeune, adulte et vieux, au moment 0 de l'incubation, ne présente pas de modifications importantes par rapport à l'âge des animaux d'expérience.

La susceptibilité à l'auto-oxydation des homogénats de cerveau de rat vieux, suivie par l'incubation des preuves à 37°C, pendant 30, 60 et 120 minutes, est visiblement diminuée par rapport au cerveau de rat jeune. L'homogénat de foie de rat vieux soumis aux mêmes conditions présente une susceptibilité très accrue par rapport au foie de rat jeune.

L'action anti-oxydante du sérum obtenu des animaux jeunes, adultes et vieux sur l'auto-oxydation des homogénats de foie et de cerveau de rat de différents âges est comprise entre 70% et 90% pour un volume de 60 µl sérum, sans modifications par rapport à l'âge.

L'acide ascorbique a une action soit pro-oxydante, soit anti-oxydante, en fonction de sa concentration dans le milieu de réaction, de la nature de l'homogénat (foie ou cerveau) et de l'âge de l'animal d'expérience.

La vitamine E (DL-α-tocophérol) exerce une action anti-oxydante diminuée pendant les 30 premières minutes d'incubation des homogénats de foie et de cerveau de rat adulte.

REFERENCES

1. Tappel A.L., *Will antioxidant nutrients slow ageing processes?* Geriatrics, 1968, **23**, 97–105.
2. Gutteridge J.M.C., Stocks J., *Peroxidation of cell lipids.* Med. Lab. Sci., 1976, **33**, 281–285.
3. Comfort A., Youhotsky-Gore I., Pathmanathan K., *Effect of etoxyquin on the longevity of C3H mice.* Nature, 1971, **229**, 254–255.
4. Goldberg L., Martin L.E., Batchelor A., *Biochemical changes in tissue of animals injected with iron. 3. Lipid peroxidation.* Biochem., J., 1962, **83**, 291–298.
5. Harman D., *Role of free radicals in mutation, cancer, ageing and the maintenance of life.* Radiat. Res., 1962, **16**, 753–763.
6. Stocks J., Dormandy T.L., *The autoxidation of human red cell lipids induced by hydrogen peroxide.* Brit. J. Haemat., 1971, **90**, 95–111.
7. Lowry O.H., Rosebrough N.J., Farr A.L., Randall R.J., *Protein measurement with the Folin phenol reagent.* J. Biol. Chem., 1951, **193** 265–275.
8. Manta I., Benga G., Cucuianu M., Hodârnău A., *Metode biochimice în laboratorul clinic.* Ed. Dacia, Cluj-Napoca, 1976, p. 275.

9. KANUNGO M.S., PATNAIK B.K., *Ascorbic acid and ageing in the rat. Uptake of ascorbic acid by skin and bone marrow, and its concentration in various organs.* Biochem. J., 1964, **90,** 637–638.
10. WILLS E.D., *Mechanisms of lipid peroxide formation in animal tissues.* Biochem. J., 1966, **99,** 667–676.
11. SLATER T.F., *Free Radical Mechanisms in Tissue Injury.* Pion Ltd, London, 1972, p. 50.
12. AL-TIMIMI D.J., DORMANDY T.L., *The inhibition of lipid autoxidation by human caeruloplasmin.* Biochem. J., 1977, **168,** 283–288.
13. DI LUZIO N.R., *Antioxidants, lipid peroxidation and chemical-induced liver injury.* Symposium on Free Radical Pathology presented at the 54th Annual Meeting of the Federation of American Societies for Experimental Biology, Atlantic City, N.J., April 16, 1970, p. 1875–1881.
14. SHARMA O.P., *Age related changes in lipid peroxidation in rat brain and liver.* Biochem. Biophys. Res. Comm., 1977, **78,** 469–475.
15. TIMIRAS P.S., *Developmental Physiology and Aging.* Collier-Macmillan Ltd, London, 1972, p. 612.
16. STOCKS J., GUTTERIDGE J.M.C., SHARP R., DORMANDY T.L., *The inhibition of lipid autoxidation by human serum and its relation to serum proteins and tocopherol.* Clin. Sci. Mol. Med., 1974, **43,** 223–233.
17. BENEDETTI A., CASINI A.F., FERRALI M., COMPORTI M., *Effects of diffusible products of peroxidation of rat liver microsomal lipids.* Biochem. J., 1979, **180,** 303–312.
18. BARBER A.A., *Inhibition of lipid peroxide formation by vertebrate blood serum.* Arch. Biochem. Biophys., 1961, **96,** 39–43.

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CATEPSINE D ET LACTATE-DÉHYDROGÉNASE DES TISSUS DE RAT VIEUX. L'EFFET DU TRAITEMENT À L'ASLAVITAL

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Résumé. On a examiné l'activité de la catepsine D et de la lactate-déhydrogénase des tissus hépatique, rénal et splénique provenant des rats jeunes (3–5 mois), adultes (8–10 mois), âgés (23–25 mois). L'activité de la catepsine D diminue de façon significative chez les animaux adultes par rapport aux animaux jeunes; les valeurs enregistrées pour les animaux âgés se situent à un niveau réduit d'une manière similaire. L'activité de la lactate-déhydrogénase est également beaucoup réduite chez les animaux adultes par rapport aux animaux jeunes; quant aux animaux âgés, les valeurs se situent entre les valeurs enregistrées pour les animaux jeunes et adultes. Le traitement à l'Aslavital induit la réduction de l'activité des enzymes; on constate une tendance de rapprochement du niveau observé chez les animaux adultes. Nos données suggèrent un parallélisme entre l'activité de la catepsine D et celle de la lactate-déhydrogénase, aussi bien dans les modifications induites par l'âge que dans le cas du traitement des animaux au médicament biotrophique Aslavital.

La signification biologique des protéases tissulaires est rattachée au métabolisme et à la fonction spécifique des tissus respectifs [1]. Les données existantes ont conduit à la conception moderne de l'intégration du système des enzymes protéolitiques dans les structures sous-cellulaires et dans les fonctions de divers tissus, en lui conférant de la sorte un caractère ubiquitaire et différencié ([2] — [4]); la participation de ce système enzymatique à la relation organisme-milieu semble être de plus en plus précisée.

Quoique la protéolyse enzymatique soit considérée comme une réaction économique du point de vue énergétique, les données expérimentales indiquent la dépendance de l'activité de certaines enzymes protéolytiques des processus oxydatifs [5] ou de la production d'énergie des tissus [6]. Dans ce travail nous nous sommes proposé, d'un côté, de comparer l'évolution de l'activité d'une enzyme protéolytique, lysosomale, la protéinase acide (catepsine D, E.C. 3.4.4.23) de différents tissus de rats de divers âges avec l'évolution de l'activité de la lactate-déhydrogénase (LD, E.C. 1.1.1.27), et, de l'autre côté, de constater l'effet du traitement au médicament biotrophique Aslavital sur leur activité.

MATÉRIEL ET MÉTHODES

Les déterminations ont été effectuées dans les homogénats de tissus hépatique, rénal et splénique provenant de rats Wistar (jeunes de 3–5 mois, adultes de 8–10 mois, âgés de 23–25 mois), maintenus en conditions normales de vie et d'alimentation.

L'activité de la catepsine D (protéinase acide, pH optimum 3,5) a été investiguée en homogénat tissulaire en eau bidistilée, en utilisant comme substratum

hémoglobine dénaturée à acide citrique, en présence de Triton-X-100 [2], en appréciant l'extinction à 280 nm (ΔE/mg protéine/h) [7]. Pour l'activité LD, l'homogénéisation a été effectuée en tampon phosphate (pH 7,8) et la détermination de l'activité selon Bergmeyer et collab. [8], en poursuivant la modification de l'extinction à 340 nm (ΔE/mg protéine/minute). Le contenu de protéine a été déterminé selon Lowry et collab. [9].

Les mêmes déterminations ont été effectuées chez un lot de rats âgés (23—25 mois) traités pendant 5 mois au produit biotrophique Aslavital, administré intramusculaire, tous les jours la dose correspondant à 4 mg procaine/kg corps.

Les données obtenues ont été traitées selon le test « t » de Fischer (tabl. 1—4; figs 1—4).

RÉSULTATS

L'activité de la catepsine D diffère en tant que niveau selon le tissu dont elle provient, ainsi que d'après l'âge des animaux (tabl. 1, fig. 1). Chez les rats jeunes, le niveau de l'activité décroît dans l'ordre: rate, rein, foie, ordre qui se maintient aussi chez les animaux adultes et âgés. La comparaison de l'activité de la catepsine D des tissus provenant des animaux de divers âges fait ressortir une réduction statistiquement significative chez les animaux adultes par rapport aux animaux jeunes; le niveau de l'activité dans les tissus des animaux âgés est rapproché de celui des animaux adultes. Le traitement à l'Aslavital (tableau 2, fig. 4) est accompagné de la réduction de l'activité de la catepsine D dans les tissus analysés, par rapport aux animaux témoins.

Tableau 1

Activité de la catepsine D (ΔE/mg protéine/h, valeurs moyennes M ± ESM) du foie, du rein et de la rate de rat

[( ) = nombre des animaux;* = $p \leqslant 0{,}05$ par rapport aux animaux jeunes]

Groupe d'animaux	Foie	Rein	Rate
Jeunes (3—5 mois)	0,104±0,003 (9)	0,208±0,030 (12)	0,339±0,040 (11)
Adultes (8—10 mois)	0,056±0,005* (10)	0,108±0,009* (10)	0,178±0,028* (9)
Vieux (23—25 mois)	0,062±0,010 (9)	0,091±0,009 (10)	0,198±0,010* (10)

L'activité LD a aussi des niveaux divers, selon le tissu analysé ou l'âge des animaux. Ainsi, la plus grande activité est enregistrée dans le tissu hépatique, puis dans le tissu rénal et splénique (tableau 3, figs. 1), ce pattern étant retrouvé aussi bien chez les animaux jeunes que chez les animaux adultes ou âgés. La comparaison de l'activité LD provenant des tissus des animaux de divers âges indique un niveau plus réduit chez les animaux jeunes par rapport aux animaux adultes, mais les valeurs observées pour les animaux âgés sont plus grandes que celles pour les animaux adultes. Le traitement à l'Aslavital réduit l'activité LD; la réduction est significative du point de vue statistique pour le tissu splénique (tabl. 2, fig. 4).

Le contenu de protéine des homogénats de foie, rein ou rate diffère également selon le tissu ou l'âge des animaux (tableau 4, fig. 3); après le traitement à l'Aslavital, le contenu de protéine des homogénats respectifs tend à accroître (tableau 2).

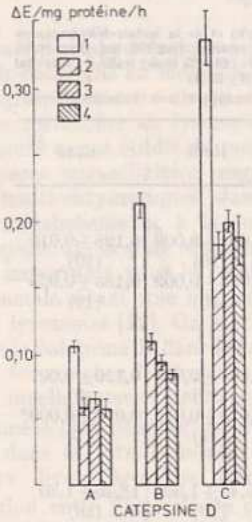

Fig. 1. — Activité de la catepsine D des tissus de rat.

A — foie, B — rein, C — rate. 1 = animaux jeunes; 2 = animaux adultes; 3 = animaux âgés; 4 = animaux âgés traités à l'Aslavital.

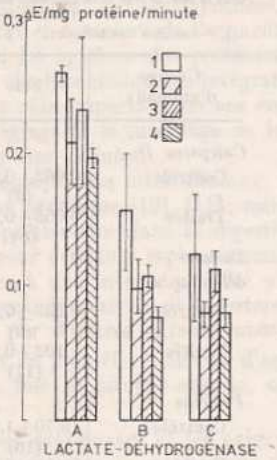

Fig. 2. — Activité de la lactate-déhydrogénase des tissus de rat.

A — foie, B — rein, C — rate. 1 = animaux jeunes; 2 = animaux adultes; 3 = animaux âgés; 4 = animaux âgés traités à l'Aslavital.

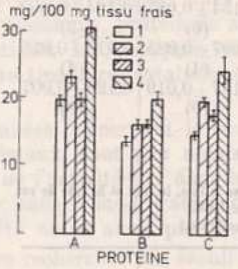

Fig. 3. — Le contenu de protéine des tissus de rat.

A — foie, B — rein, C — rate. 1 = animaux jeunes; 2 = animaux adultes; 3 = animaux âgés; 4 = animaux âgés traités à l'Aslavital.

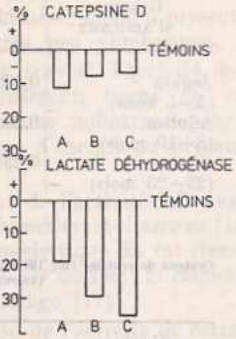

Fig. 4. — Modification en pour-cent de l'activité de la catepsine D et de la lactate-déhydrogénase des tissus de rat âgé après le traitement à l'Aslavital, par rapport aux animaux témoins.

A — foie, B — rein, C — rate.

Tableau 2

Activité de la catepsine D (ΔE/mg protéine/h) et de la lactate-déhydrogénase (ΔE/mg protéine/minute) et le contenu de protéine (mg/100 mg tissu frais) dans le foie, le rein et la rate chez les rats âgés (23—25 mois) traité à l'Aslavital (valeurs moyennes M±ESM)

[( ) = nombre des animaux;* = $p \leqslant 0{,}05$ par rapport aux animaux jeunes]

Groupe d'animaux	Foie	Rein	Rate
Catepsine D			
Contrôle	0,062±0,010 (9)	0,091±0,009 (10)	0,198±0,010 (10)
Traités	0,055±0,007 (8)	0,083±0,009 (10)	0,183±0,035 (10)
Lactate-déhydrogénase			
Contrôle	0,233±0,060 (9)	0,107±0,019 (10)	0,120±0,007 (9)
Traités	0,192±0,012 (11)	0,075±0,012 (11)	0,077±0,009* (11)
Protéine			
Contrôle	19,70±1.60 (10)	16,40±1,50 (10)	18,40±1,80 (10)
Traités	31,00±2.50 (11)	19,30±0,70 (11)	24,20±2,20 (11)

Tableau 3

Activité de la lactate-déhydrogénase (ΔE/mg protéine/minute, valeurs moyennes M±ESM) du foie, du rein et de la rate de rat

[( ) = nombre des animaux]

Groupe d'animaux	Foie	Rein	Rate
Jeunes (3—5 mois)	0,262±0,008 (6)	0,154±0,057 (6)	0,124±0,050 (5)
Adultes (8—10 mois)	0,208±0,055 (4)	0,097±0,035 (4)	0,076±0,016 (4)
Vieux (23—25 mois)	0,233±0,060 (9)	0,107±0,019 (10)	0,120±0,007 (9)

Tableau 4

Contenu de protéine (mg/100 mg tissu frais) dans le foie, le rein et la rate de rat (valeurs moyennes M±ESM)

[( ) = nombre des animaux]

Groupe d'animaux	Foie	Rein	Rate
Jeunes (3—5 mois)	19,09±1,40 (11)	13,70±0,60 (11)	14,60±0,33 (11)
Adultes (8—10 mois)	23,09±1,67 (10)	16,00±0,90 (10)	19,00±1,60 (9)
Vieux (23—25 mois)	19,70±1,60 (10)	16,40±1,50 (10)	18,40±1,80 (10)

DISCUSSION

La dégradation physiologique ou pathologique des protéines *in vivo* constitue un domaine de recherche au moins autant important que leur synthèse. On a enregistré des progrès, dans cette direction, au fur et à mesure de l'acquisition de nouvelles données rattachées au lysosomes [4]. Le système des protéases intracellulaires est demeuré moins étudié du point de vue biochimique. L'intégration structurale des protéases intracellulaires suggère le rôle important de ces enzymes dans les systèmes multi-enzymatiques, dans le réglage et le modelage de leur activité, rattaché au métabolisme et à la fonction des cellules.

La catepsine D, la plus répandue endopeptidase intracellulaire, semble être aussi la plus importante pour le catabolisme protéique [10], [11]; celle-ci est une enzyme lysosomale ayant une importance particulière dans la digestion des protéines par les lysosomes [12]. On a établi, pour certaines espèces animales, la prédominance de la catepsine D dans les organes à une intense activité phagocytaire. Lapresle [13] trouve chez le lièvre, la plus grande activité de la catepsine D dans la rate et la moelle osseuse, fait confirmé par d'autres auteurs aussi.

Nos données font ressortir, pour le rat, le plus élevé niveau d'activité de la catepsine D dans la rate, — le rein et la foie se situent ensuite, ordre qui se maintient aux divers âges des animaux.

La relation entre l'activité de certaines protéinases et les exigences énergétiques a été établie pour les protéinases neutres. Ainsi, le catabolisme des protéines endogènes des tranches de foie, à pH neutre, est dépendant des processus oxydatifs; il est inhibé aussi par l'anaérobiose et le dinitrophénol [14]. On a mis en évidence dans la fraction mitochondriale du foie et du cerveau, la dépendance de l'activité protéolytique à pH neutre, de la libération d'énergie [15].

L'activité des catepsines acides semble être indépendante des sources d'énergie; il est pourtant à supposer que l'intégration intracellulaire de ces enzymes impose une dépendance indirecte énergétique dans la formation et la cinétique des structures phago-lysosomales et cyto-lysosomales; mais, à présent, les données qui confirment une telle supposition sont très peu nombreuses.

Nous avons investigué, dans le présent travail, l'activité de la catepsine D, enzyme lysosomale, protéinase acide, de différents tissus de rat, parallèlement à l'activité LD, enzyme considérée comme indicateur pour la glycolyse anaérobiotique tissulaire, catabolisme générateur d'énergie au niveau cellulaire et tissulaire.

Les données concernant le comportement de l'activité LD avec l'âge, dans les tissus animaux, sont peu nombreuses. Schmukler et Barrows [16] soulignent la réduction de l'activité LD dans le muscle squelettique du rat (femelle) pendant la sénescence, sans la modification de l'activité LD du foie; la réduction de l'activité LD a été notée aussi par Singh et Kanungo [17].

D'autres recherches ont établi la réduction de l'activité de certaines enzymes impliquées dans le métabolisme énergétique, à mesure de l'avancement en âge des animaux. On a démontré ainsi la diminution de l'activité de l'ATP-ase du muscle squelettique [18] mais non pas du foie de rat [19]; on a constaté aussi la réduction de l'activité de la succinoxydase du tissu rénal de rat, sans la modification avec l'âge de l'activité de la même enzyme du tissu hépatique [20]. De telles données suggérent que, avec l'avancement en âge, le turnover énergétique diminue.

Nos données mettent en évidence un parallélisme accentué entre le sens des variations dans l'activité de la catepsine D, enzyme lysosomale, et de la lactate-déhydrogénase et entre l'âge des rats; ces données montrent ainsi de manière nette l'interrelation du métabolisme énergétique avec l'activité des protéases acides, en l'espèce la catepsine D.

Dans le même sens se situent aussi nos données concernant le traitement à l'Aslavital, données qui montrent la réduction, de façon parallèle, de l'activité LD et de la catepsine D dans les tissus hépatique, rénal et splénique, chez les rats âgés traités. Étant donné que la modification dans l'activité des enzymes étudiées après le traitement des animaux au médicament biotrophyque Aslavital s'inscrit dans le sens d'une similitude au niveau d'activité décelé chez les animaux adultes, non traités, cela nous suggère l'intervention de ce médicament dans la reconstitution de certains métabolismes déréglés par l'âge.

Abstract. The activity of cathepsin D and lactate-dehydrogenase was determined in liver, kidney and spleen tissues from young (3—5 months), adult (8—10 months) and old (23—25 months) Wistar rats. The activity of cathepsin D is significantly reduced in adult animals as compared to the young ones; as a similar reduced level are the values for the old animals. Lactate-dehydrogenase activity is also reduced in tissues from adult animals as compared to the young ones; the values for the old animals are situated between those observed in young and adult animals. The Aslavital treatment induces reduced enzymic activities for both enzymes; there is a tendency to reach the values observed in adult, untreated animals. Our data suggest a parallelism between the cathepsin D and lactate-dehydrogenase activity modifications with age, and also in the case of the treatment with the biotrophical drug Aslavital.

BIBLIOGRAPHIE

1. A.J. Barrett, J.T. Dingle, *Tissue proteinases*. North Holland Publ. Company, Amsterdam, Holland, 1971.
2. N. Marks, A. Lajtha, *Protein breakdown in the brain subcellular distribution and properties of neutral and acid proteinases*. Bioch. J., **89**, 438—443, 1963.
3. — *in Handbook of Neurochemistry*, edit. by A. Lajtha, Plenum Press, New York, *V*, part A, 49—139, 1971.
4. C. De Duve, in *Lysosomes in Biology and Pathology*, edit. by J.T. Dingle and H.B. Fell, North Holland Publ. Cie., Amsterdam, Holland, *I*, 1—50, 1973.
5. A.W. Simpson, mentionné par E. Gabrielescu, *Structural integration of neuroprotease activity*, Intern. Rev. Neurobiology, ed. by C.C. Pfeiffer and J.R. Smythies, Acad. Press, New York, San Francisco, London, **17**, 180—232, 1975.
6. N.W. Penn, mentionné par E. Gabrielescu, *Structural integration of neuroprotease activity*, Intern. Rev. Neurobiology, ed. by C.C. Pfeiffer and J.R. Smythies, Acad. Press, New York, San Francisco, London, **17**, 180—232, 1975.
7. J.H. Northrop, M. Kunitz, R.M. Herriott, *Crystalline Enzymes*, Columbia University Press, USA, 1956.
8. H.U. Bergmeyer, E. Bernt, B. Hess in *Methoden der Enzymatische Analyse*, ed. by H.U. Bergmeyer, Verlag Chemie Weinheim, 736—739, 1962.
9. O.H. Lowry, M.J. Rosebrough, A.L. Farr, R.S. Randall, *Protein measurement with Folin Phenol Reagent*, J. Biol. Chem., **193**, 265—275, 1951.
10. E.M. Press, R.R. Porter, J. Cebra, *The isolation and properties of a proteolytic enzyme, cathepsin D from bovine spleen*, Bioch. J., **74**, 501—510, 1960.
11. H. Keilova in *Tissue proteinases*, ed. by A.J. Barrett and J.T. Dingle, North Holland Publ. Cie., Amsterdam, Holland, 45—65, 1971.

12. J.O. Young, F. Liao, D. Hanes, A.L. Tappel, *Role of cathepsin C and D in the pathway of protein digestion by lysosomes*, Fed. Proc., **28**, 266–270, 1969.
13. Cl. Lapresle, in *Tissue Proteinases*, ed. by A.J. Barrett and J.T. Dingle, North Holland Publ. Co., Amsterdam, Holland, 135–149, 1971.
14. N. Marks, A. Lajtha, *Separation of acid and neutral proteinases of brain*, Bioch. J., **97**, 74–80, 1965.
15. W. Meier-Ruge, K. Reichlmeier, P. Iwangoff, in *Neurobiology of aging*, ed. by D.R. Terry and Gershon, Raven Press, New York, 379–384, 1976.
16. M. Schmukler, Barrows C.H., *Age difference in lactic and malic dehydrogenases in the rat*, J. Gerontol., **21**, 109–115, 1966.
17. S.N. Singh, M.S. Kanungo, *Alterations in lactate dehydrogenase of the brain, heart, skeletal muscle and liver of rats of various ages*, J. Biol. Chem., **243**, 4526–4529, 1968.
18. M. Rockstein, K.F. Brandt, *Changes in Phosphorus Metabolism of the Gastrocnemius Muscle in aging white rats*. Proc. Soc. exp. Biol., N.Y., **107**, 377–380, 1961.
19. M.H. Ross, J.D. Ely, *Aging and Enzyme Activity*, J. Franklin Inst., **258**, 63–66, 1954.
20. C.H. Barrows Jr., J.A. Falzone Jr., N.W. Shock, *Age differences in the succinoxidase activity of homogenates and mitochondria from the livers and kidneys of rats*, J. Gerontol., **15**, 130–133, 1960.

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EFFECTS OF GEROVITAL H_3 TREATMENT ON THE LEVEL OF SOME SERUM OLIGOELEMENTS IN SUBJECTS PROFESSIONALLY EXPOSED TO CHEMICAL AGENTS

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Summary. In order to determine the serum oligoelements we used the emission analysis method with X-rays excited by accelerated particles. Our study included 50 persons (19–51 years old) professionally exposed to metallic chemical agents and 30 persons (21–54 years old), living in the same geographical area, as a control group. The elements detected in the serum were: Fe, Cu, Zn, Mn, Ni, Br. The variations in the concentrations of serum oligoelements experimentally evaluated are discussed in relation to their physiopathological significance.

INTRODUCTION

The human organism contains such small amounts of oligoelements that we wonder whether they are important or not from a biological point of view. As regards the mechanism of action, it is more and more obvious that they act by means of proteins and especially enzymes. Up to the present we know over 1800 enzymes, each containing at least one metallic ion. Unfortunately, we the have not yet discovered activating and inhibiting ions for all the enzymes, but for those known, it is almost certain that they operate in concentrations of the order of micrograms. Metals, essential oligoelements from a biological point of view, can be considered as inorganic counterparts of some vitamins. In comparison with some vitamins they cannot be synthetized and have to be taken from the environment in adequate concentrations.

Starting from the assumption that the level of oligoelements in biologjcal fluids can point to human body exposition to polluting factors in the environment or in the working medium, we decided to control them by means of a method of high sensitiveness, precision and reproducibility. On the other hand, taking into account the concern for the prolongation of active life span and the results of some studies about the therapeutic action of GH_3 in acute and subacute intoxications with chromium compounds, we were interested in the effects of biotrophic medication on workers in a non-ferrous agent plant (Cu, Zn, Al, Pb, etc.).

MATERIALS AND METHODS

The elementary analysis of the serum was made using the PIXE method (X-ray emission induced by charged particles), initiated by Johansson and his assistants, in 1970 [1]. The method consists in producing holes in the deep electro-

nic shells of the atoms, caused by an ion impact, and in the immediate rearrangement of the electrons, as a result of ionization by two types of de-excitation, by means of X-ray emission and emission of low energy electrons (Auger). The energy of the emitted X-rays represents a smooth function of $Z_{effective}$ of the bombarded atoms.

The measurements were made on Cyclotron U-120, with variable energy of IFIN. We used 3MeV protons. X-rays spectra were measured with a spectrometer having a detector with semiconductors (Si(Li)) and a resolution $\Delta E/E = 5\%$. The amplification, generation and analysis of electric signals produced by dissipating X-rays energy in the semiconductor crystal, were achieved by an adequate electronic device which contains: a sensitive-to-charge preamplifier with field effect cooled at the liquid nitrogen temperature, a linear amplifier and a multichannel analyser with 4096 channels (TRIDAC), having a typewriter for data output. The X-ray spectra analysis was performed using a computer fitting programme taking Gaussian functions for the peaks and polynomial "m" order functions, Pm (x) or exp. (Pm (x)), for $m < 10$ for the background. This computer programme was adapted to a PDP-15 computer.

Measurements were made on targets prepared with serum obtained from a group of 50 workers 19—51 years old and working in a polluted medium affected by metallic chemical agents. The subjects were administered an intensive GH_3 treatment in two series, 12 daily injections each, with two weeks' pause between them. Before and after the treatment the elementary concentrations were compared to each other and to the oligoelements concentrations obtained from a control group of 30 persons 23—54 years old, living in the same geographical area with the above mentioned subjects (therefore the same exposition to pollution in the environment).

RESULTS AND DISCUSSION

The measurements by fluorescence of X-rays excited with charged particles pointed out the following elements in serum samples collected from the workers professionally exposed to some metallic polluting agents, as well as from the subjects belonging to the control group: Fe, Cu, Zn, Mn, Ni, Br.

The average serum content of Fe was about two times higher in comparison with the control group (Table 1). After the treatment we noticed a 29% increase in the serum Fe. Future deep-going studies on Fe metabolism could clear up its intestinal absorption, its binding with carriers or excretion.

Copper has also higher values — about two times greater than the average value of the control group (Table 1). By comparing the average values of copper concentrations, no statistically significant variation is noticed in comparison with the pre-treatment situation. On the other hand, the high values of copper concentration relative to the normal value evaluated in the serum [2, 3] can be explained by individual variations from the mean. Taking into account this fact, we initiated a data processing by selecting only cases in which Cu concentrations were at least two times greater, before or after treatment, than the average concentration considered as normal for the control group. Thus we chose 11 cases in which exceptions from the normal average concentration appeared before treatment. By calculating the variation in the concentration after treatment, in comparison with the concentration before treatment (D/I — I, %) for each subject,

we obtained for the selected group a 37% reduction of the serum Cu level, so that 11 of the 50 investigated subjects reached the normal level.

Copper is the main constituent of several enzymes, the most important one being cytochrome oxidase. It was also assumed that desmosine biosynthesis needs a copper-dependent monoamine oxidase. The experimental studies [4] show

Table 1

Concentrations of serum oligoelements (in mg/l) in subjects professionally exposed to chemical agents and in the control group (in brackets standard exceptions from the mean)

Element	Control group	Experimental group		D/I − I %
		Before treatment (I)	After treatment (D)	
Fe	1.41 (0.19)	2.57 (1.24)	3.32 (0.93)	+20
Cu	0.70 (0.10)	1.77 (0.55)	1.96 (0.79)	unsignificant*
Zn	0.49 (0.08)	2.41 (0.55)	1.66 (0.40)	−31
Br	1.76 (0.29)	2.38 (0.59)	2.29 (0.54)	unsignificant*

* Smaller than the error of the experimental method.

that copper deficiency inhibits the formation of cross-links in collagen and elastin. Rise in the copper level is accompanied by a growth in the reaction rate of molecular oxygen with cellular constituents.

Before treatment zinc has a high value in relation to the normal (reported by us: 0.49 mg/l and by other authors: 1.67 mg/l [5]; 1.34 mg/l [3]), and after treatment we can notice a return to the normal, by a 31% reduction (Table 1).

Up to the present more than 80 enzymes are known which contain Zn. Zinc can be bound to thiol groups, thus blocking iron binding and inhibiting the oxidizing reactions and those producing free radicals — destructive reactions catabolized by iron. Zinc also inhibits lipid peroxidation and fixes the cell membranes, making them more resistant to the free radicals attack.

Bromine does not significantly vary from a statistical point of view, after treatment. The average values of bromine concentration (Table 1) are very similar to those in the literature: 2.9 mg/l [5]; 2.81 mg/l [6].

Previous studies on human serum reveal very low levels of Mn and Ni. These new elements were found in only some of the samples. In literature very low serum concentrations of these elements are reported. Manganese: 0.12 mg/l [5], 0.00057 mg/l [7]. Nickel: 0.066 mg/l [5]. Of the total of 50 subjects, 15 had high concentrations of Mn in the serum before GH_3 treatment, and the cure lowered the Mn level by 80%, bringing it to normal level. Manganese is required by fatty acids biosynthesis, thus it may play a prominant part in the mechanism of atherosclerosis.

As far as Ni is concerned, of the total of 50 investigated workers only 33 presented detectable Ni concentrations with increased level. With the control group it was detected only in three samples. GH_3 treatment lowered the Ni concentration by 78% in comparison with the one before treatment, in 18 of 33 persons, a reduction that led to normal serum level.

We have not cleared up the role played by Ni in human organisms. It is known that nickel blocks the enzymes existing in the alveolate epithelium cell. Metal in contact with the sulfhydryl groups of these enzymes gives mercaptides. Thus, high Ni concentrations in the environment or food can facilitate the occurrence of pulmonary cancer.

We must point out that no lead traces are to be found in serum, not even with persons (11 in our lot) who work in a medium polluted by chemical agents, among which lead is the most important.

Results of measurements of serum Fe, Zn, Cu in the control group point to average values about two times lower in comparison with those in literature. Considering the high statistical significance of the determined means, we may assume that this difference is due to a reduced pollution degree in Romania as compared with the geographical areas in which the measurements quoted in literature were made.

Résumé. Pour la détermination des oligo-éléments sériques, on a utilisé la méthode d'analyse par émission de radiations X excitées par l'intermédiaire des particules accélérées. On a étudié 50 personnes (19—51 ans) professionnellement exposées aux agents chimiques métalliques et 30 personnes (21—54 ans) de la même aire géographique, comme lot témoin. Les éléments identifiés dans le sérum ont été: Fe, Cu, Zn, Mn, Ni, Br. Les variations des concentrations des oligo-éléments sériques mesurées sont discutées par rapport à leur signification physiopathologique.

REFERENCES

1. Johansson T.B., Akselsson R., Johansson S.A.E., *Proton-induced X ray emission analysis*, Nucl. Instrum. Meth., 1970, **142**, 67—86.
2. Vis R.D., Van Der Kam P.M.A., Verheul H., *Elemental trace and lysis in serum proton-induced X-ray fluorescence*, Nucl. Instrum. Meth., 1977, **142**, 159—163.
3. Valkovic V., *Proton-induced X-ray emission: application in medicine*, Nucl. Instrum. Meth., 1977, **142**, 151—159.
4. Graham Carla L.G., *Copper levels in livers of turkeys with naturally occurring aortic rupture*, Avian Dis., 1977, **21**, *1*, 113—119.
5. Mangelson N.F., Hill M.W., Nielson K.K., Ryder J.F., *Proton-induced X-ray emission analysis of biological samples: some approaches and applications*, Nucl. Instrum. Meth., 1977, **142**, 133—151.
6. Van Rinsvelt H.A., Lear R.D., Adams W.R., *Human diseases and trace elements*, Nucl. Instrum. Meth., 1977, **142**, 171—189.
7. Hasselmann W. Koenig, Richter F.W., Steiner U., Watjen U., Bode J.C., Ohta W., *Application of PIXE to trace elements analysis in biological tissues*, Nucl. Instrum. Meth., 1977, **142**, 163—171.

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GLI EFFETTI DELL'ETÀ E DEL GEROVITAL H_3 SULL'ATTIVITÀ DELLA SUCCINATOSSIDASI DAL FEGATO E DAL CERVELLO DI RATTO

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Riassunto. Si è studiato l'effetto dell'età e del Gerovital H_3 (GH_3) sull'attività del sistema succinatossidasico dalla mitocondria dal fegato e cervello di ratto.

I risultati dimostrano la mancanza delle modifiche dell'attività della succinatossidasi in rapporto all'età degli animali dai quali si è prelevata la frazione mitocondriale.

Nella prova « in vitro » l'aggiunta di Gerovital H_3 viene ad influire sull'attività del sistema della succinatossidasi, e le modifiche che appaiono sono dipendenti dalla concentrazione del Gerovital H_3 e dal tessuto dal quale provengono le frazioni mitocondriali. L'aggiunta di ridotta concentrazione di Gerovital H_3 (che corrisponde a $4{,}67 \cdot 10^{-6}$ M procaina) nell'ambiente d'incubazione ha effetto forte stimolante sull'attività della succinatossidasi, più intenso nel caso delle mitocondrie dal cervello che dal fegato. L'aumento della concentrazione di Gerovital H_3 (oltre $6 \times 4{,}67 \cdot 10^{-6}$ M procaina) inibisce il complesso enzimatico. I risultati suggeriscono che la stimolazione del sistema enzimatico succinatossidasico di Gerovital H_3 fosiase determinata da un aumento nella mobilità delle lipidi nella membrana mitocondriale modulando cosi la funzione delle proteine di membrana.

PREMESSE

La riduzione, che avviene coll'età, nelle funzioni fisiologiche dei tessuti puo essere provocata da molteplici cause, tra cui la diminuzione del numero di cellule dai tessuti, la riduzione dell'attività metabolica delle cellule individuali, ecc.

Numerose richerche provano di elucidare il meccanismo di azione dei farmaci biotrofici Gerovital (GH_3) e Aslavital (GH_4) al livello delle cellule.

Nella composizione dei detti farmaci si trova la procaina [1, 2] che agisce sulla membrana cellulare, ristabilendo il potenziale fisiologico, agisce sul metabolismo cellulare e stimola la funzione trofica del sistema nervoso. In piccole concentrazioni la procaina ha effetto attivante sulla respirazione del lievito di birra [3] e determina un consumo elevato di O_2 sull'omogenato di fegato di ratto [4] che avviene probabilmente per la stimolazione delle strutture enzimatiche che intervengono nella ossidoriduzione.

In un anteriore lavoro si è dimostrata l'influenza stimolante del GH_3 sulla fosforilazione ossidativa dalle mitocondrie dal fegato e dal cervello di ratto [5], Nella letteratura esistano alcune indicazioni riguardandi l'effetto dell'età sull'attività della succinatossidasi nei tessuti e nelle mitocondrie di ratto [6, 7, 8].

La riduzione dell'attività della succinatossidasi dalle mitocondrie dal rene di ratto viene spiegata da Barrows et al. [7] per la possibilità di perdita delle

mitocondrie dai tessuti e non per la diminuzione dell'attività della succinatossidasi per mitocondria [6].

Nel presente lavoro ci siamo proposti di studiare un aspetto del metabolismo energetico della frazione mitocondriale dal fegato e dal cervello di ratto, il sistema enzimatico della succinatossidasi in correlazione coll'età, nella misura in cui questo sistema puo essere influenzato dalla presenza "in vitro" del GH_3.

MATERIALI E METODI

LA PREPARAZIONE DELLA FRAZIONE MITOCONDRIALE

Si è lavorato sui ratti femmine Wistar di età: giovani 2—3 mesi; adulti 6—8 mesi; anziani 22—24 mesi.

La frazione mitocondriale dal fegato e dal cervello di ratto si è ottenuta secondo il metodo di Hageboom e Schneider [9], l'ambiente di separazione e lavaggio essendo di 0,25 M zucchero di barbabietola in tampone 0,005 M Tris HCl, ph 7,4.

La proteina mitocondriale si è determinata per il metodo Hartree [10] con l'albumine sierica di bovino come standard.

L'ATTIVITÀ DELLA SUCCINATOSSIDASI

L'attività complessiva del sistema della succinatossidasi è stata misurata tramite la determinazione della velocità di consumo dell'ossigeno in presenza di un eccesso di succinato. Abbiamo usato la tecnica manometrica Warburg descritta da Schneider e Potter [11]. L'ambiente di reazione (3 ml) è stato: 0,5 mM succinato di sodio; 20 mM tampone fosfato di potassio, ph 7,4; 0,002 mM cloruro di calcio; 0,02 mM citocromo C; 4—5 mg proteina mitocondriale. La soluzione di GH_3 è stata preparata fresca in 20 mM tampone fosfato di potasio ph 7,4 in concentrazioni tra $4{,}67 \cdot 10^{-5}$ Me $8 \cdot 4{,}67 \cdot 10^{-5}$ M. L'aggiunta di queste soluzioni nell'ambiente di reazione si è fatto prima dell'introduzione dei manometri nell'apparecchio Warburg. Il tempo di incubazione per il consumo di ossigeno, è stato di 20 minuti, la temperatura di 37°C. La fase gasosa è stata l'aria, il biossido di carbonio è stato assorbito con 0,2 ml idrossido di potassio 20%, introdotto sul centro dei vasi di reazione.

RISULTATI

L'attività del sistemo enzimatico succinatossidasi è data dal consumo di O_2: Q_{O_2} e vienne espressa in μl O_2/mg proteina / 30 min.

I valori ottenuti per le succinatossidasi dalla frazione mitocondriale dal fegato di ratto sono più alti dei valori per l'attività delle succinatossidasi dal cervello.

Non si sono osservate delle modifiche significative per la succinatossidasi dalla frazione mitocondriale di fegato e di cervello di ratto (Tabella 1) in relazione all'età degli animali dai quali provenivano le mitocondrie.

L'azione "in vitro" del GH_3 al livello della succinatossidasi nella frazione mitocondriale dal fegato e cervello di ratto vecchio dipende dalla concentrazione di GH_3 e dal tessuto da cui derivano le mitocondrie (fig. 1).

Il GH_3 agiunto in piccole concentrazioni ($4{,}67 \cdot 10^{-5}$ M procaina) nell'ambiente di reazione ha un effetto stimolante tanto sull'attività della succinatossidasi nella frazione mitocondriale dal cervello, quanto su quella dal fegato; l'intensità della stimolazione dipende dal tessuto analizzato.

Tabella 1

L'attività della succinossidasi nella frazione mitocondriale di fregato e cervello di ratto in relazione all'età (Q_{O_2}: µl O_2/mg proteina/30 min)

Gruppo	Frazione mitocondriale	
	Fregato	Cervello
Giovani	68,75±7,3	41,75±5,1
Adulti	66,97±9,9	40,52±6,8
Vecchi	66,14±8,9	39,80±4,8

La succinatossidasi della frazione mitrocondriale dal cervello di ratto è più sensibile all'azione del GH_3 (aumenta di 162,5%) di quella dal fegato (aumenta di 37,3%). Alle concentrazioni di GH_3, che oltrepassano aluni limiti ($6 \times 4{,}67 \cdot 10^{-5}$ M procaina) si osserva una inibizione della succinatossidasi.

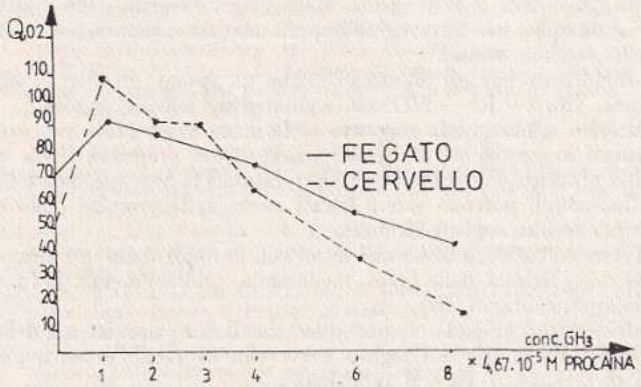

Fig. 1. — L'azione del GH_3 sull'attività della succinatossidasi dalla frazione mitocondriale dal fegato e cervello di ratto vecchio.

DISCUSSIONI

La diminuzione delle funzioni fisiologiche dei tessuti coll'età, puo essere una conseguenza della perdità del numero delle cellule dei tessuti, della riduzione dell'attività metabolica dei tessuti, o ambedue le possibilità.

Maier e Haimovici [12] trovano che coll'invecchiamento diminuisce la capacità di ossidazione dei sistemi della succinatossidasi e citocromossidasi nell'aorta umana, ma mancano le modifiche nel caso della vena cave e del fegato. Gli studi

effetuati in parallelo, sugli stessi tessuti di lepre e cane non indicano delle variazioni coll'età.

Barrows et altri [6] hanno studiato il modo in cui le modifiche del metabolismo avvenute coll'età, sono provocate della perdità delle cellule. Usando omogenati di tessuti constata la mancanza delle modifiche dell'attività del sistema succinatossidasi nel fegato di ratto coll'età e la riduzione della stessa nei reni e nel cuore; il rapporto si fà alla concentrazione di ADN dagli omogenati tissulari. Gli stessi autori [7] riprendono le esperienze con le mitocondrie dal fegato e dai reni di ratto, su due gruppi di età: giovani (12—14 mesi), vecchi (24—27 mesi), e la loro conclusione è che la riduzione dell'attività del sistema della succinatossidasi coll'età viene provocato piuttosto dalla perdità delle mitocondrie dei tessuti (reni) che dalla modifica nella concentrazione di enzima per mitocondria.

I nostri dati dimostrano che l'attività del sistema enzimatico succinatossidasi delle mitocondrie dal fegato e cervello di ratto non subisce delle modifiche coll'età (tab. 1); i gruppi di animali usati sono stati giovani (2—3 mesi), adulti (6—8 mesi), vecchi (22—24 mesi) dunque iniziando coll'età più piccole di quelle indicate da Barrows ed altri [7].

Il sistema enzimatico succinatossidasi è un sistema complesso, collocato al livello della membrana interna mitocondriale e comprende succinato-deidrogenasi, un numero di cofattori (cit. b, c, a, a_3) e la coenzima FAD. L'attività della succinatossidasi dipende da un certo grado di organizzazione, ciascun componente dovendo essere situato in una ottima correlazione spaziale di fronte alla componente con la quale sarà in interazione. Mantenere l'integrità della struttura mitocondriale è, dunque, un fatto di un'importanza straordinaria per l'attività del sistema della succinatossidasi.

Si è dimostrato che gli anestesici hanno un'azione „in vitro", sugli enzimi di membrana ($Na^+ - K^+ -$ ATP-asi, coliesterasi, adenilat ciclasi), con degli effetti inibitori o stimolanti in rapporto al farmaco usato [13].

I farmaci anestesici ed analgesici hanno come proprietà fisica comune la liposolubilità, proprietà che conferisce ai detti farmaci la non specificità dell'azione; i farmaci liposolubili potendo essere fissati anche sulle proteine della membrana [13] e cioè per le loro regioni idrofobe.

Per l'interazione degli anestesici locali con le lipidi dalla membrana ha luogo un'aumento della fluidità delle lipidi, modulando, probabilmente, le funzioni delle proteine dalla membrana [15].

I nostri risultati (Fig. 1) montrano la stimolazione del sistemo della succinatossidasi delle mitocondrie dal fegato e cervello di ratti vecchi, a piccole concentrazioni di GH_3 ($4{,}67 \cdot 10^{-5}$ M procaina).

Detti risultati possono essere spiegati per l'interazione della procaina — anestesico locale, — che aggiunta nel sistema di incubazione delle mitocondrie puo aumentare l'accessibilità mutua dei componenti dal sistema enzimatico per gli effetti di membrana.

Il trasporto del succinato per la membrana della mitocondria puo essere, a sua volta, influenzato.

A concentrazioni alte di GH_3 ($6 \cdot 4{,}64 \cdot 10^{-5}$ M procaina) l'attività della succinatossidasi è probabilmente inibita per cause dell'alterazione della struttura della membrana interna della mitocondria. L'effetto del GH_3 è più forte al livello della mitocondria dal cervello che a quella dal fegato.

I nostri risultati ottenuti „in vitro" mostrano, dunque, l'intervento del GH_3 su alcuni processi metabolici caratteristici alla mitocondria. È possible che quest'

azione, evidenziata „in vitro" partecipi al complesso meccanismo che si trova alla base della medicazione biotrofica con il GH_3.

Résumé. On a recherché l'effet de l'âge et l'addition du Gérovital H_3 sur l'activité du système succinatoxidasique des mitochondries de foie et cerveau de rat.

Les données relèvent l'absence des modifications de l'activité de la succinatoxidase en corrélation avec l'âge des animaux d'où provenait la fraction mitochondriale. L'addition de petites concentrations de GH_3 (correspondant à $4{,}67-10^{-5}$ M procaïne) dans le milieu d'incubation, a un effet stimulateur puissant de l'activité de succinatoxidase, plus intense dans le cas des mitochondries de cerveau que dans les cas des activités du foie. L'augmentation de la concentration de GH_3 de plus de $6\times4{,}67-10^{-5}$ M procaïne, inhibe le complexe ensymatique. Les résultats suggèrent que la stimulation du système ensymatique succinatoxidasique, à l'addition de petites concentrations de GH_3 est due à l'augmentation dans la mobilité des lipides de la membrane mitochondriale, modulant ainsi la fraction des protéines de membrane.

BIBLIOGRAFIA

1. Ana Aslan, Alex. Vrăbiescu, C. David, *Gerovital H_3* (1977).
2. Ana Aslan, Alex. Vrăbiescu, C. David, *Aslavital* (1975).
3. Ana Aslan, S. Cîmpeanu, *Die Wirkung von Novocain und p-Amino-Benzoesäure auf den Sauerstoff*, Verbrauch der Bierhefe. Arzneimittel-Forschung 8 (1958), pag. 116–120.
4. Ana Aslan, I. Irimescu, L. Cîmpeanu et al., *Die Wirkung von p-Amino benzoyldiäthyl aminoäthanol auf des Leber-Homogenat Weisser Ratten.* Agressologie 1: 381–388, (1960); Arzneimittelforsch 11 (1961), 36–37.
5. Ana Aslan, C. Rusu, S. Cofaru, L. Brazdeș, E. Constantinescu, *Study of Gerovital H_3 action on mitochondrial fraction in rat liver and brain.* Romanian J. of Geront. and Geriatrics, 1,1 (1980), 47–53.
6. C.H. Barrows Jr., M.J. Yiengst, N.W. Shock, *Senescence and the metabolism of various tissues of rats.* J. Geront. **13**, *1–4* (1958), 351–355.
7. C.H. Barrows Jr., J.A. Falzone, N.W. Shock, *Age differences in the succinoxidase activity of homogenates and mitochondria from the liver and kidneys of rats.* J. Geront., **15**, *1–4* (1960), 130–133.
8. C.H. Barrows Jr., L.M. Roeder, J.A. Falzone, *Effect of age on the activities of enzymes and the concentrations of nucleic acids in the tissues of female wild rats.* J. Geront. **17** (1962), 144–147.
9. G. Hageboom, W. Schneider, G. Palade, J. Biol. Chem., **172** (1948), 619.
10. E.F. Hartree, *Determination of Protein. A modification of the Lowry Method that gives a linear Photometric Response.* Anal. Biochem., **48** (1972), 422–427.
11. W.C. Schneider, V.R. Potter, *The assay of aminal tissues for respiratory enzymes II. Succinis Dehydrogenase and cytochrome oxidase.* J. Biol. Chem., **149** (1943), 217.
12. Nelicia Maier, H. Haimovici, *Metabolism of Arterial Tissue Oxidative Capacity of intact arterial Tissue.* Proc. Soc. exp. Biol. Med., **95** (1957), 425–429.
13. P. Seeman, Pharmacol. Rev., **24** (1972), 583.
14. P. Seeman, in *Cell membranes. Biochemistry, cell biology & pathology* (ed. G. Weissman, R. Claiborne), pH Publishing Comp. New York, 1975, 239–247.
15. B. Fourcans, M.K. Jain, in *Adv. Lipid Res.* (ed. R. Paoletti, D. Kritchevsky), vol. 12, Academic Press, New York–London, 1974, p. 147–226.

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CRITICAL STAGES IN OLD AGE RELEVANT FOR THE BIO-PSYCHO-SOCIAL EQUILIBRIUM OF THE INDIVIDUAL

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Summary. The research was carried out on a group of 338 old persons (over 60 years), selected from 6 urban areas (Bucharest, Călimănești, Eforie, Băile Felix, Băile Herculane, Mangalia), by social investigations at home, based on a questionnaire containing questions on: identity data, family status, health condition, special events occurring in the last years which affected their health condition and psycho-social equilibrium.

The answers with regard to critical events occurring in the last years were listed according to their frequency, as follows: occurrence of some invaliding diseases (57.0%); widowhood (33.1%); loss of independence (31.7%); retirement (23.4%); relocation (22.5%); separation from children (8.6%).

The research pointed out that the above mentioned critical stages frequently corresponded to the worsening of health condition by aggravation of the already existing diseases or the occurrence of some complications, especially those implying a psychic stress.

Our study also underlined that in most of the cases the worsening of health condition had severe psycho-social consequences.

The rate of old people who displayed a worsening of the health condition with bearings on the psycho-social status is 5 times higher with the aged who experienced such critical stages in the last years, in comparison with those who have not met with such events during their life time.

The phenomenon of aging is considered nowadays a physiological process and the final stage in the life of living organisms. The researches regarding this complex process in human beings have pointed out different aging rates both with regard to individuals and to groups of population. As far as the factors which influence the aging rate are concerned, three categories are to be taken into consideration. F. Bourlière [1] listed them as follows:

— the first one is heredity, whose importance and limits are demonstrated by studies concerning the senescence of monozygote twins;

— of second importance are the living conditions or the ecological factors (climatic, nutritive, professional, social), which are responsible for the great differences noticed between aging rates of various human populations and even within the same population, or between various socio-economic categories;

— thirdly, there are pathological factors which, by producing injuries to some organs or functions, cause an earlier senescence of the individuals under study.

Based on certain studies H. Le Compte and St. Idesbold [2] showed that negroes fall ill easier, age faster and live less than whites. The study also revealed that even with negroes there are some differences as not all of them are growing old at the same time, the differences being related to their living standard. Among

the factors which stimulate the processes of aging the authors mention: the lack of vital substances, absence of physical exercise, occupation, social relations, mental equilibrium.

Yet, some studies show that there is also a relationship between the emotional stress and the occurrence of some diseases having different clinical aspects. Alvin Toffler, in *Future Shock* [3] referring to the studies made by Holmes and Rahe shows that changes in the manner of life which require a difficult adaptation and a great self-control are correlated with disease no matter whether these changes depend or not on the individual, whether he wants them or not. The more important these changes, the higher the risk of falling seriously ill. The same author, pointing to some studies carried out in England, shows that the shock induced by widowhood with both women and men weakens the organism resistance and tends to stimulate aging. The investigators from the Institute of Community Studies in London, after analysing the documents and interviewing 4486 widowers, state that there is a real surplus of mortality in the first six months, that widowhood among men seems to bring about a rapid growth of the death rate, about 40% in the first six months.

Our research starts from the hypothesis that psychic traumas caused by certain events occurring in old age can produce changes, can break the bio-psycho-social equilibrium of the aged, contributing also to accelerate the aging rate.

Against this background we decided to find out the events which frequently induce psychic traumas capable of breaking the equilibrium of the aged, with a view to establishing measures that can lead to preventing or reducing such disorders.

The methodology of the research. The research was carried out by investigations at home, based on a questionnaire with cued and uncued answers. The questions referred to: identity data, family status, health condition, physical condition, special events occurring in the last years which affected the subjects to a particular extent, as well as their biological and psycho-social consequences.

Taking into consideration the answers given by old people, we made an inventory of the events that determined psychic traumas, together with the frequency of their occurrence.

In our study a "stage" is the period of time following some events that caused a stress capable of influencing the health condition and psycho-social equilibrium of the aged. We have not imposed strict delimitations regarding its duration.

The *group under study* comprised 338 old agers (over 60 years) selected from six urban areas (Bucharest, Călimănești, Eforie, Băile Felix, Băile Herculane, Mangalia). The group was selected by the sampling method, the main criteria being age and sex.

RESULTS

The research data collected enabled us to classify and arrange in series the events supposed to cause disorders in the bio-psycho-social equilibrium of the aged and which can be evaluated as "critical stages" in their lives, as follows:

— *The occurrence of invaliding, severe illnesses*, especially mental diseases, diseases implying long-term sufferings and privations, which lead to dependence and require various therapeutic procedures with an unforeseeable prognostication. Invaliding diseases were obvious with 57.1% of the persons in the group under study.

— *Widowhood* was indicated by 33.1% of the persons under study, men and women. It was appreciated that widowhood influences in particular the equilibrium of social life, in a period when the old person needs even more help and social assistance.

— *Loss of independence* was considered to be a critical stage by 31.7% of the aged, although not implying total dependence in all of the cases. Some of them complained of a psycho-social dependence, of the fact that for some activities and in certain periods, they have to appeal to other members of the family, even if only because they no longer trust their own abilities. Loss of independence was considered to be a serious problem with single old people without legal tutors, when immobilization totally isolated them from social life and when it was necessary to call for assistance.

— *Retirement* was appreciated as a critical stage by 23.4% of the group. It was considered a delicate problem, as it changed the social status of the old person and influenced his way of life.

— *Relocation* was noticed with 22.5% of the subjects; it is also a critical stage with old agers, because it causes breaking off social relations with their neighbours and friends and changes some of their customs and habits, adaptation being more difficult in advanced age. In our cases, relocation involved moving from one district to another or from rural to urban areas to live with their children. We did not consider the cases when people changed residence in order to enter public institutions for old agers — an even more difficult situation from the point of view of adaptation.

— *Separation from children* was found with 8.6% of the old persons and was considered a difficult stage for single, sick old people, especially when it took place without their consent.

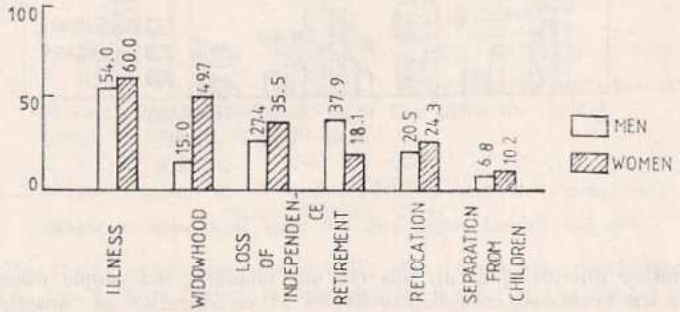

Fig. 1. — Critical stages with old agers in relation to sex.

As far as sex is concerned, women mentioned more frequently as critical stages "widowhood" (49.7% as against men — 15.0%), "illness" (60.0% — 54.0%) and "loss of independence" (35.5% — 27.4%), in contrast with men who pointed out "retirement" (37.9% — 18.1%).

As far as age is concerned, it has been ascertained that people under 70 years old mentioned more frequently "retirement" — 27.4% as against 12.9% for those over 80 —, while old people over 80 showed more frequently "loss of indepen-

dence" (77.8%), "illness" (68.5%), "widowhood" (59.3%) and "relocation" (44.4%).

More significant variations regarding the indication of critical stages were noticed in relation to the level of education and the health condition.

Thus, persons with higher education considered retirement as being the most difficult stage, three times more frequently than the persons with elementary education (66.7% against 18.8%).

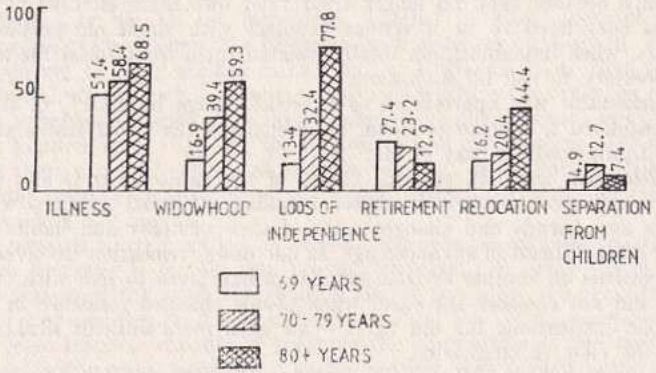

Fig. 2. — Critical stages with old agers in relation to age.

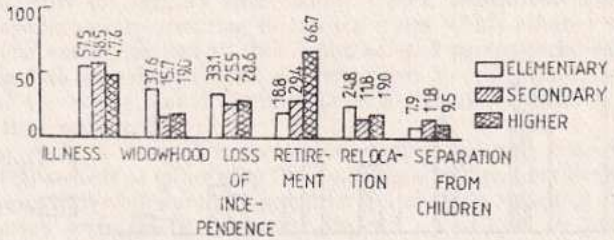

Fig. 3. — Critical stages with old agers in relation to studies.

Another interesting group was the one including old people whose health condition was evaluated, according to Rogers' [4] classification, as "unsatisfactory" or "bad", especially those with reduced ability to move and ensure self-service, who in most cases (over 90%) pointed out as difficult stages: "illness" or "loss of independence".

The research also emphasized the fact that the above mentioned critical stages frequently corresponded to the worsening of the health condition by aggravation of the already existing diseases or the occurrence of some complications.

It was also noticed that in most cases the worsening of the health condition involved psycho-social changes. The aggravation of the diseases or the occurrence of complications require more medical and family care, additional expenses, thus affecting the relations with the other members of the family. Under such circum-

stances the old person becomes suspicious, he develops a sense of uselessness, he finds himself abandoned or neglected. It is important to notice in this respect that the percentage of old people found to have a worse health condition with psycho-social consequences is 5 times greater with persons who experienced such critical stages, in comparison with those who have not met with such events (65.5% as against 12.6%).

We should also mention that psycho-social implications are more obvious with persons included in older age groups. Thus, while such problems were present

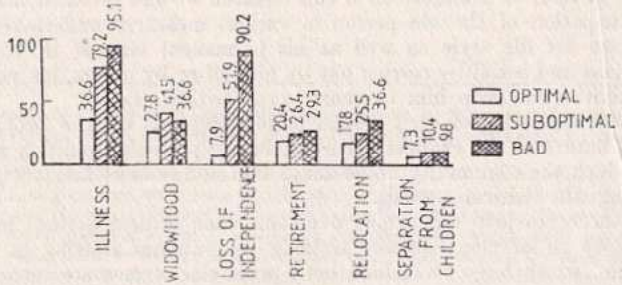

Fig. 4. — Critical stages with old agers in relation to health condition.

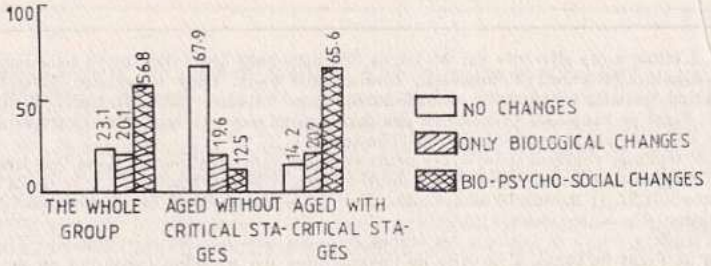

Fig. 5. — The worsening of the health condition and its consequences in relation to critical stages.

with 12.7% of the aged persons under 70, with people over 80 the proportion was 55.5%, i.e. 4 times higher. Overlapping of several of the critical stages is also possible.

CONCLUSIONS

— Our research demonstrated that stress induced by different events occurring in advanced age causes disturbances in the bio-psycho-social equilibrium of the individual and the worsening of the health condition contributes to the acceleration of the aging rate.

— Among the events that bring about stress and cause changes both on the biological and psycho-social planes, the following were pointed out more

frequently; the occurrence of some invaliding diseases, widowhood, loss of independence, retirement, relocation, separation from children.

During the time when such events occur and even afterwards, the old person is more susceptible to new diseases, to the aggravation or complication of the already existing ones, to mental disorders of a psycho-social origin; that is why such periods are considered to be "critical stages" requiring some measures meant to surmount them.

— It was noticed that avoiding or alleviating the stress produced by such events can be achieved only by giving the old person psycho-social information. As a matter of fact, on the occasion of this research we also revealed that the conscious participation of the old person in various measures undertaken in order to investigate his life style as well as his permanent interest in the different preoccupations and activities carried out by himself or by others, his participation in new activities can help him overcome such critical stages.

— The overcoming of such critical periods depends on the proportion and unexpected nature of the changes occurring in the person's condition and on the extent to which the community understands him and renders him adequate assistance during the critical periods.

— In order to help old people overcome such critical periods more easily, it is necessary to develop complex training programmes starting in the course of active life, which have to include both prophylactic measures concerning the health condition and a psycho-social training meant to help him face the changes occurring in the last years of life and including means of overcoming them.

Résumé. L'étude a été effectuée sur un lot de 338 personnes âgées (60 ans+) sélectionnées de 6 zones urbaines (Bucarest, Călimănești, Eforie, Băile Felix, Băile Herculane, Mangalia) par investigations sociales au domicile, en utilisant un questionnaire visant l'état civil, la situation familiale, l'état de santé, les événements des dernières années qui ont influencé d'une manière negative l'état de santé ou l'équilibre psycho-social.

Les réponses concernant les événements critiques sont mentionnées selon leur fréquence, à savoir: l'apparition des affections d'invalidité (57,0%); le veuvage (33,1%); la perte de l'indépendance (31,7%); la mise à la retraite (27,4%); le changement de l'habitation (22,5%); la séparation d'avec les enfants (8,6%).

L'étude a relevé le fait que les étapes critiques mentionnées correspondent à la détérioration de l'état de santé, à la suite de l'aggravation des maladies existantes ou de l'apparition des complications et surtout des affections dans l'étiologie desquelles le stress psychique a un rôle très important.

On a relevé aussi que l'aggravation de l'état de santé a de graves implications sur le plan psycho-social.

Le pourcentage des personnes âgées qui ont fait mention de l'aggravation de l'état de santé et des implications sur le plan psycho-social est 5 fois plus grand chez les personnes âgées qui ont passé par telles étapes, que chez celles qui n'ont pas vécu pareils événements.

REFERENCES

1. Bourlière F., *Evaluating methods of man's biological age* (in Romanian). Probleme gerontologice, I.N.G.G., 1965, *14*, 1.
2. Le Compte H., Idesbold St., *Le Compte's Law*, Z. Alternsforsch., 1965, Heft 2, Sept.
3. Toffler Alvin, *Future Shock* (Romanian translation). Ed. politică, București, 1973, p. 314–315.
4. Rogers E.S., *Human Ecology and Health*, New York, 1960.

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DEVELOPMENT OF A SYSTEM OF SOCIAL INDICES FOR THE ASSESSMENT OF THE AGEING PROCESS

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Summary. Based on modern principles using social indices in the study of ageing the author investigated over the period 1977–1979 a group of 847 active subjects from 2 industrial enterprises as well as retirees for age limit.

The study pointed out some correlations between biogenic, sociogenic and psychogenic factors in the ageing process, with a view to developing a system of social indices for the assessment of the ageing rhythm and a methodology of evaluating social ageing. The study also revealed significant peculiarities of social age based on a methodology which made use of acquired and manifest social roles, as well as of a significant correlation between the fulfilment of social roles and the health status of the subjects. The combination of social indices regarding acquired and manifest social roles, their quantification on the basis of criteria of acting levels and intensity degrees allowed for the completion of the biological tests battery with the social age test with practical applicability in the field of social gerontology.

Social indices are modern concerns with practical applicability in gaining a better knowledge of such complex processes as the care for ensuring the health of the population, preventing a precocious ageing of the work-force and maintaining the social usefulness of the elderly population. We have to mention that the specialty literature emphasizes the new requirements of the development of bio-medical and socio-medical instruments for measuring the health status and the ageing process of the population; such guidelines are based on the complex observations resulting from medical and socio-medical practice and research. International agencies like WHO have expressed the need to introduce social indices into the health status measurement criteria. Noticing both the differential character of the ageing process and the individual rhythms as far back as 1963, WHO suggested, on the occasion of the Kiew Seminar on Gerontology, the study of "such tests as to enable the measurement of the biological age", under the form of general thematics. The differences between the individual rhythms of ageing have been tested using medical and biological criteria, the clinical age criteria developed as far back as 1951 by Acad. Prof. Dr. Ana Aslan being well known. Although numerous papers have under-scored the effects of social factors on the ageing pace, on health status and on age-linked changes, systematic studies including the relevant social factors for the assessment of these processes are rarely encountered.

It is within this context that we undertook our research whose main aim was to develop a system of social indices for the assessment of the ageing pace, and a methodology of evaluating the social ageing process, based on the presumed presence of some correlations between biogenic, sociogenic and psychogenic factors

in the ageing process. On the other hand, the manifest expression of the ageing pace involves apart from the biological ageing also the psycho-social level. We felt that we could discuss, as a feature of the ageing process, the social ageing of the individual who, as a member of structured social groups, was also a holder of social status and expressed himself or herself by means of his or her social roles. When an imbalance emerges within the framework of the individual's social roles system, when his social roles diminish in number or intensity of expression, or when he is faced with the impossibility of fulfilling them, we can point to the "beginning of social ageing".

At the same time we felt that retirement when reaching the age limit, despite representing an important moment in the change of the social status of the aged, cannot be considered as the beginning of social ageing since there are numerous social roles which the individual concerned may continue to perform, as our society offers the elderly such an opportunity. These substitution modalities of the essential role in the occupational activity period can lead to reestablishing the balance in the social relations system and to an intensification of the social roles which are latent at the retirement date. Thus, the classification criterion of the social indices for the assessment of the ageing process consists in the commitment degree, in the social participation in, and responsibility for the social roles system of the individual, which is a general criterion for assigning the individual an adequate social place.

In order to totalize all representative social indices and to establish the correlations between the phenomena being dealt with, our research investigated, over the period 1977—1979, a number of 847 elderly subjects (45.4% men and 54.6% women). Our lot included 19.2% working subjects aged 45—60, employed by two units with different industrial structures, i.e. metallurgical works "Vulcan" and textile mills "Suveica", and 80.8% retired elderly over 55 (women) and over 60 years (men).

The data were collected by means of a complex social survey using the standard interview and the questionnaire methods, in view of covering the widest possible area of data regarding the specific fulfilment of social roles in work, family, community culture, within the framework of micro-group interpersonal relations. We had in view both the intensity of participation and the degree of satisfaction; the social status of the subjects was established by recording their occupational activities.

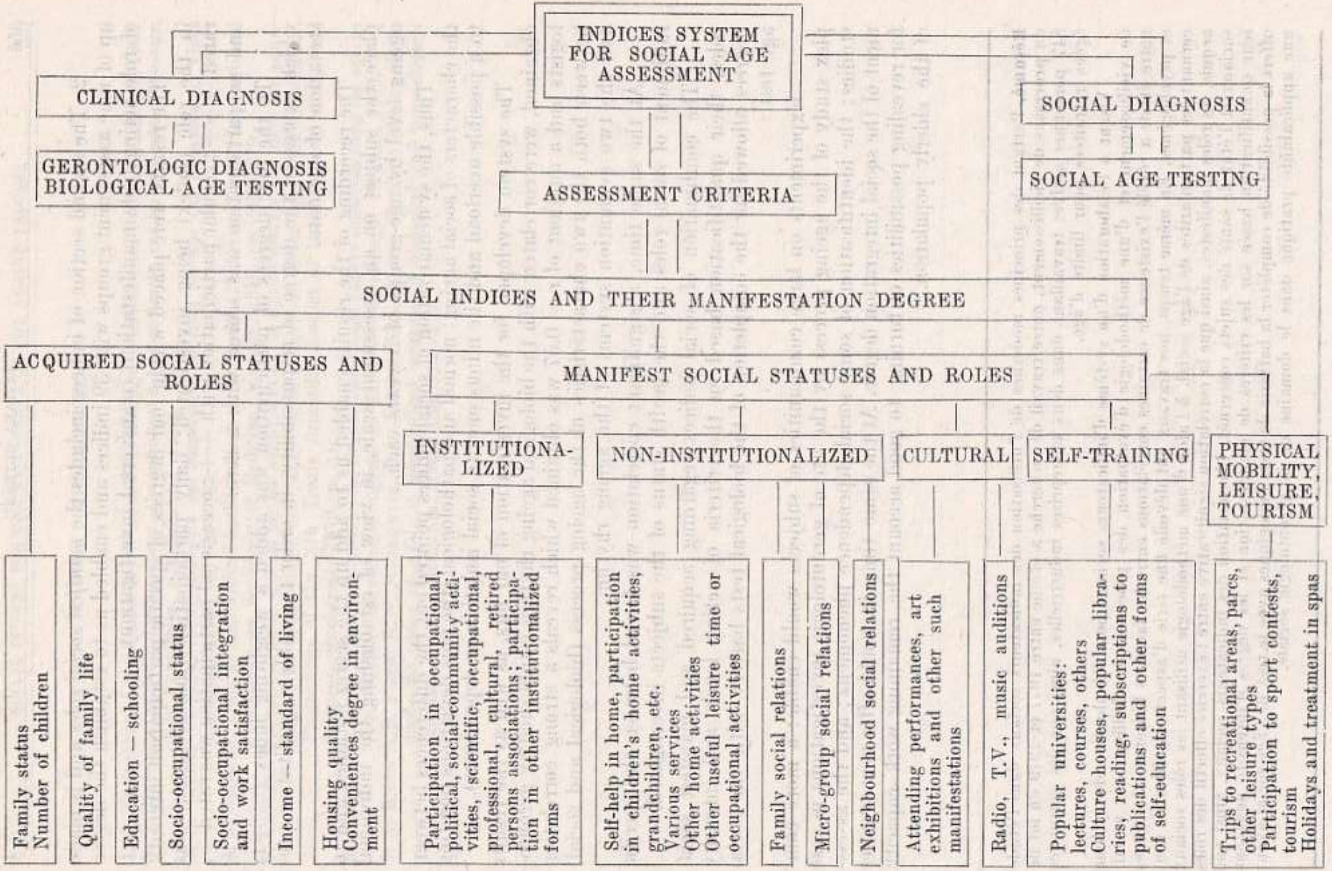
The analysis of the health status was carried out by the company's medical dispensary and by the gerontologic medical consulting units which aimed at establishing the gerontologic diagnosis, that is the biological rhythm.

For the statistical data processing we used specific techniques; all actions, roles and their expression at the social level were analyzed by age group, following which an average index was computed for each age-group (5 years interval each) and for each role-type investigated in order to achieve an assessment by scoring.

The results of our study after processing, categorizing and ordering the data obtained, led us to a first arrangement in two large sections of social indices resulting from the analysis of the social roles fulfilment:

1. The first section reflects the *acquired social roles*, which supply us with the framework for placing the subject within the socio-familial and socio-occupational parameters (inclusive of the social status) viewed on an "age continuum" (longitudinal survey), and includes 9 groups with 23 indices investigated based on four degrees of satisfaction (see Table 1).

Table 1


INDICES SYSTEM FOR SOCIAL AGE ASSESSMENT
CLINICAL DIAGNOSIS
GERONTOLOGIC DIAGNOSIS BIOLOGICAL AGE TESTING
SOCIAL DIAGNOSIS
SOCIAL AGE TESTING
ASSESSMENT CRITERIA
SOCIAL INDICES AND THEIR MANIFESTATION DEGREE
ACQUIRED SOCIAL STATUSES AND ROLES
MANIFEST SOCIAL STATUSES AND ROLES
INSTITUTIONALIZED
NON-INSTITUTIONALIZED
CULTURAL
SELF-TRAINING
PHYSICAL MOBILITY, LEISURE, TOURISM
Family status
Number of children
Quality of family life
Education – schooling
Socio-occupational status
Socio-occupational integration and work satisfaction
Income – standard of living
Housing quality
Conveniences degree in environment
Participation in occupational, political, social-community activities, scientific, occupational, professional, cultural, retired persons associations; participation in other institutionalized forms
Self-help in home, participation in children's home activities, grandchildren, etc.
Various services
Other home activities
Other useful leisure time or occupational activities
Family social relations
Micro-group social relations
Neighbourhood social relations
Attending performances, art exhibitions and other such manifestations
Radio, T.V., music auditions
Popular universities: lectures, courses, others
Culture houses, popular libraries, reading, subscriptions to publications and other forms of self-education
Trips to recreational areas, parcs, other leisure types
Participation to sport contests, tourism
Holidays and treatment in spas

2. The second section of indices includes the *manifest social roles* and is made up of nine assessment groups with 39 indices and enabled us to establish the degree of role acting (role manifestation) (transversal investigation).

The results were placed within four degrees of specific participation intensity in the role (index) being investigated: daily participation (manifestation) was rated +++; regular participation with ++; occasional participation was rated +, and no participation was scored with a zero.

To the four degrees of participation was added a weighting index (= +1) which expressed the degree of responsibility, in order to enable a qualitative presentation of our data.

The recording of the results enabled us to add up the scores obtained and to place the subject on an assessment scale, in view of establishing the individual ageing level by age-groups of 5 years each.

Thus, the systematization of social indices pointed out the differences between the characters of social ageing: normal and pathological (the plus deviations pointing to a possible overload and the minus ones to social isolation or dependence).

The system developed for the investigation of our lots, as well as the results obtained, were correlated with the biological ageing rhythm established by gerontologists and a quotient of $r = 0.57$ was obtained which reveals a strong correlation between both the two characteristics of the ageing process (biological and social) and the two evaluation systems of the ageing rhythm.

At the same time, a significant correlation was found between the specific fulfilment of social roles and the health status of the subjects investigated.

The combination of social indices regarding acquired and manifest social roles, their quantification based on the criteria of acting levels and intensity degrees allowed for the completion of the biological tests battery with the social age test.

Experiments on large communities of subjects would enable: a more complex study of the ageing process by the use of gerontologic investigations in case studies; the identification of some social dependence phenomena; and the assessment of the social integration degree. At the same time it would offer new avenues for revealing possibilities of turning to good account the remaining work capacity of the elderly population.

Résumé. Partant des principes modernes de l'utilisation des indicateurs sociaux dans l'étude du processus de vieillissement, notre travail de recherche a étudié entre 1977 et 1979 un lot de 847 personnes actives travaillant dans deux entreprises industrielles, ainsi que des personnes âgées retraitées pour limite d'âge.

Visant à l'élaboration d'un système d'indicateurs sociaux pour l'évaluation du rythme de vieillissement et d'une méthodologie d'évaluation des processus de vieillissement social, notre étude a révélé l'existence de certaines corrélations entre les facteurs biogènes, sociogènes et psychogènes. En même temps, nos travaux ont dévoilé une série d'aspects significatifs concernant les particularités de l'âge social, à l'aide d'une méthodologie utilisant les rôles sociaux acquis, les rôles manifestes, ainsi que la corrélation significative entre l'exercice effectif des rôles sociaux et l'état de santé des sujets concernés. L'association des indicateurs sociaux, ainsi que leur quantification basée sur les critères de manifestation et les degrés d'intensité nous ont offert la possibilité de compléter la batterie de tests biologiques avec le test de l'âge social ayant une applicabilité pratique dans le domaine de la gérontologie sociale.

REFERENCES

1. F. Bourlière, *Les méthodes de mesure de l'âge biologique chez l'homme*, Bulletin OMS, **245**, 1963.
2. J. Delors, *Les indicateurs sociaux. Contribution à une recherche sur les indicateurs sociaux*, Ed. Futuriples, S.E.D.E.I.S., Paris, 1971.
3. A. Ciucă, Vl. Jucovschi, *Biologic age assessment in field surveys* (in Romanian), Viața medicală, 1973, *16*, 739–743.
4. J. Elinson, *Towards sociomedical health indicators*. In *Health, Medicine, Society*, International Conference on Sociology of Medicine, Warsaw, 1973, pp. 267–279.
5. Tatiana Olteanu, *Social criteria for the assessment of the ageing process and steps for maintaining the health status and for the social integration of the elderly* (in Romanian), Proceedings of the Xth Yearly Scientific Session of the Academy of Medical Sciences, Bucharest, 1979, p. 11.
6. Rodica Petolea, Tatiana Olteanu, A. Ciucă, *Some risks factors in accelerating the ageing rate*. VIIIth European Congress on Clinical Gerontology, Neptun, 1979.
7. S. Katz, A.B. Ford, R.W. Moskowits, B.A. Jakson, M.A. Jaffe, *Studies of illness in the aged: the index of ADL, a standardized measure of biological and psychological function*. J. Am. Med. Ass., 1963, **185**, 914–919.

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LA VIE SCIENTIFIQUE

Les 29–31 mai, à la Section Clinique Otopeni de l'Institut National de Gérontologie et Gériatrie, ont eu lieu les travaux de la II[e] Session: «Les jours de la Gérontologie roumaine» – organisée par L'Académie des Sciences Médicales, U.S.S.M. – Société de Gérontologie et l'Institut National de Gérontologie et Gériatrie, avec la thématique:

– La pharmacologie des produits biotrophiques à base de procaïne: Gérovital H_3 et Aslavital;

– La biochimie de la sénescence au niveau cellulaire;

– Aspects médicaux et sociaux dans la pathologie psychique du vieillard.

Plus de 300 spécialistes y ont participé.

Dans le cadre du thème « Pharmacologie des substances biotrophiques à base de procaïne », les rapports présentés par Ana Aslan, Al. Vrăbiescu, Lidia Hartia, Georgeta Enăchescu, C. Crăescu et coll., ont apporté de nouvelles données concernant les résultats obtenus les dernières années et qui constituent une contribution importante dans la connaissance des mécanismes d'action et de l'efficience de la thérapie biotrophique dans la prévention et le traitement du processus de vieillissement et de la pathologie chronique associée.

En ce qui concerne les recherches de pharmacologie clinique, des résultats importants ont été obtenus dans l'étude longitudinale effectuée dans notre Institut, sur les lots de traitement à longue durée, au Gerovital H_3 et Aslavital.

L'analyse statistique des données cliniques, fonctionnelles, psychologique, biochimiques et hématologiques sur une période de 23 ans, a mis en évidence l'amélioration ou la normalisation de la majorité des indicateurs appliqués, et l'influence favorable sur l'état psychique et physique, la diminution de la morbidité et le prolongement de la durée de vie.

On accorde une attention toute spéciale aux recherches pharmacologiques concernant l'action antidépressive du Gérovital H_3; les exposés ont porté sur les résultats des recherches effectuées chez nous ainsi qu'a l'étranger, de même que sur les recherches de la méthode « double-blind ». On a relevé la relation entre les modifications de l'activité enzymatique de la cellule nerveuse et tout d'abord de la monoaminooxydase chez les âgés et les états dépressifs ainsi que l'intervention du Gérovital H_3 à ce niveau.

L'inhibition de l'activité MAO due au Gérovital H_3 a fait l'objet des recherches expérimentales qui ont relevé les caractéristiques de cette action, par exemple: la durée, l'intensité, la réversibilité, la compétitivité, l'appartenance au type B et les différences par rapport aux inhibiteurs classiques.

D'autres recherches ont relevé le fait que les produits à base de procaïne améliorent la capacité intellectuelle, la mémoire, le comportement, une meilleure adaptabilité au stress, le rétablissement de l'équilibre homéostatique corticostéroïdes catécholamines et le retour aux valeurs antérieures au stress, de la plupart des indicateurs histochimiques étudiés.

Les résultats obtenus seront utilisés à l'appui des indications thérapeutiques, concernant les effets des états de sursollicitation dans le processus de vieillissement.

Les recherches cliniques-biologiques des dernières années ont accordé une attention toute spéciale à la propriété antitrombophilique de la médication au Gérovital H_3. Cette action, plus évidente dans le cas de l'Aslavital, a été relevée par l'amélioration des indicateurs huméraux, thrombophiliques, l'hyperagglutinabilité thrombocitaire à ADP l'hypofibrinolyse, le déficit d'anticoagulants physiologiques et la dislipidémie. L'Aslavital est devenu une médication antithrombophilique efficace dans le traitement des facteurs huméraux, de risque et de la prévention des accidents thrombotiques chez les âgés.

Les produits Gérovital H_3 et Aslavital influencent d'une manière favorable les mécanismes immunologiques. On a fait remarquer: l'accroissement de la capacité de phagocytose des histomacrophages du péritoine des rats et des leucocytes humaines, après le traitement « in vitro » ou « in vivo »; un pourcentage accru de lymphocytes porteurs de récepteurs Fc; une plus grande capacité de former les rosettes du lymphocyte T; le niveau diminué des autoanticorps par rapport aux témoins. Ces données contribuent à la connaissance des mécanismes des produits biothrophiques à base de procaïne, augmentent la résistance de l'organisme aux maladies aiguës et chroniques, préviennent les phénomènes d'autoagression.

En ce qui concerne l'action au niveau cellulaire, on a constaté: l'augmentation de la durée de vie des cellules des cultures traitées; les modifications de l'équipement enzymatique des

cellules des cultures traitées, le maintien de la structure et du fonctionnement des principaux organites cellulaires et d'une intense activité métabolique; on a constaté aussi la stimulation des processus de la synthèse ADN, l'intensification des processus de phosphorillation oxydative; et de respiration mitochondrielle dans le cerveau de rat traité de même que la stimulation des enzymes de la chaîne respiratoire, la stimulation des enzymes protéolytiques, la stimulation de la stabilité de la membrane, effet fluidifiant qui facilite le transport passif par membrane, etc.

Les recherches sur les membranes biologiques, cellulaires, et souscellulaires pendant la sénescence, ont montré que la médication biotrophique garde la capacité de moduler la dynamique membranaire et de contrôler certains aspects fonctionnels, à savoir le transport ionique et l'excitabilité, la réactivité immunologique, la réaction à l'irradion, etc.

En ensemble, les récentes recherches de pharmacologies des produits biotrophiques Gérovital H_3 et Aslavital, ont apporté d'importantes contributions dans l'approfondissement de la connaissance de leurs mécanismes d'action, dans l'identification des propriétés thérapeutiques, afin de différencier le traitement, comme à l'interrelation avec d'autres médicaments utilisés dans la clinique gériatrique. Ces recherches ont pour but d'acquérir de bons résultats au cours des actions de gérontoprophylaxie et de thérapie gériatrique élargies sur le plan national.

Dans les comptes rendus présentés par Ana Aslan, Cornelia Rusu, Elisabeta Constantinescu, Al. Vrăbiescu, Theodora Ionescu et coll., sur la biochimie de la sénescence au nivel cellulaire, on y a envisagé les mécanismes de réglage et de contrôle du processus d'altération de l'intégrité de structure de la matière vivante et le rôle des radicaux libres dans le processus de vieillissement. Parmi les facteurs les plus importants impliqués dans les mécanismes de réglage et de contrôle des processus biochimiques au niveau cellulaire, liés au processus de vieillissiment, on a présenté les données concernant le rôle des acides nucléiques de même que les systèmes enzymatiques, en insistant sur l'aspect de l'induction enzymatique dans le processus de vieillissement. Les travaux présentés ont porté également sur les importantes contributions roumaines à la connaissance très approfondie du processus de vieillissement. On insiste sur le fait que les enzymes, par leur rôle fonctionnel contribuent au contrôle des différents métabolismes et de l'interrelation, au réglage adaptable des fonctions des organes, des tissus, des cellules, d'organite souscellulaire.

On conclut sur la nécessité de continuer les études sur les modifications de posttranslation, de l'induction enzymatique, en tant qu'indicateur du réglage de l'adaptation des organismes, des processus de détérioration, de leur fonctionnalité et des substances natives.

Un autre thème présenté à la Session a été le thème des aspects médicaux et sociaux dans la pathologie psychique de l'âgé.

Les rapports présentés par Ana Aslan, C. Bălăceanu, M. Dumitru, V. Jucovschi et coll., ont souligné, sous l'aspect clinique, l'importance des états dépressifs, la gravité des affections psychoorganiques et les aspects des urgences psychiatriques en gériatrie.

On a analysé aussi les mécanismes de la genèse des états dépressifs, en relevant l'apparition des changements biochimiques intraneuraxiaux (la baisse des catécholamines) et des déterminations exogènes.

On a prouvé l'importance théorique et pratique de la pathologie mentale pendant le III[e] âge, en insistant sur la fréquence des troubles psychiques des âgés, sur les problèmes médicaux des affections géro-psychiatriques, de même que la grande responsabilité de la famille et de la société.

On a précisé que la pathologie mentale de la vieilliesse doit être abordée par une intervention multidisciplinaire, représentée par la psychologie, les sciences médicales et psychosociales. Cet abord multidisciplinaire représente une solution pratique des problèmes de l'âgé à affections psychiatriques.

La solution de ces problèmes a une triple perspective: prophylactique, curative et de protection familiale et sociale.

Il faut faire la mention des résultats favorables du traitement des états dépressifs au Gérovital H_3 et Aslavital; on a relevé également le rôle des préparations biotrophiques à base de procaïne dans le traitement des affections psychoorganiques, arthériopates et dégénératives. On a prouvé l'importance du traitement gériatrique par la méthode Aslan dans la prophylaxie géro-psychiatrique.

Sous l'aspect médical et social les travaux présentés ont relevé l'importance de l'implication médico-sociale de la géro-psychiatrie de même que leur étendue et actualité. Il résulte les priorités:

1. La nécessité de la contribution de l'Institut National de Gérontologie et Gériatrie INGG à l'extension des recherchers épidémiologiques et géronto-psychiatriques, ainsi que la connaissance plus approfondie du nombre et de la proportion des malades psychiques âgés et vieillards, les types des maladies psychiques fréquentes chez les âgés, la distribution de ces mala-

dies sur le plan territorial, de même que les facteurs responsables de leur apparition et évolution.

2. Du point de vue pratique a résulté la nécessité de la collaboration des spécialistes du domaine de la gériatrie et de la psychiatrie, aussi que des organisateurs de la santé publique, dans l'élaboration des programmes de mesures prophylactiques, y compris l'éducation sanitaire, dans les problèmes de géronto-psychiatrie et dans l'action d'organiser les services psychiatriques pour les âgés et les vieillards. On a relevé l'importance du médecin généraliste dans la solution de cas de géronto-psychiatrie, étant donné le fait que le réseau psychiatrique existant ne peut intervenir que partialement. On a souligné aussi la nécessité du développement des cabinets de gériatrie afin de résoudre les problèmes des affections psychiques des âgés et des vieillards.

On a accordé une importance toute spéciale aux problèmes d'expertise du malade psychique, d'élaboration des critères de retraite, d'invalidité et d'explorer les possibilités de récupération et réinsértion sociale.

3. Il a résulté aussi la nécessité de l'approfondissement des recherches concernant les problèmes spécifiques de l'assistance sociale, demandée par cette catégorie de malades, selon la gravité de l'affection et la possibilité de soigner et de maintenir le malade au milieu de la famille.

4. En conclusion il faut retenir que les multiples et difficiles problèmes de la géronto-psychiatrie peuvent être résolus seulement dans les conditions de l'existence du personnel médical et auxiliaire spécialisé et dévoué, ce qui constitue encore un desideratum même pour les pays les plus avancés.

Pour terminer, on considère que les travaux présentés ainsi que les discussions très précieuses, ont souligné l'actualité de ces problèmes et la nécessité de leur developpement par de nouvelles recherches et par des mesures appliquées.

Les travaux de synthèse et les communications ont mis en évidence les contributions originales de, la gérontologie roumaine, de première importance étant la méthode originale du Prof. Dr. Ana Aslan de prophylaxie et traitement aux substances biotrophiques.

On considère que les conceptions actuelles et les orientations de la gérontologie et de la gériatrie roumaine vont contribuer à l'amélioration de l'assistance médicale et sociale des personnes âgées et vieilles. Dans ce but on a proposé des mesures pratiques. L'Institut National de Gérontologie et Gériatrie en qualité de forum de recherche et méthodologie du Ministère de la Santé, doit soutenir leur réalisation.

Al. Vrăbiescu

ROMANIAN J. GERONT. GERIATRICS, 1980, 1, 2, p. 363–364

BOOK REVIEWS

BAZELE GERONTO-CARDIOLOGIEI (Bases of Geronto-cardiology), by M. Dumitru. Ed. medicală, Bucharest, 1979, 231 pages

Already quoted in recent works on clinical gerontology, Dr. Mircea Dumitru's book appears as an urgent editorial necessity not only for the Romanian geriatricians, at present renowned throughout the world, but for numerous other specialists, particularly in internal medicine, who attend aged patients.

From the introductory chapter, the author specifies the framework and conditions under which geriatrics has developed during the last years, emphasizing the importance of the longitudinal screening investigations and pointing out the Romanian gerontological researches conducted by Marinescu, Parhon, Aslan.

The fundamental clinical concepts of human aging are dealt with in the first chapter, according to the required essential differentiations between aging and old age, the latter being a stage in the course of ontogenesis, whereas the former is a dynamic continuous process. 'Aging means not only involution but also evolution' (p. 19). The heart of the aged is defined on the basis of anatomic, physiological, electrocardiographic criteria. They are completed by radiologic criteria among which the coronarographic ones remain 'an exceptional method for the investigation of the coronary tree' (p. 46).

It is the merit of the book to lay stress on the importance of the decisive clinical criteria. The clinical element is essential and the author emphasizes the fact that these (classical semeiological methods) 'are of topical interest . . .'. The data on vascular involution (ch. 3), known from both the old and current literature are also fully presented, and completed by the contribution of the researchers from the National Institute of Gerontology and Geriatrics. The chapter entitled "Cardiovascular pathology with the aged" is comprehensive. With excellent illustrations, the author's arguments based on numerous references, regarding the peculiarities of this pathology with the aged are convincing because of the highly scientific demonstration. The author suggests the term 'coronary ischemic cardioangiopathy (CICA)' for the coronary ischemic cardiopathy; a new term has thus been introduced in the geriatric cardiology based on a plausible argumentation (p. 67).

In relation to physiopathological elements, with the skepticism resulting from the exhaustive knowledge of the facts, with clinical understanding, reflecting routine, Dr. Mircea Dumitru states that: 'the nonuniform character of chronic CICA is essential for its pathogenesis and physiopathology' (p. 82).

In the case of acute CICA, its olygosymptomatic, atypical aspect is considered with good reason as characteristic of the aged. In this respect, the case P.T. aged 78 is edifying and useful for the argument. The myocardial failure in the aged has a severer evolution and prognostic than in adults (p. 107). The author considers quite difficult the diagnosis of the latent myocardial failure.

Emphasizing the fact that chronic atrial fibrillation is the most frequent rhythm disturbance in chronic CICA, Dr. Mircea Dumitru based on his own researches states that: 'a differentiation is required between the orthogers with AFI and the aged with chronic CICA and AFI' (p. 111).

The therapeutic approach is the classical one to which the simultaneous administration of Aslan biotrophic products is recommended in aged. The general assistance is particularly important. The treatment of chronic CICA with myocardial insufficiency or/and rhythm disturbances is considered a problem of 'the myocardial pathology in the aged' (p. 126). The administration of tonicardiac and diuretic drugs to the aged is also mentioned. Quite useful specifications are made on the treatment of chronic CICA with rhythm and conduction disturbances (p. 137–146).

Cerebral vascular pathology is presented to the extent to which information is required in this volume by some data regarding cardiogerontology. The chapter on "Arterial hypertension with elderly and aged" (p. 156–171) is also quite useful; the space allows us only to mention it because of the diagnosis and therapeutic problems raised by this disease with the aged. The final chapter mentions briefly aspects specific to the advanced age pathology of cardiovascular diseases which are not frequent with the aged or did not make the direct object of this volume. These diseases are: congenital myocardial diseases, subacute bacterial endocarditis, rheumatic myocardial diseases, chronic pulmonary heart, thyroid cardiopathy, sclerosis of the aorta, peripheral ischemia.

Over the course of more than 200 pages, the author pleads convincingly and competently, on the basis of his own experience and numerous selected references, for the better understanding of cardiovascular peculiarities in the third age. The objective is thus achieved of presenting selective data which should be the bases of gerontocardiology; in this sense the book is essential for all the researchers interested in the cardiology of the aged and, generally, in clinical gerontology. We heartily recommend the volume of Dr. Mircea Dumitru, considering that it opens new prospects to the study of human aging.

Prof. Gh. Creţeanu
5th Medical Clinic, Iaşi

PATHOBIOLOGY OF CELL MEMBRANES, edited by B.F. Trump and A.U. Arstila. Academic Press, New York, 1975, 497 pages

This inaugural volume in a multivolume treatise reflects the rapidly expanded interest in the mechanisms of membrane alterations in disease processes. The book includes 11 chapters with 14 outstanding contributions of pathologists and cell biologists, on concepts related to membrane alterations in cell injury as well as methods for elucidating such changes.

In the last years much information has accumulated on the membrane structure and function and it has been pointed out that alterations in the membrane structure and physiology play an important role in the cellular pathological processes.

In the first chapter *B.F. Trump* and *A.U. Arstila* deal with the general concepts of cellular alterations and give some details concerning the role played by membranes in the molecular pathology and premature aging.

In the second chapter *R.B. Henkens* treats of the applications of circular dichroism in the study of membranes. This technique and other methods such as nuclear magnetic resonance, spin electronic resonance, and infra-red spectroscopy contributed to the development of a new conception on the molecular architecture of membranes and led to new conclusions on the protein structure, lipid mobility, lipid-proteic interactions and on the functional changes in the membrane molecular structure. Although at present little is known concerning the circular dichroism spectra of pathologically altered membranes, it is obvious that this approach may give extremely important new informations on the molecular mechanisms involved in the aging process.

In the next chapter *A.L. Tappel* talks about the significance and role played by changes induced by peroxidation in certain aspects implied in the aging process. Damage to membraneous parts of the cell by lipid peroxidation has been implicated as one of the deteriorative mechanisms involved in aging.

J.R. Robinson presents the main aspects concerning the regulation of the cellular volume and its changes due to the primary or secondary injuries of cell membranes. The experiments are presented on the basis of current membrane theory and concepts of ion pumps. All changes in membrane permeability are accompanied by intracellular ionic changes, many of them being very important in the functional changes that lead to various damages implicated in the aging process.

J.S. Cook reviews the pathogenesis of cell swelling and lysis following interactions of ultraviolet light with the erythrocyte membrane and discusses it in the context of rapid cation fluxes. Ionizing and ultraviolet irradiation are important models of cell damage, loss of viability and aging.

J.L.E. Ericsson and *U.T. Brunk* discuss the alterations in the membranes of lysosomes which may constitute important factors in both pathogenesis and aging.

P.J. Jacques points out the important role of endocytosis not only in normal cell physiology but also in pathophysiology. It has become increasingly evident that defects in the endocytic apparatus may lead to cell injury within the cell's phagolysosome system.

R. Seljelid, H.J. Helminen and *W.O. Dobbins* present the role played by hormones in the cellular mechanisms of tissular atrophy and the action induced by thyroid lysosomes. Many of the thyroid dysfunctions can be described in terms of impaired lysosome function or membrane defect. The application of cell biological methods to the study of functional disturbances in the thyroid seems particularly promising in the study of premature aging.

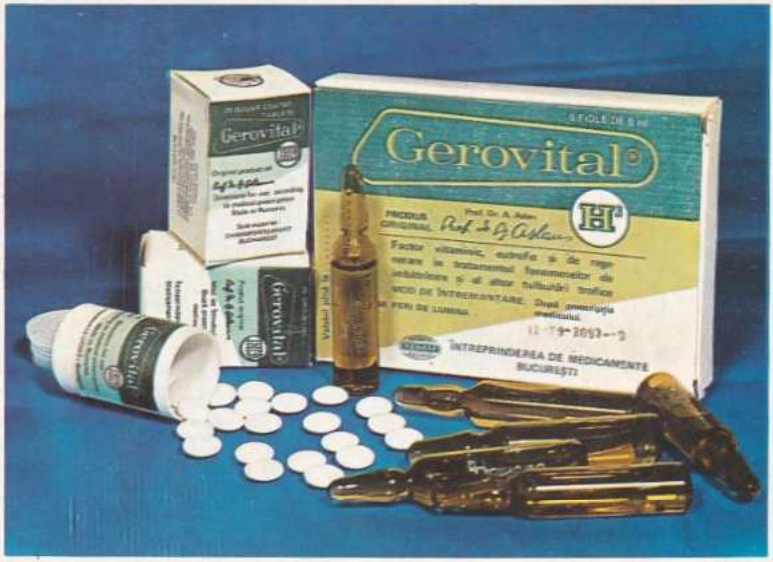
A. Goyer and *Bonnie C. Rhyne* discuss the effects of toxic materials on the mitochondrial membrane and function, the possibility of using mitochondria as experimental model.

At present it is necessary to study thoroughly the normal and pathological membrane physiology as well as to increase the cell biologists' knowledge in the field of pathological processes related to the aging process. The work "Pathobiology of cell membranes" meets these requirements.

Theodora Ionescu

original products of Prof. Dr. A. Aslan

GEROVITAL H3



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- dystrophies of the skin, nails and hair; neurodermitis; eczemas, alopecia, sclerodermia, psoriasis, vitiligo;
- vascular spasms;
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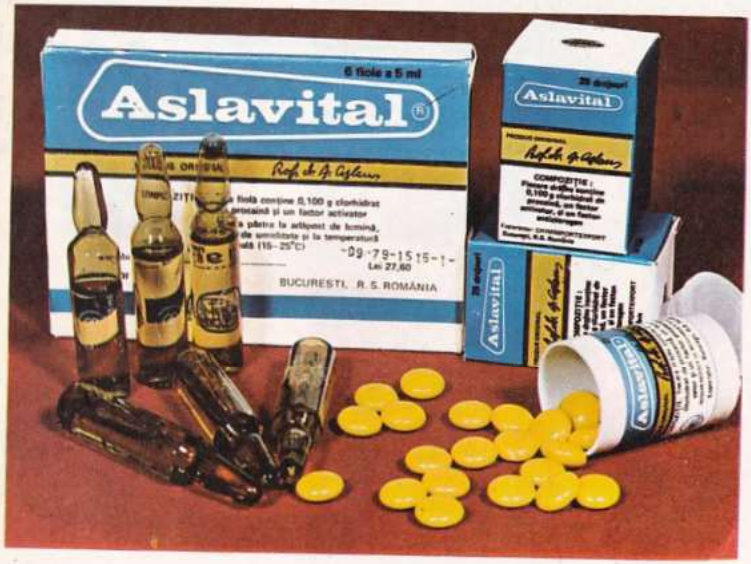

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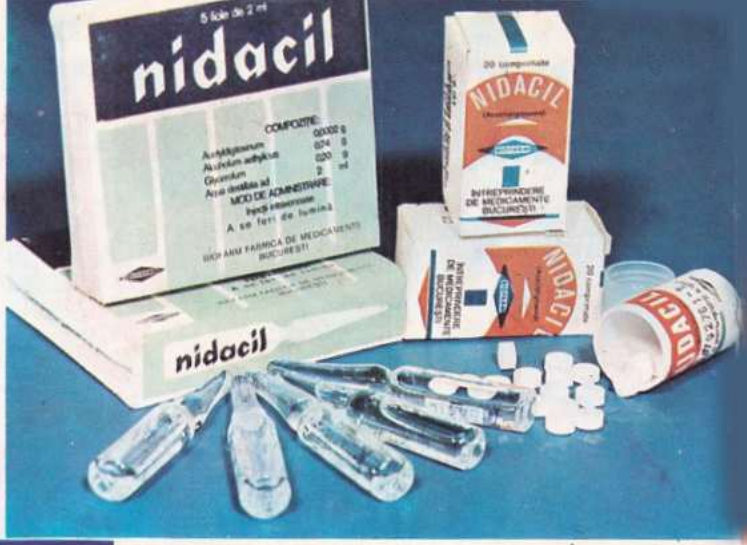

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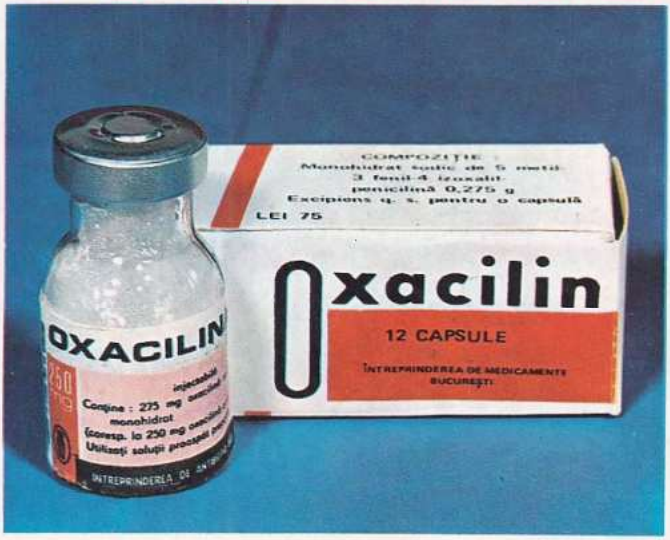
Solution of 0.050 g in 100 ml.
Suppositories.

Producer: Biofarm Factory, Bucharest, Romania

Oxacilin



Semisynthetic penicillin; acid- and penicillinase-resistant.

Indications: Infections produced by staphylococci resistant to other types of penicillin; cutaneous infections; respiratory infections, urinary infections, osteomyelitis

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Producer: Antibiotics Factory Iaşi, Romania.

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DRUG FACTORY
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A geriatric center on the precincts of Palace Hotel provides treatment with Gerovital H 3 and Aslavital according to Prof. Dr. Ana Aslan's method.

Otopeni

At a distance of some 17 kms from Bucharest, on the Ploiești motorway that goes to the mountain resorts of the Southern Carpathians, stands the "Otopeni" clinical section of the National Institute of Gerontology and Geriatrics in the midst of a beautiful 70 ha park.

Prof. Dr. Ana Aslan's treatment method with *Gerovital H3* and *Aslavital* is being applied for about ten years. The excellent accommodation and services, the quiet and picturesque ambient as well as the low altitude of the place recommend it to geriatric patients.

BĂILE HERCULANE

Herculane Spa (160 m altitude) is situated in the south-west of Romania, not far from the Iron Gate, in the picturesque valley of the Cerna river. The resort was recorded as early as the time of the Roman Empire for its curative properties and mild climate with Mediterranean influences. It is especially recommended for locomotive ailments (arthrosis, spondylosis, etc.), but also for affections of the peripheral nervous system, of the digestive tract (colitis, hypoacid gastritis, etc.), of the respiratory apparatus (chronic bronchitis), and for gynecological treatment.

A geriatric section staffed with physicians from the National Institute of Gerontology and Geriatrics provides a Gerovital H3 and Aslavital therapy according to Prof. Dr. Ana Aslan's method. Open all the year round.

BAILE FELIX

In the north-west of Romania, close to Oradea city, lies Felix Spa.

Its microclimate and low altitude are indicated for various neurotic states, but what has made the resort famous is its treatment center against various types of rheumatism.

A geriatric section, where treatments with Gerovital H3 and Aslavital according to Prof. Dr. Ana Aslan's method are administered by physicians from the National Institute of Gerontology and Geriatrics, is open all the year round.

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1. The size of the manuscript (including illustrations, tables, references and summaries) should not exceed 10 pages. Reports and syntheses should not outnumber 15 pages.

The manuscript should be typed with double-spacing (31 lines per page). Two summaries containing a maximum of 15 lines, one written in a different language than the manuscript, should be included.

Illustrations will be considered as pages (one page = 150 cm^2).

2. The paper should be consistent with the following plan: title; authors' names; the name of the institute where the authors have conducted their research work and the respective address; summary (in the manuscript language); introduction; material and method; results; discussion; conclusions; summary (in a different language); references.

3. Figures should be drawn on tracing, white or scale paper, in India ink, preferably the size intended for publication (1/1).

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Whenever microphotographs are used, staining and × should be mentioned. The place of figures and microphotographs will be noted in the manuscript.

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5. References should be numbered in the text with parenthetic Arabic numerals, in order of occurrence. A double-spaced bibliography at the end of the paper will include:

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Example: Vasiliu A., Popescu I., *Peripheral circulation in the aged*, Romanian J. Geront. Geriatrics, 1980, 1, *1*, 201—210.

b) for books, monographs, treatises: author/s; full title; publisher; town; year; page.

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PRINTED IN ROMANIA

EDITURA ACADEMIEI REPUBLICII SOCIALISTE ROMÂNIA
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ROMANIAN J. GERONT. GERIATRICS, 1980, 1, 2, BUCHAREST

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