Revitalization

The endeavour to retard or to repair losses of the somatic and mental functions due to age has been a very old wish dream of medicine. Tales and legends of «the fountain of eternal youth» or of the magic drug, which garantees eternal youth, are expression of this human wish dream.

Since cell therapy entered the public consciousness, it has been labeled with the idea of being a *«rejuvenating cure»*; this is very appropriately expressed by the English term *«rejuvenation»* . In fact, the therapeutic endeavours do not aim at rejuvenation but at the restablishment or improvement of biological functions, the total capacity of which is referred to as «vitality» . If vitality is interpreted as optimal performance of the functions (capacities) existing in a living being, «revitalization» means a re-establishment of lost functions.

Vitality is moreover a concept comprising the total organism with its triad «body, soul, spirit». Although the dysfunctions relate mostly to partial spheres (difficulties in findings words, disturbed potency, depressive ill-humour), the term «loss of vitality» means the restricted vital expansion of the entire personality (Tab. 37, 39).

This statement must be realized when the objective character is necessarily restricted to individual parameters whereas the patient expects a subjective treatment in order to feel subjectively better and free from complaints. In other words: a research worker is interested in measurable data of individual factors, the physician and patient hope for an improvement of the general condition to re-establish the well-being.

Losses of vitality can be due to illness or old age. In youth, the progressive

Tab. 37: **Leading symptoms of «devitalisation»**

Lacking initiative
loss of activity
rapid exhaustion
reduced physical achievements
reduced psychological reactivity
reduced tolerance to alcohol
reduced tolerance to nicotin
loss of ambition
reduced self-confidence
unfounded depressive ill-humour
dullness, despair
lack of concentration
impaired memory
insomnia

phase of life, a living being develops its biological capacities, uses them during the phase of maturity, and loses them in a reciprocal succession during the regressive phase. Problems of revitalization, therefore, are chiefly problems of old age. «Geriatrics» are offered in large quantities, beginning from the good advice «to take plenty of exercise» to mysterious magic roots from a possibly far-off country.

Cell-therapy, probably, is the only of many «geriatrics» likely to do justice to the two postulates of

a) an experimental establishment of statistical significance –

b) a practically proved effectiveness.

Effects of revitalization demonstrated by experiments

Revitalization has been defined by A. KMENT as follows: «Revitalization is the prolonged maintenance of re-establishment of a vitality level substantiated by several age parameters after transgressing the maximum of vitality, which corresponds to an age biologically younger than suiting to the organism chronologically». KMENT and his co-workers have fulfilled the postulates of this definition in a so far unique manner by experiments conducted from 1960–1983.

Various parameters have been tried on substantial groups of animals by long-term tests, the extent and arrangement of which appear from the representative Tab. 38. Of these series of tests, the following are of importance for the questions of revitalization:

Labyrinthian tests

A multiple T-shaped labyrinth with 7 crossings was used to test the learning capacity and memory of rats. Animals treated with lyophilised cells (testis, placenta) showed a significantly reduced running time and number of errors as against a control group. Especially, the memory of the treated rats was improved (KMENT, 1956).

Tissue respiration

During tissue respiration (biological oxidation), substrates rich in energy are transformed into compounds poor in energy. The energy so released is used for the intracellular processes needing energy. Tissue-respiration and age are interrelated. Direct measurements in the Warburg apparatus have shown that tissue homogenates of heart, liver, kidney and aorta consume less oxygen in old rats. Tissue of 2-year-old rats absorbs about 50% less than tissue of 6-months-old rats. Tissue lyophilisates injected into 12 and 17-month-old animals effected, at ages of 20 to 24 months, rates of consumed oxygen that corresponded to much earlier biological ages (10–12 months) (KMENT 1960).

Mitochondria

The increase of the energetic cellular performances by fetal tissue lyophilisates was proved moreover by the numbers and sizes of the mitochondria (KMENT, 1971). The activity of the enzyme succinic-dehydrogenase was also increased.

Collagen-experiments

The degenerative dysfunctions of the supporting apparatus and connective tissue are caused above all by the aging collagen. The collagenous fibres lose elasticity, grow more rigid, the cross-linked pattern of the thread-molecules increases same as fibrillary structures at the expense of the amorphous gelatin-

Tab. 38: **Parameters of age for long-term tests on rats** (by KMENT). Determinations at 5 points of time (9, 15, 21, 27, 32 months) on 168 animals at a time.

Parameter		measured per animal	measurements/group
Motor activity	electronic kinematographic	240	40320
running		1	168
ECG		60	10080
tail tendon	isometr. contraction	120	20160
	therm. solubility	2	336 336
	hexosamin	2	
skin	thermically soluble		
	collagen	1	168
	hexosamin	1	168
elasticity of the aorta		40	6720
lipofuscin	chemical: heart, brain	4	772
	histolog: frontalbrain		
	hippocampus	150	12000
	cerebellum		
succinodehydrogenasis	heart	4	672
	liver		
plasmalipids		2	372
plasmacholesterol		2	372
minerals trace elements	heart, kidney	10	1680
		total	94324
		total test:	ca. 472000 measured values

ous part of the volume. Tendinous threads of rat tails, which virtually consist only of collagen, were treated with heat to prove with biostatistically established significance that after the use of testicular lyophilisate the contractibility of the collagen in the tendons of rat-tails corresponds to earlier ages (KMENT et al., 1963, 1967).

Elasticity and tensile strength of the skin

According to these results seen on collagenous fibres, the statistical significance of an improved elasticity and tensile strength of the skin was established. KMENT and co-workers (1967) availed themselves of the method described by WENZEL (1950).

Further experimental studies

The authors demonstrated the same rejuvenating effect in another experimental group for the elasticity of the aorta.

- The following tests served for the substantiation of the revitalizing effect on animals:
- Tests on the thyroid activity in guinea-pigs with radio-isotopes (J 131) after siccacell products (KMENT, 1958). Quantitative electron-microscopic studies on cardial mitochondria of rats after injections of placenta or testicular tissue (KMENT, 1966).
- Tests on the revitalizing effect by myocardial cells, myocardial nuclei and myocardial mitochondria in rats (KMENT, 1974).
- Analyses of the spontaneous activity in old and revitalized rats by means of electronic registration (KMENT and HOFECKER, 1972).
- Tracer elements in the heart, liver and brain of rats of various ages and after revitalization by cell injections (KMENT, HOFECKER and NIEDERMÜLLER, 1973).
- Studies on the effect of the revitalization in rats on the absorption, dispersion and secretion of penicillin V (KMENT and NIEDERMÜLLER, 1973).
- Article on the method of the cinematographical registration of the activity of rats, as part of the research into revitalization (JELENIK 1971).
- Gerontological studies on the revitalization (KMENT, 1977).

Identical are the results obtained by WRBA (1961/62) respecting the influence of organic extracts and sera on the metabolism of organic cultures.

The revitalization in clinic and practice

Whereas, experimentally, success or failure can well be demonstrated and reproduced by means of individual parameters, effect and substantiation on a clinical level are confronted with difficult problems. Success or failure of a treatment are items of objectively conceivable factors and subjective sensations that cannot be defined by analytical-scientific standards.

In the *life profile of man*, three periods can be abstracted:

a) the *progressive period* of ripening in infancy, childhood and adolescence (from 0–20 years);
b) the *maturity-period* between the 3rd and 5th decades of life;
c) the *regressive period*, which begins in the 5th decade and reaches to the end of biological existence.

The biological functions for the maintenance of existence subside in the regressive period of senescence inversely to the succession of acquisitions during the ripening period. At the end of these losses there is a living being unable to guarantee its existence by its own strength. In the extreme case, man at a high age is in the same situation as a newborn: he cannot move on, must be fed, has lost his cleanliness functions and is no longer conscious of what happens around him. The loss of vitality sets in during the (4th) 5th decade and proceeds at an individually different pace, with «logarithmical» progression; it comprises all parts of the biological functions, the rough and fine movements, coordination, speech, social behaviour and the intellectual performances.

These functions fit organismically into each other and sum up the total image of personality. The biological position of man in his environment is defined by the

extremes rather than by the average of these capacities. Special achievements in one or several fields or particular shortcomings determine the sociological position more than the average qualities.

Findings on various levels of perception

Development and senescence are processes following biological laws; they are the consequence of permanently changing structures and their functions; both influence each other mutually i.e. changes of structures cause changes of functions, and changes of functions transform the structures. For instance the muscles: they can be augmented and strengthened by increasing the functions (training) and undergo atrophy when the functions are restrained (immobilization, long rest in bed). On the other hand, a defective structure or an inadequate innervation i.e. a structural shortcoming will impair the functional power. One must bear in mind the close connections between function and structure for all evolutionary and involutionary processes, especially for the mental and somatic disintegration caused by senescence.

The findings are individual according to our abilities to perceive and to establish proofs in the various dimensions, and the interpretations of the connections between these dimensions (cell – tissue – organism) is incomplete.

Cellular level

The familial cumulative occurrence of long-lived and short-lived persons, of good or bad natural resistance to illness, early or late senescence in a family suggest a genetic fundament.

Here, the nucleic-acid-protein-synthesis apparatus is of central importance. As a carrier of genetic information, the desoxyribonucleic acid (DNA) transcribes its potential and pattern of information to the ribonucleic acid (RNA). This *transcription* is followed in the area of the ribosomes (fig. 32) by the *translation* into the sequence of amino-acid of the (characteristic) protein. STREHLER supposes that the growing «internal disorder» in senescence is due to a gradual loss of genes. Of the about 500 genes available for the formation of protein in the nucleolus (fig. 8) at birth, approximately 50 per cent are functioning in old age so that there is, partly, no organ left to effect a sufficient translation into proteins. Functionally, the genetic information is increasingly reduced as the genes diminish.

A statement of account rendered at the first Viennese symposium on experimental gerontology gave the following picture (A. KMENT and G. HOFECKER, 1977):

The *perichromatin granules* (storage and transport form of the m-RNA) diminish in old age (BERTONI-FREDDARI et al., 1977) same as the protein-synthesis apparatus of the rough endoplasmatic reticulum (GIULI et al., 1977). Using a UTP-H3-tagging on isolated nuclei of rat-brain, SZESZAK et al. investigated the activity of transcription and found a nucleolar and extranucleolar *RNA-polymerase activity* diminished according to the age.

The *adaptive mechanisms* of the RNA-synthesis (H. MARTIN) and the *repairs effected by DNA-polymerase* (SANDHOFER et al.) are diminished. For the enzyme proteins, SCHOCH and PLATT showed in three 97-year-old persons a declining activity of Mg^{++}–Na^{+}–ATPase and Mg^{++}–Na^{+}–K^{+}–ATPase in the erythrocyte membranes of old persons. The protein kinase turned out to be independent of age in the cerebral cortex (man, ox), the *cyclic amino-mono-phosphate (c-AMP)* was reduced in old age. (REICHELMEIER et al.).

Tissue level

The tissular and organic systems have their own laws of ripening and regression (fig. 265). The central nervous system occupies a special position: it is the only tissular system that has not yet completed the fetal stage at birth but attains it in in the fourth year when the medullary sheath has matured. The numbers of neurons do not increase after birth: in question is an irreversibly post-mitotic condition of the nerve cells. This indivisibility is a prerequisite for the stability of the information stored in the brain. The *senile atrophy of the brain* is morphologically characterized by a diminution of volume, by dystrophy of the glia and by accumulations of lipofuscin. According to TREFF, every species of cells in the brain has its « own life history». As far as mobility is concerned, the *supporting tissue* plays a special part. While the connective tissue grows old, the divisibility of the connective-tissue cells is restricted, the heterochromatisation and polyploidisation increase, the synthesis of *collagen and elastin changes* and the spectrum of the glycosaminoglycanes shows aberrations. The proliferation of connective tissue and the *generation of fibroblasts* are prolonged (KRANZ).

The collagen, as the reduction of the cutaneous collagen in old age shows, undergoes changes due to senescence, which NIEDERMÜLLER et al. SKALICKY et al. have summarized as follows:

1. the cutaneous and the tendinous collagen have different metabolic dynamics;
2. the formation of the polymere collagens slows in old age;
3. stabile and labile polymere collagens originate from various tropocollagens; the relation between the syntheses of these two forms changes during senescence;
4. both cellular and extracellular senescent processes account for the changes of the tendinous and cutaneous collagens in old age.

These senescent changes shown for the brain and connective tissue could be discussed at length also for the skin, vessels, heart, liver, kidneys, lungs and bones. The lung shall be picked out as an example. According to P. BRUNNER(1980), the *physiological aging processes* in the lung are accounted for chiefly by the structures of the connective tissue in the respiratory organs, not by their epithelial constituents. The important factor is the changed structure of the elastic fibre system, which reduces the retractability and augments the collagen. Atrophy of alveolar septa, dilation of alveolar ducts, reduction of the alveolar net-capillaries as well as calcareous and osseous stiffness of the skeleton of the bronchial respiratory tracts have led to the morphological term «senile lung», and to the restriction of nearly all parameters of pulmonary functions in old age. The senile lung, therefore, is a sound lung with restricted functions.

The collective term «senile involution» comprises the processes of morphological regression and reduction of functional efficiency in the tissues.

Personality level

The logical evolution, the multicellular organism, which consists of organic systems, does not quite correspond to the concept of human individuality. The forms and functions of the organs, with all their manifestations, measuring and functionary results cannot conceive the properties of the individual. Abilities and shortcomings in the motor, coordinative, social and intellectual fields are more distinctive of the position of an individual than this formal properties (ap-

pearance) unless they differ too much from the standard (fig. 266). «Individuality» is more than «organism». Vitality and loss of vitality must therefore be judged from the individuality, the subject, objective findings of organs do not necessarily conform thereto. An «organically» ill person can by discipline and strength of will be a professionally, culturally or socially great personage whereas an «organically» healthy individual may be just the reverse.

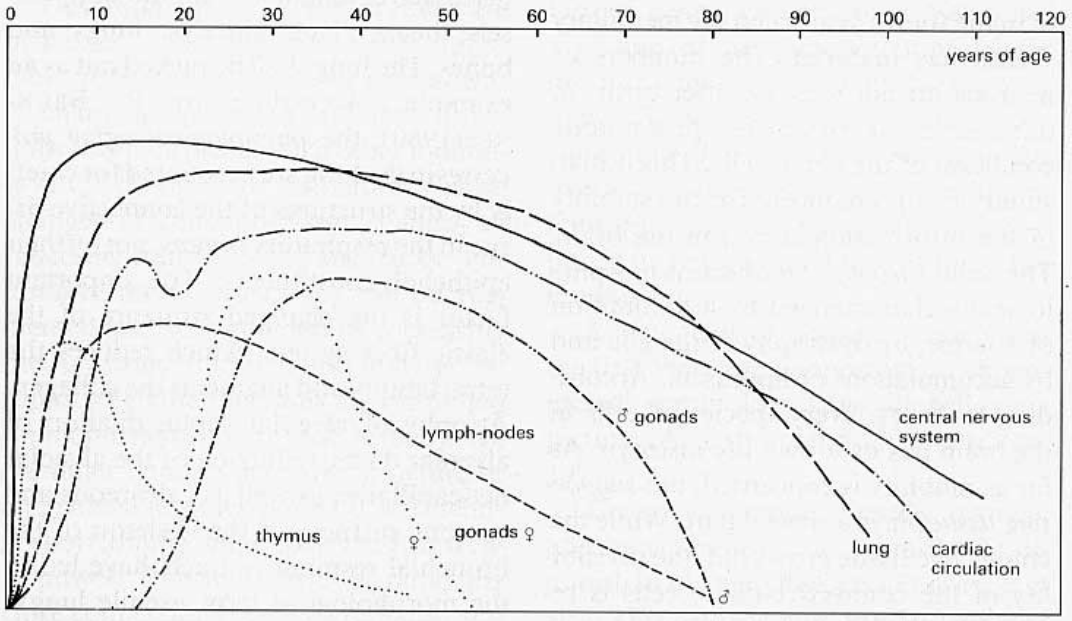

Fig. 265:
Ripening and aging of various tissues in the life-profile, projected on the «genetic» expectation of life.

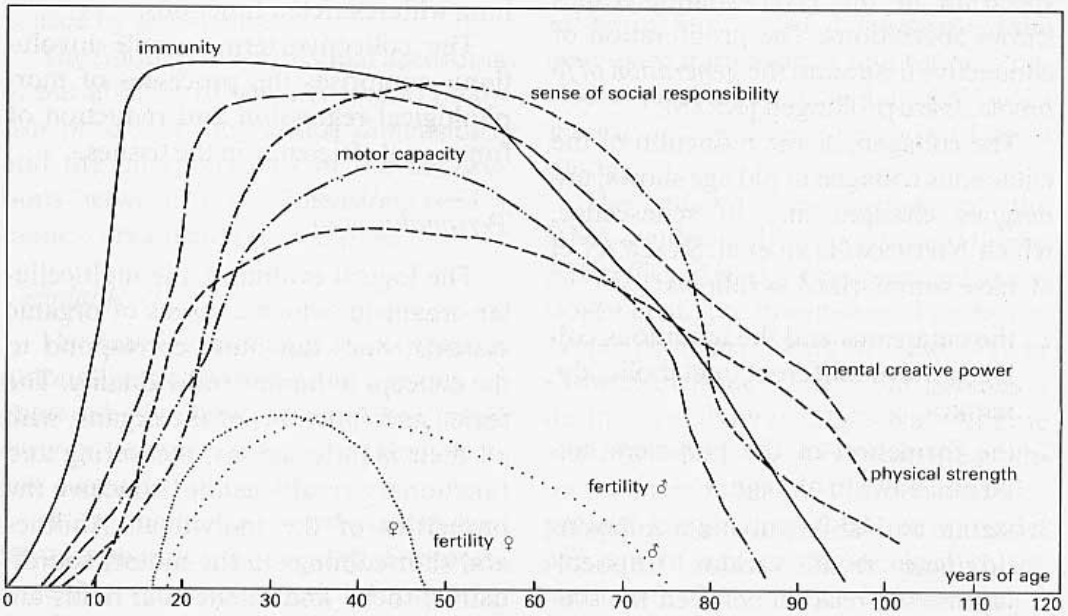

Fig. 266:
Maturation and aging of various individual characteristics.

Tab. 39: **Devitalization symptoms**

«Personality»

Loss of initiative «debility»
affective «emptiness»
lack of inspiration and experience
general uncertainty
egocentric
incapability of acting
loss of accountability

Rough movements

Stiff posture
uncertain gait
tripping gait
reduction of walking distance
trouble when walking up stairs
walking with expedients

Fine motoric and coordination

Subsiding mimics
reduced gestures
fine tremor
trembling
unsteady hand
restlessness

Socio-psych. behaviour

Ill-humour
self-reproach
loss of social relations
anxiety for life
eremitism
Loss of interest in
sports
politics
acquaintances
environment
hobbies

Intellectual performances

Perceptive faculty impaired
perceptive power permeable
«senseless» failures
disturbance of memory
reduced concentration span
memory reduced
hard of remembering
taciturnity
stereotype monotony (complaints, praise)
loss of short-term memory
reduction of vocabulary
lacking orientation

Old-age regression of organs

Senile atrophy of the skin
vascular sclerosis
cerebral sclerosis
cardiac insufficiency (senile)
pneumoemphysema
digestive insufficiency
decline in potency
senile diabetes
loss of hepatic functions
insufficient immunity in old age

To perceive the change of individuality is, summarily, an observation, it may be findings for certain characteristics (e.g. arthrosis, emphysema, reduced walking distance). Summing up the regressive senile changes would probably require an analysis of reciprocal development with several hundreds of criteria (see fig. 263). In practice, the judgment of vitality must be confined to important steps of regression, which have been outlined for the various functional spheres in Tab. 39:

From this detailed symptomatological analysis of senescence, conclusions can be drawn especially as to which organs should be selected for the cell therapy (Tab. 42).

STEIN and GIANOLI have drawn up for the practical use a concise list of symptoms, which gives a good idea of the loss of general vitality but does not lead direct to therapeutic consequences (Tab. 37).

The treatment and care of aging persons is medically and sociologically in the teething stage. The futile postulate to integrate old people into society, is mostly completed by the doctor's advice «to take longer walks» and by the prescription of combinations of polyvitamin-trace-elements. However, the therapy must same as in cases of retardation in infancy, aim at the entire individuality, and the training of the somatic, social and mental capacities should be given priority.

The function of cell therapy in this field, for which it has earned legendary fame, consists in the regeneration of performances of the organs and organ systems affected by senescence. Experimental data and considerable practical experience are available. The following typical «combinations for revitalization» are recommended:

for women:

hypothalamus	placenta
adrenal gland female	connective
ovary	tissue

for men:

hypothalamus	liver
frontal brain	placenta
adrenal gland male	testicles

The doses of these preparations are 100–150 mg of lyophilisate. These combinations provide good results in the revitalization but do not meet the differentiation of individual cases. The following survey is intended to show possibilities of rendering the revitalization more individual with regard to the symptoms (Tab. 40). There is a direct relation between the symptoms and the tissues to be selected. Care must be taken that for an

Tab. 40: **Selection of tissues according to symptoms in revitalising therapy**

Symptoms	*Selection of tissues*
Disturbances of rough movements	cerebrum, cerebral cortex, spinal medulla
Disturbances of refined movements	thalamus, diencephalon, basal ganglia, cerebellum
disturbed coordination	thalamus, diencephalon, basal ganglia, cerebellum
Disturbed impulse, initiative	frontal brain, thalamus, hypothalamus
Disturbed memory	temporal brain, frontal brain
reduced intellect	cerebral cortex, cerebral hemisphere
cerebral sclerosis	placenta, fet. artery, cerebrum
vascular sclerosis	placenta, fet. artery, connective tissue
senile heart-complaints	heart, placenta, artery, liver
hyperuricaemia	kidney, placenta, liver
impaired hepatic functions	liver, gastric mucosa, placenta
senile pulmonary complaints	lung, connective tissue, placenta
disturbed potency	testicles, adrenal gland male, hypothalamus (diencephalon), (liver)
menopause	ovary, adrenal gland female, hypothalamus, diencephalon, placenta of female foet.
degenerative changes of skeleton and joints	cartilage, bone-marrow, connective tissue, placenta, parathyreoidea
insufficient immunity	thymus, adrenal gland, spleen

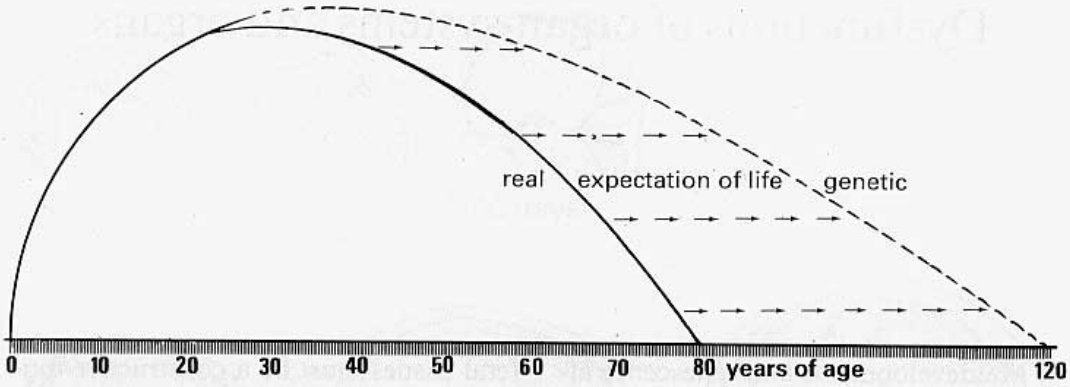

Fig. 267:
Difference between biological «debit and credit». The earlier revitalising measures are taken up, the more vitality persist.

individual treatment usually not more than 5–6 tissue preparations (500–800 mg of the lyophilisates in all) are used as otherwise the stress after the implantation would be too great. These tissues combined can be distributed on 2 simultaneous injections. The more weakened, run-down and emaciated a patient is, the more he needs a good preliminary examination and a methodical aftertreatment (fig. 267). Fatiguing physical work and brain work should be avoided within the phase of stress of 7–14 days. Combinations of medicaments stimulating the metabolism (combinations of polyvitamin trace elements, membrane activators, neurodynamics on a biological basis and enzyme preparations) ought to be included into the aftertreatment. The remarks specially on the enzyme preparations in the chapter «Mental and multiple physical disability» apply analogously.

Repeated treatments as part of revitalization use to be necessary and indicated at intervals of 1–3 years. For the question from what age a revitalization can be looked upon as reasonable, the individuality of the senescence must be taken into consideration. Generally, revitalization will be the more effective the earlier it begins (fig. 267) and the more regularly in the course of senescence it is effected. The 5th decade of life is regarded as the optimal age for the beginning of a revitalizing therapy. Measurable results are obtained also if a treatment is started in the 8th and 9th decades, but it should be realized that already existing degenerative tissular processes may restrict the expected degree of the therapeutic improvement.