

Senility and Chronic Malnutrition

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Introduction

*"Do not go gentle into that goodnight
old age should burn and
rave at close of day
Rage, rage, against the
dying of the light."*

Dylan Thomas, in my view, expresses the only appropriate attitude toward senility and premature death. My inclusion of a brief portion of this poem represents a triumph of Orthomolecular medicine for one elderly man. A few weeks ago, by the side of a pool in Hawaii, C.P., on discovering I would participate in this conference on memory and aging, recited the entire poem. In 1960 he had completed 16 years of chronic invalidism, crippled, in pain, prematurely aged, and his memory so shattered he could not have recited any poem. That year he began to take 3 grams of nicotinic acid daily. Within two weeks he was well and has remained normal except for a brief episode in 1962 when he went on a vacation in the Canadian Rocky Mountains and forgot to take this vitamin with him. Within one week all his symptoms began to recur. By the time he reached home and was able to take nicotinic acid again he was as ill as he had been in 1960. Within a few days he was again well.

Institute for Biosocial Research on "The crisis in Health Care for the Aging," New York City, March 6, 1972.

G.P. has never been my patient. In 1960 I had requested his cooperation for a study of nicotinic acid as an antisenility substance. He was administrator of an institution which housed a number of very old and infirm people. He agreed but before starting wished to familiarize himself with the side effects of nicotinic acid. He felt this would make it easier for him to discuss this with the subjects who had volunteered for the study. He expected no beneficial effect on himself. At that time I was unaware of his chronic disability.

Surprised and delighted by his rapid recovery, he began to inform his physician and friends. His physician warned him he would damage his liver but he decided he would gladly die of severe liver disease if in the meantime he could retain his present state of health and feeling of well-being. Over the past 12 years he has remained well.

G.P. is one-example from several thousand made prematurely senile by 44 months of severe stress and malnutrition in a Japanese prisoner-of-war camp, beginning after the fall of Hong Kong in 1940. On release from camp he had lost one-third of his body weight and suffered from pellagra, beriberi, ariboflavinosis, and scurvy. Between 1944 and 1960 the Department of Veterans' Affairs had accumulated two huge files requiring a large box to house them. These contained

¹ This paper was read in abbreviated form at the National Conference sponsored by The Huxley

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results of numerous, fruitless examinations and reports. Over the past 12 years his file has grown very little. I will outline his illness further on when I consider the Hong Kong veterans' syndrome.

By 1960 my belief in the inevitability of senility had been severely shaken, and I could not accept the view that senility is a chronic hopeless condition built into us by genes controlling an intrinsic senility factor (Kral, 1962). In 1954, HC, my mother, then 67 years old, was very nervous and depressed and complained of severe pain in her joints, failing vision in one eye, generalized weakness and fatigue, and severe arthritis of her hands. Her fingers were drawn into the typical ulnar deviation of rheumatoid arthritis, and Heberden's nodes were prominent. Her memory was beginning to fail. It was clear she was aging very quickly. I knew no treatment was effective but as I was by then familiar with nicotinic acid used in megadoses, I decided to start her on 3 grams per day, more or less as a placebo. I was aware it was a very good hypercholesterolemic substance (Altschul, Hoffer, and Stephen, 1955) and that it could increase rate of tissue repair. It was relatively less toxic than is senility itself. To my amazement, mother was nearly well six weeks later. Her arthritis had cleared, her fingers were straight, and Heberden's nodes began to soften and regress. Her vision in both eyes was normal, and her tension, anxiety, and depression were gone. Over the next year she did a good job of nursing my father who was dying of cancer of the prostate. She came through this very stressful period and its aftermath without any recurrence of her earlier condition. Today (1974) at 86 she is physically weaker, does not hear as well, but is mentally well. Several years ago she was co-author of a book dealing with her pioneer days as a homesteader in rural Saskatchewan, and currently she is working on her extensive memoirs. She has been taking 3 grams each

day of nicotinic acid for 18 years. I have not seen any evidence of toxicity, and there has been no progression of mental senility which was so apparent 18 years ago.

These two dramatic responses to nicotinic acid led me to conclude that senility is due to chronic malnutrition and that it is a vitamin-dependent condition which comes from many years of mild or moderate chronic vitamin deficiencies. Experts in geriatric medicine have not observed spontaneous cures of senility so one cannot ascribe these recoveries to those nebulous concepts of faith, placebo, etc. Neither one of these subjects had any faith or any expectation that nicotinic acid would be of any value to them.

Many nutritionists have suggested that senility is partially due to chronic malnutrition, but the concept that megadoses of nicotinic acid might be required has not been widely accepted. I hope my report will stimulate wide interest and will persuade someone to run adequate large-scale treatment trials, for there will be no solution to the immense problems facing our society because of senility except by its prevention. In my experience, old people who are mentally normal and physically reasonably well present very few problems to society, nor are they lonely or bored, or suffering from the other common afflictions of old age.

Pathological Changes During Aging

It is convenient to describe both physical and mental changes of aging. Both sets of symptoms are interrelated and merely express the impact of senility on one or another set of tissues and organs. It is more important to locate the basic biochemical defect for senility usually affects all the cells and tissues. Until this pathological process is identified, we can stave off senility only by repairing organs which are not functioning well.

Physical changes include vascular changes in vessel walls and in the blood itself, especially in the brain and heart. Arteriosclerosis appears to be a generalized disease which has a predilection for certain vessels. There is mounting evidence that in

most cases these vascular changes are due to excessive consumption of sucrose and sucrose-rich foods, and in a smaller number of cases to excessive calories from saturated fats. The average annual consumption of sucrose in the United States and Canada in 1900, before the so-called degenerative diseases of Western civilization became rampant, was under 80 pounds per year. Today it is about 120 pounds per year.

Cerebrovascular changes decrease blood supply to the brain and so lead to repeated attacks of tissue anoxia. These eventually lead to senility and to major strokes. There are also changes in structure and function of the joints which become more severe with age. Kaufman (1949) developed an accurate method of measuring joint movement. Subjects with no joint dysfunctions had average scores between % and 100. Low scores represented varying degrees of joint disability due to arthritis. From a large number of patients Kaufman reported the following: indices for age 5-90, for age 33-78, for age 69-63, and for age 81, a score of less than 55. A score of 55 indicates very severe arthritis, a score of 56-70 indicates severe arthritis, a score of 71-85 moderate arthritis, and a score of 86-95 slight dysfunction.

Most bodily functions deteriorate with age. Homeostasis becomes sluggish, responses to stress are impaired, activity is reduced, and recuperation is slower; as an example, glucose is absorbed more slowly and its storage is impaired. Regulation of electrolyte and fluid balance is faulty and dehydration easily produced. Vital capacity is reduced. It is increasingly difficult to dissipate heat and cold; sensitivity is increased. Bones become more fragile and brittle.

These changes are remarkably like changes induced in a large group of healthy Canadian soldiers who, like C.P., were incarcerated in Japanese prisoner-of-war camps. The stress and malnutrition was so severe that 27 percent of these POWs died in camp compared to a 4 percent mortality in European camps.

Because the majority of Hong Kong POWs like C. remained chronically ill and continued to demand adequate treatment and pensions to compensate for their service-related disabilities, Richardson (1964) carefully examined 100 Hong Kong POW veterans. For his controlled comparison group he examined 50 men, brothers of the Hong Kong veterans, who had served in Europe. At the time of enlistment both groups had been equivalent in average age and health. Richardson (1964) found that the Hong Kong veterans were a much sicker group; they suffered more apathy, fatigue, insomnia, nervous tension, anxiety, irritability, depression, and neurological and psychiatric conditions. They had a high incidence of irritable bowel syndrome and peptic ulcer. Parasthesias of feet and legs were universal while in camp and continued to plague many of them. Their teeth were very poor. Deaths from arteriosclerotic heart disease were very much higher between 1946-64, reaching a total of 47 when on the average only 30 should have died. Richardson found "conclusive evidence in the medical literature and in this report of the nature and course of their disabilities such as optic atrophy, neurological, muscular and minor circulatory defects of feet and legs, inferior dental health and the abnormally high death rate from arteriosclerotic disease." He also found impressive evidence of widespread gastrointestinal, cardiovascular, and nervous symptoms and fatigue disproportionate to identifiable physical factors.

In a companion study, Kral et al. (1967) found that, compared to their brothers, Hong Kong veterans had a very high incidence of psychiatric and neurological disability. Out of 20 Hong Kong veterans, 12 had psychiatric symptoms, 13 suffered autonomic changes, and 15 neurological changes. From the 20 controls the incidence was 2, 0, and 4. Psychiatric complaints included tension, anxiety, depression, and memory impairment. Neurological changes included hypesthesia, diminished vibration and position sense, ataxia, cranial nerve involvement, tremor of the hands, and reflex

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changes. Kral concluded the Hong Kong veterans were suffering from what clinically appeared as chronic depression with tension and anxiety. They complained of nervous tension, anxiety, depression, fatigue, slowness, sleep disturbance, and decreased sex interest and potency. They showed tensions, anxiety, depression, dependency, and passivity. The Bender Gestalt results suggested early or mild brain changes that impaired adequate functions.

If we give up our preconception about senility as being inevitable, it is clear that this group of POWs had been prematurely aged by 44 months of severe malnutrition and stress, perhaps by several decades.

These chronic changes are reversible. G.P. was the first of the Hong Kong group to start on nicotinic acid in 1960. At that time he suffered nearly all the symptoms described by Richardson. After release from camp, he was treated in hospital with a highly potent vitamin preparation then available, but it contained too little B vitamins to help very much. After discharge from hospital, he remained chronically crippled as described previously. It took up to an hour each morning before he could move his joints freely enough to walk. He was very intolerant to cold, and he suffered continually from pain. He continually demanded medical help and received huge quantities of amphetamines and barbiturates. Eventually he was classified as a psychoneurotic and admitted to a psychiatric ward for a few days. This experience left him even more anxious and tense. However, after two weeks on 3 grams per day of nicotinic acid, he was well. He lost all his pain and his arthritis vanished. He was no longer cold intolerant and no psychiatric complaints and findings were present. Over the past year he taught me how to swim. His striking response became known to about a dozen other POWs of whom three came to me for help. All responded in as dramatic a way and remain well. This subgroup of nicotinized Hong Kong veterans is entirely different from the untreated veterans who

continue to suffer as before.

Physicians dealing with these POWs recognized that they suffered from vitamin deficiencies and gave them what was before 1950 considered adequate doses. But it did not occur to them that megadoses of water-soluble vitamins could reverse the deficiency symptoms. In their training in medical school, vitamins and deficiency diseases were usually a part of their biochemistry courses and were mostly ignored in their clinical training. In common with most physicians today they believed: 1. that extra vitamins are needed only for the classical simple deficiency diseases such as pellagra, scurvy, and beriberi, and these conditions were seldom seen and less frequently recognized; 2. that average diets in North America contained sufficient quantities of vitamins; 3. that if one gave more than the minimal recommended doses the extra quantity was simply excreted and did not benefit the patient; 4. that larger doses were harmful as well as wasteful. All these ideas are completely erroneous and by their presence have prevented large numbers of patients from benefiting from above-average vitamin doses.

Within the past two decades, the finding that megadoses of vitamin have important therapeutic effects has led to the concept of vitamin-dependent conditions. In children, several variants of Pyridoxine dependency have been described, as well as a vitamin B12 dependency where 1000 ug is required each day as compared to the usual requirement of 1 ug per day.

A vitamin-dependency condition is one where much larger than average quantities of a vitamin are required in order to prevent deficiency symptoms from occurring. If, for example, a normal person is forced to eat a diet too low in nicotinic acid, he will develop pellagra. If, however, he requires much more than the average quantity, he will develop the same deficiency symptoms on a good diet. The end result is the same in that both subjects suffer from a relative deficiency of nicotinic acid, i.e., from subclinical or from well-developed pellagra.

A deficiency condition will in time become

a dependency if it is present long enough. Many years ago it was found that dogs kept on a pellagrogenic diet for a short time quickly recovered when given vitamin doses (small). However, if fed the same diet for many months they would no longer respond to small doses and instead required megadoses the rest of their lives to prevent relapse into pellagra.

This also occurred with chronic pellagrins. Spies et al. (1938) used placebo-controlled experiments to establish the fact that nicotinic acid in doses up to 600 mg per day promptly relieved most of the neurotic symptoms of pellagrins. They reported, "we have attempted to observe specifically the relief of such prodromal symptoms of pellagra as fatigue, insomnia, anorexia, vertigo, paresthesia, palpitation, nervousness, headache, forgetfulness, apprehension and distractibility." They found it essential to give repeated large doses of nicotinic acid to prevent development of mental symptoms in subclinical pellagra and in mild pellagrins.

The Hong Kong veterans represent an experiment which could never have been deliberately done but which led to the same results, i.e., a conversion of a large number of healthy male adults into vitamin B3 dependent patients by 44 months of severe malnutrition and stress. I would expect that survivors from German concentration camps suffer equally from various vitamin-dependency conditions. I have treated one such survivor with equally dramatic results.

Perhaps these conditions are better described as acquired dependency conditions to be contrasted with similar conditions appearing during infancy. Pediatricians would see the congenital forms where the dependency occurs very early. According to my view, geriatricians are seeing an acquired form in their patients.

Evidence of Malnutrition in Aged

Nearly every study on aged people by nutritionally oriented physicians has shown that they suffer a multitude of vitamin

deficiencies. Stieglitz (1949, 1950) concluded, "in many respects the changes in senescence are primarily consequences of cellular malnourishment." All the so-called degenerative diseases, he wrote, have one characteristic in common, impairment of the nutrition of parenchymatous cells. He listed the following reasons why this was the case:

- (1) inadequate supply — lack of essential nutrients in the diet
- (2) inefficient distribution because of circulatory impairment
- (3) ineffective utilization due to enzyme deficiencies
- (4) accumulation of injurious metabolic debris or, as they have been called, clinkers.

He stated that minor degrees of vitamin deficiency can be assumed to be the rule and recommended doubling the usual intake of vitamins. "Wise nutrition is a most powerful tool for the attainment of vigor in later years," he concluded. My conclusion nearly 20 years later is that his first factor is the most important one and can be corrected only by massive doses of the essential vitamins such as vitamin B3, B6, and ascorbic acid. As will be shown later, nicotinic acid not only is essential in large quantities but improves distribution of all foodstuff by improving circulation.

Kral (1962) also concluded that malnutrition is important in the etiology of senility. Droller and Dossett (1959) found senile patients low in serum vitamin B12. These conclusions do not clash with recent work showing the importance of genetic factors in senescence (Jarvik et al., 1960; Falek et al., 1960). Naturally long-lived individuals probably were better endowed genetically to extract vitamins, minerals, and other essential nutrients from average diets.

Etiology of Senility

The functioning of the brain is determined by the number of functional units, presumably chiefly neurons, and their relationship to each other and the integrity of

the cells, i.e., its biochemical integrity.

A. Biochemistry of Senility

Any theory of senescence must deal with metabolic changes at the cellular level. The most appealing theory to me is the cross-linkage one proposed by Bjorksten and his colleagues (Bjorksten, 1960, 1963, 1964, 1968, 1971; Bjorksten et al., 1962; Bjorksten et al., 1971). This theory suggests that certain oxidizing intermediary metabolites bind long protein molecules to each other. The cross-linked protein is prevented from functioning properly and is degraded with difficulty since no enzymes have evolved in the body to deal with them. This is analogous to what happens to natural latex when it is vulcanized to rubber. Sufficient cross-linkages are introduced to bind long rubber molecules to each other. If too many cross-linkages are produced, the rubber becomes hard and brittle. The same sort of process occurs in aging protein. Skin, for example, becomes inelastic, parchmentlike, and brittle.

A large number of different types of small molecules are present in the body. Their number is increased by exposure to radiation and ultraviolet. They include quinones, chrome indoles such as dopachrome, noradrenochrome, and adrenochrome, aldehydes and metallic ions such as copper. Senility is accelerated by procedures which increase the quantity of these small molecules. These conditions include diabetes mellitus, chronic smoking, and radiation. I would expect excessive intake of oxygen to be equally harmful (Houlihan et al., 1970).

Harman (1956, 1962, 1969) postulated that free radicals contributed to aging. Free radicals are groups of atoms intermediate between molecules undergoing oxidation and reduction. They are extremely reactive and have a transient life. Plasma which is rich in oxygen is a natural site for free radical formation. It is also rich in oxidizing enzymes such as Ceruloplasmin, a copper-containing enzyme, and iron-containing enzymes; these

free radicals would crossbind proteins. In certain tissues this would be especially harmful. Thus in small vessel walls cross-linked proteins would shorten proteins and make them inelastic, fibrotic, and generally inefficient in transferring blood and nutrients. In other tissues such as hair, skin, and nails, cross-linkages would be much less damaging. It is possible integument is used as a major method of eliminating cross-linked proteins. Harman and Piette (1966) found direct evidence for the presence of free radicals in serum using an ESR spectrometer. In the presence of oxygen the concentration of free radicals was greater. They concluded their experiments "indicate that the reaction of oxygen with naturally occurring substances such as epinephrine, norepinephrine, ascorbic acid may contribute to the serum signal," i.e., to the presence of free radicals derived from these substrates.

Bjorksten and Andrews (1960) found that the curve which expressed change in mortality with time in humans and the curve expressing congelation of proteins being cross-linked under specific conditions were very similar to each other. This supported the idea that similar changes occurred in vivo in the body's proteins. Warburg (1966, 1967) in a series of provocative papers discussed the extreme importance of maintaining normal aerobic respiration in cells. He showed that cancerous tissue tended to use anaerobic respiration. The more malignant the tumor, the more anaerobic was its respiration. He suggested that some cancers could be prevented by insuring full aerobic respiration of tissues. Anaerobic respiration would also produce more cross-linkaging molecules and would lead to premature senescence.

Bjorksten (1968, 1971) summarized the present state of the cross-linkage theory of aging as follows:

"Crosslinking is damaging to the tissues and involves loss of elasticity, reduced swelling capacity, increased resistance to hydrolases and probably enzymes generally, and thus an increase in molecular weight and a tendency toward embrittlement. There is a

growing amount of direct evidence and much indirect evidence for postulating the relationship between crosslinking and aging.

"Crosslinking agents present in the living organism include aldehydes, lipid oxidation products, sulfur, alkylating agents, quinones, free radicals induced by ionizing radiation, antibodies, polybasic acids, polyhalo derivatives and polyvalent metals. The latter four types of compound are slow-acting but can also accumulate in the body to form a frozen metabolic pool. Sufficient amounts of all these potential crosslinking materials are present in the body to make the changes of aging unavoidable."

The evidence supporting the cross-linkage theory is substantial.

Warburg's (1966) conclusions about the need for oxygen saturation of oxygen-transferring enzymes may explain some of the exciting findings reported by Jacobs (1972) and Jacobs et al. (1969), and extended by Boyle (1972). Jacobs demonstrated that hyperbaric oxygen carefully applied to senile patients in many cases dramatically brought back their memory. Since no one has yet shown that there is a spontaneous recovery from senility, no double-blind experiments are required. However, Boyle did use blind controlled experiments and corroborated her findings. Three atmospheres of pure oxygen given over a two-hour period between five and 10 times had a remarkable effect in restoring normal use of memory for recent events which is the chief deficit of memory in senility. However, the restoration is not permanent; other methods will be required to sustain the improvement. These observations are of extreme importance for they will ultimately dispel the notion widely held that senility is inevitably a one-way process leading to total deterioration, and support Boyle's conclusion (1972) that those neurons and other cells in the brain serving memory function are not dead as is generally believed but are instead quiescent or asleep. In other

words, they are unable to perform their prime differentiated function (memory) but retain sufficient sources of energy to remain alive and perhaps to serve other functions.

Warburg (1966) suggested that normal tissues lacking oxygen would dedifferentiate and become cancerous. In his excellent examination of this phenomenon, Warburg reviewed the process by which anaerobic individual cells living before we had oxygen in our atmosphere were able to differentiate to produce higher aerobic forms of life. Differentiation, that is the development of cells able to have specific and unique functions such as memory, is possible only by cells enjoying aerobic respiration. The reverse process, de-differentiation of life, according to Warburg, is the reason why cancer develops. Oxygen respiration falls, fermentation appears, and highly differentiated cells are transformed to fermenting anaerobes. They have lost all their body function and retain only the now useless property of growing. When respiration disappears life may remain but not its meaning, and the body is destroyed.

Warburg applied this reasoning to cancer tissue but had he given it any thought, or had he known about Jacobs' and Boyle's results, there is no doubt he would have applied the same reasoning to the problem of brain deterioration and memory loss. Most cells in the body have not lost the ability to reproduce (grow), but neurons have. If, therefore, Warburg's de-differentiation occurs in neurons due to anoxia, they will not become cancerous. However, they would lose their specific function which is to acquire new information, i.e., memory. I suggest that senile memory loss is due to neuron de-differentiation comparable to de-differentiation which leads to cancer. The neurons remain alive but have lost their meaning of life.

Warburg further shows the thermodynamic changes which are involved. The differentiation of plants and animals from unicellular life is the most improbable process in the world. Improbable processes require work (consumption of energy). Thus it

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requires work to maintain different concentrations of potassium and sodium inside and outside of cells. Equalization of concentration requires no work; oxygen respiration provides this energy. In its absence, de-differentiation begins at once. Differentiation represents a forced steady state, but de-differentiation is the true equilibrium state.

Warburg assumes that only oxidative phosphorylation, but not fermentative (anaerobic) phosphorylation, can differentiate.

Glucose can be metabolized by two main pathways. The end product of fermentation reached by one single reaction is reduction of pyruvic acid by NAD (nicotinamide adenine dinucleotide — reduced) to lactic acid. The end product of oxidation of pyruvic acid to water and carbon dioxide is reached by 30 additional reactions requiring turnover of five times as much NAD.

There are two ways of influencing cell respiration. The first is by altering oxygen pressure in growing cells. Decreasing oxygen insures that transferring enzymes are no longer saturated with oxygen. Normal respiration will decrease, and normal cells will transform into facultative anaerobes. The second method is to alter the quantity of active groups of the respiratory enzymes in our food. Increasing the quantity of these vitamins like riboflavin, vitamin B3, and Pyridoxine will improve the state of aerobic respiration.

If senile memory loss is de-differentiation, as seems likely, it will be initiated or accelerated by any process which interferes with oxidative respiration. These are factors which prevent delivery of sufficient oxygen to the cells and factors which reduce the quantity of respiratory enzymes in the cells. The first set of factors includes delivery of oxygen to the red cells, circulation of the blood which must contain enough cells which are homogeneously dispersed throughout the plasma, release of oxygen to the tissues, and

rapid revascularization of injured tissues. The second set of factors includes provision of an optimum diet containing optimal quantities of respiratory vitamins and minerals. Warburg suggested that cancer can be prevented by maintaining normal circulation of the blood, by maintaining high concentration of hemoglobin, and by fortifying our diet with essential respiratory nutrients.

This, in my opinion, is also the prescription for preventing senility for which I will present data further on. I am convinced that Warburg's prescription applied to the prevention of senility works.

Warburg recommends that, to treat cancer, further de-differentiation must be prevented. One could indeed never succeed in re-differentiating the differentiated cancer cells, since during the short duration of human life the probability of such a back-differentiation is zero. But one might increase the respiration of growing metastases and thereby inhibit their fermentation and the growth of metastases to such an extent that they might become as harmless as the so-called "sleeping" cancer cells in the prostates of elderly men.

Since neurons do not become cancerous and so do not destroy the brain, their de-differentiation will not destroy life. They merely cease to perform their specific function and handicap the brain with the production of senility. As more and more cells dedifferentiate, so will memory become even more unreliable until all we have left is a human body, completely devoid of recent ability to recall for more than five or 10 seconds.

Warburg's theory now provides an explanation for Jacobs' and Boyle's results. It is obvious that by using hyperbaric oxygen and supersaturating plasma and brain, they have been able to differentiate neuron function again, even if only for a short period of time. They have reawakened quiescent neurons, fortunately still alive, which have not been destroying their fellow neurons by rapid multiplication. But since it is impractical and perhaps even harmful to provide main-

tenance hyperbaric therapy, one must develop a mechanism for preventing these neurons from dedifferentiating again. This is very likely, and my work with vitamin B3 in preventing senility and Boyle's finding that vitamin B3 improves the duration of memory recovery after hyperbaric treatment indicates we must follow Warburg's ideas by giving our senile patients megadoses of all the respiratory enzymes.

Jacobs (1972) discussed negative results of hyperbaric treatment in a New York study on senile patients who had suffered persecution in Germany under the Nazis. She felt this was due to the psychological stress, anxiety induced by the hyperbaric chamber which reminded them of the gas chambers used in extermination camps. To me this explanation remains unlikely for it is difficult for me to understand how a senile patient with hardly any memory could draw such an association until after they had their memory restored. I believe there is a more probable explanation.

For anaerobic respiration, the amount of NAD required is much less than for aerobic respiration. Thus it would be impossible to convert anaerobic to aerobic respiration in the absence of adequate quantities of NAD (vitamin B3). The conclusion of the Hong Kong experiment where normal men were converted into Vitamin B3-dependent men provides the clue. I suggest that vitamin B3-dependent individuals not receiving vitamin B3 supplements cannot respond to hyperbaric therapy unless they are given megadoses of vitamin B3 and that the European veterans from Nazi concentration camps would have responded to hyperbaric oxygen therapy if they had been receiving megadoses of vitamin B3. The New York negative results were due, in my opinion, not to psychological factors but to the B3-dependent state of their extermination camp prisoners. The experiments by Boyle and Jacobs were positive because their subjects had not been deprived of essential nutrients for many months and suffered a

much milder form of vitamin B3 dependency.

If we accept the cross-linkage theory, we can plan an attack on the aging process by (1) stimulating and maintaining aerobic respiration while preventing oxygen toxicity, (2) maintaining the maximum oxygen carrying capacity of blood, (3) maintaining optimum fluidity and homogeneity of blood, (4) removing cross-linkaged proteins. As I have shown earlier, this is also the essential prescription for the prevention of senility.

B. Anatomical Degeneration and Senility

For a long time it has been accepted that there is no correlation between anatomical (more correctly histological) damage and senility. It was generally believed that there were enough senile cases who, at autopsy, showed few degenerative changes and apparently mentally normal elderly people who did show extensive degenerative changes to invalidate any meaningful correlation.

Apparently these conclusions were derived from inadequate research. Recently Roth (1972) found a very high correlation between the number of senile plaques discovered at autopsy and the degree of senility at death measured by a senility scale; r was +0.77 which is very high. About 87 to 100 percent of a group of physically ill, confused states, affective states, and schizophrenics had fewer than 11 plaques per area counted. In sharp contrast, 79 percent of senile demented patients had more than 12 plaques. The plaques contained enlarged dendrites axons and a core of amyloid presumably due to the loss of neurons.

Roth (1972) suggested that senility is due to at least two factors which reinforce each other, (1) the loss of neurons as measured by plaque count, (2) cerebrovascular changes.

Shenkin et al. (1973) treated 28 patients who had enlarged ventricles with symptoms of senile dementia characterized by memory loss, disorientation, confusion, and incontinence. Average age was 68 (range 52-83). Of these, 12 became independent and capable of resuming previous responsibilities, and another six were moderately improved. A

recovery rate of 43 percent and a total improvement rate of 64 percent is very good for a condition up to now considered untreatable and hopeless.

He believes that all patients demonstrating senile changes of either organic dementia or gait disturbance, or both, should be examined by pneumoencephalography, and if enlarged ventricles are found, ventricular shunting should be done.

There may be not only increased pressure due to idiopathic hydrocephalus, but perhaps the brain tissue is itself edematous. Boyle (1972) reported that diamox, a diuretic, improved response of senile patients to hyperbaric oxygen. He thought it did this by improving the biochemistry of the brain, but perhaps it also reduces edema and lowers intraventricular pressure.

The importance of these findings is that it may now become possible to classify senile patients accurately. Obviously those with hydrocephalus will not respond to chemotherapy only and will require a ventricular shunt. The patients with no hydrocephalus would be the candidates for chemotherapy, i.e., megadoses of vitamins, or hyperbaric oxygen with diamox, or a combination of all.

Treating and Preventing Senility

If we accept Stieglitz's (1949, 1950) conclusion that "in many respects the changes of senescence are primarily consequences of cellular malnourishment," then prevention of senility must be aimed at preventing cellular malnourishment and treatment upon its restoration.

(A) Provision of an adequate supply of essential nutrients

We require a massive educational effort aimed at physicians, nutritionists, and the public to acquaint them with the special nutritional needs of the aged. I have suggested that senility is a form of chronic malnutrition

and will not occur in properly nourished individuals. Old people require ample quantities of high-quality proteins, high-quality fats, and very little sucrose and sucrose-enriched foods. Highly refined cereal products must be replaced by whole-grain cereals. Not only must the total daily intake be balanced with respect to essential amino acids, fats, and carbohydrates, but an attempt should be made to have each meal balanced with a minimum of three small meals per day. Because of the enormous variation in needs of specific nutrients, especially vitamins, some subjects will require megadoses. The most practical way of determining how much vitamin is required is to give increasing quantities of those nutrients which on clinical grounds seem to be required. If vitamin B3 is required, the dose is increased until maximum improvement is noted. Then it is slowly decreased until the optimum maintenance dose is determined.

(B) Adequate alimentary absorption

Essential nutrients may be absorbed poorly or not at all as in coeliac disease, pernicious anemia, sprue, etc. Many elderly people have no teeth or poorly fitting teeth and do not masticate their food properly. This will lead to overconsumption of low fiber, highly refined, low-quality foods. Also elderly people tend to lack acid in their gastric juice.

Special treatment will be required to overcome these problems. Teeth must be repaired, acid may have to be given, and consumption of coarse fibrous foods encouraged. In some cases, parenteral vitamins may be required.

Cookson et al. (1967), Cookson and Federoff (1968), Horlick et al. (1967), reported that blood serum cholesterol in rabbits fed large doses of cholesterol was kept at low levels by feeding a diet rich in alfalfa. Barichello and Federoff (1971) concluded cholesterol formed an unabsorbable complex with the alfalfa. Trowell (1972) suggests that this is a general property of vegetable fibrous material, pointing out that when Africans eat two-thirds of their calories as unprocessed foods (6-12 g per day of fiber), they have a

very low incidence of coronary disease or of diverticular disease (of the bowel). He states, "The incidence of the latter condition is the best hallmark of the degree of chronic fiber deficiency in any community."

It would therefore be prudent for everyone to consume enough bulk to prevent an elevation of cholesterol levels and so decrease the tendency for arteriosclerosis and its many dangerous sequela.

(C) Inefficient distribution

If the tissues receive too little blood because of any deficit in circulation, they will suffer malnutrition no matter how rich in nutrients the blood is. To maintain normal distribution of blood requires a normal heart, patent and elastic vessels, and the ability to deal quickly with minor infarcts by revascularization. The blood must be homogeneous and not too viscous. A problem to aging subjects is sludging of the blood. Normally erythrocytes repel each other because of electronegative charges on their surface. This insures an even distribution of cells, maximum transfer of red blood cells through the capillaries, and maximum diffusion of oxygen into the tissues. Sludging occurs when red blood cells no longer repel each other and tend to clump or adhere to each other. When this occurs, the flow of red blood cells through capillaries is impeded so that some get mainly plasma. The net effect is malnourishment of some of the tissues. Over a period of many years the tissue suffers repeated insults caused by poor circulation, and this must hasten senescence in these tissues.

Tissue anoxia will also come from too little hemoglobin in blood. Anemia must always be treated.

To maintain optimum circulation and transfer nutrients to the tissues, one should also prevent arteriosclerosis. This can be done by avoiding excessive consumption of sucrose and sucrose-enriched foods, by avoiding too much saturated fats, and by consuming

sufficient bulk. If these measures are not adequate one can use nicotinic acid, 3 grams per day. This is the only broad-spectrum hypolipidemic substance, lowering both cholesterol and fatty acids. It is one of the four substances being examined by the national coronary study. Nicotinic acid also prevents sludging of blood (Boyle, 1972) and accelerates revascularization of tissues by new capillaries. These properties of nicotinic acid may account in part for the ability of nicotinic acid to markedly reduce frequency of coronary occlusions in patients who have already recovered from one. It is relatively nontoxic (Hoffer, 1967,1969).

(D) Ineffective utilizations

Lack of hormones, e.g., insulin in diabetes mellitus, thyroid hormone, and deficiencies in enzymes or minerals will prevent normal intermediary metabolism. Many respiratory enzymes are derived from vitamins. If the intake of vitamins is too low, there will be an insufficient quantity of enzymes and blockages in metabolism. Giving thiamine will increase Decarboxylase while riboflavin, vitamin B3, and vitamin B6 will increase flavine adenine dinucleotide, nicotinamide adenine dinucleotide, and pyridoxal phosphate.

(E) Accumulation of injurious metabolic debris

The term metabolic debris has been used to describe substances formed in the body which are not readily metabolized further and which accumulate in certain tissues. An example is yellow old age pigment or lipofuscin. I believe the body does have a method of relieving itself of debris, especially polymerized protein chains. These may be the cross-linkaged proteins. They can be deposited in tissues which later shed skin, hair, nails, and surface cells of the gastrointestinal system. This would parallel excretion of waste material by deciduous trees by dropping their leaves annually. Recent work on hair analysis shows that hair does reflect changes in mineral composition of the body. Arsenic poisoning can be detected by

hair analysis, and populations breathing in lead in their air will have large quantities of lead in their hair.

I have seen the same phenomenon in a few schizophrenic patients whose skin is dark and whose nails are dark brown from increased quantities of abnormal rheomelanins. When placed upon nicotinic acid therapy, they may go through a phase of color intensification. Their skin, especially over the flexor surfaces, becomes quite brown. Clinicians unfamiliar with this phenomenon may be needlessly worried. It is temporary, and in the interim the pigmented skin can be easily removed by rubbing the moist skin vigorously. It comes off leaving normally pigmented skin much as old tan peels off the body.

One patient had dirty brown-yellow pigment deposited in her nails. After she began to recover, this pigment suddenly stopped being laid down and her nails grew out as normal pink nails. There was a sharp line of demarcation between the distal discolored area and the proximal normally colored area.

If the cross-linkage theory of aging is correct, it becomes important to follow Bjorksten and Andrews' (1960) suggestion to discover substances which will break these cross-linkages. One of the substances they reported useful in breaking cross-linkages in collagen was niacin hydrazide. They did not report whether niacin might have similar properties. I have observed elderly patients whose skin had become parchment-like and wrinkled regain some of its elasticity after taking megadoses of nicotinic acid for some time.

Generally, cross-linking molecules are oxidizing molecules or free radicals. Thus it is logical to change redox systems and reduce potentials by using natural and thus safe reducing substances such as ascorbic acid, vitamin E (K tocopherol), and the bioflavonoids. Perhaps green leafy foods contain still other valuable reducing substances not yet characterized.

Reducing substances should reduce in-

tensity of cross-linkage formation and give more time for natural reparative processes to break and eliminate cross-linked proteins already formed (Harman, 1969).

Evidence Nicotinic Acid Retards Senility

Stieglitz (1949) is very clear in his view that senility is a one-way process not subject to spontaneous recoveries. He states, "in no instance is there a noticeable tendency toward self limitation of the disease or spontaneous cure." These observations are in agreement with mine. This being the case, double-blind placebo-controlled studies which are un-proven, not validated, and expensive, and yield negative results even with powerful well-known chemicals, have even less role to play in therapeutic studies of senility. Unfortunately, they are fashionable and allow clinicians to enjoy the illusion that they can replace careful observation by method. Our best studies are those conducted by careful clinicians who can reason beyond double-blind fads in research methodology.

Sydenstricker and Cleckley (1941) first reported the usefulness of nicotinic acid in above-average doses in treating senile and presenile psychosis. Stephenson et al. (1941) found that many patients already senile and psychotic were markedly improved when given nicotinic acid, thiamine, and liver extract. Similar findings were reported by Wex-berg (1943). Moore et al. (1951) used histamine plus nicotinic acid by intravenous injections on 24 senile patients. Only one did not respond on maintenance doses of nicotinic acid. Ten months later five were well, eight were markedly improved, and eight were no better.

Gregory (1955) gave a group of senile patients one gram per day of nicotinic acid. Improvement depended on age of the patients. Eight out of 14 under 66 were much improved, while out of 65 patients older than this only four were better.

Evidently treatment should be started before senility is too firmly established. However, perhaps many more over 66 years would have responded if higher doses had

been used, going up to 3, 6, or even 9 grams per day. Hoffer (1962) provides a review of previous investigators who found nicotinic acid helpful in treating confusional states.

In 1962 I reviewed treatment results on 15 elderly patients, most of whom were suffering from early or late senescence, with or without psychiatric changes. They had been treated with nicotinic acid between 1954 and 1960. In 1954 their average age was 71 — range 58-80. Each patient had been on nicotinic acid, 3 grams per day, for three months to six years (mean 1³/₄ years). In 1960, 10 were well, two were improved, and three had shown no improvement.

Patient H.C., now age 86, remains mentally well, but there has been a hearing loss and she is physically frailer. F.C. died in 1969 from a cerebrovascular hemorrhage following a couple of minor episodes in the previous nine months. During this nine-month period he remained mentally normal. I have not tried to trace the other 13 subjects.

Experience gained in the past decade with a much larger number of elderly patients suffering from depression, anxiety, irritability, memory loss, confusion, and disorientation has convinced me that they should all be given megadoses of nicotinic acid plus whatever other medication they require. Nicotinic acid is more specific as an anti-senility medication than any other chemical I have had much experience with. If it is started before there are irreversible anatomical or biochemical changes, the results will be much superior, but even after it has started it will probably prevent or slow down rate of senescence.

Other evidence that vitamin B3 can reverse senile changes was provided by Kaufman (1949) whose work has already been reviewed. After treating his patient population with megadoses of nicotinamide, there was a marked improvement in their joint function as measured by the mean joint range index. This is also proven by his careful clinical description of some of his patients and their improvement. The entire group from age

under 10 to 60 now fell into the slight dysfunction category, and the 60 to 80-year group now suffered moderate disability, whereas before treatment age group 51 to 80 suffered severe joint range index of 83 as equivalent to joint dysfunction of the average teenager. We can conclude that nicotinamide has reversed joint disability of subjects over 70 to the amount commonly found in young subjects between 10 and 20.

Glutavite

Another interesting nutrient is glutamic acid which is metabolized in the brain and can cross the blood brain barrier. So far there have been conflicting reports on its efficacy primarily because two of the three available forms, glutamic acid, hydrochloride, and free glutamic acid are poorly absorbed. Monosodium glutamate is absorbed by mouth much more effectively and is the form which should be used. Many workers used too little. Much better therapeutic trials would be reported if workers ran dose-response curves before starting their trials. There seems little point in reporting trials on inadequate doses. Himwich et al. (1955), using a double-blind crossover design with placebo controls, found that monosodium glutamate produced an appreciable and gratifying improvement in mental state of a significant number of patients. Katz and Kowaliczko (1956) examined the response of a group of 27 senile patients to 1-glutavite. This mixture in one day provided 135 mg of nicotinic acid, 90 mg of ascorbic acid, 10 grams of monosodium glutamate, some calcium and phosphate, and insignificant quantities of thiamine, riboflavin, and iron. This group, averaging 72 years in age, had been static or deteriorating in their mental state. After 12 weeks they found that 12 showed a good or excellent response and six a fair response.

Altogether 67 percent were improved. Not surprisingly, patients who had not deteriorated organically responded best. They concluded that glutavite was very

useful in the management of elderly people suffering from fatigue, apathy, depression, and some decline in mental function. The small amount of nicotinic acid in this preparation could have been responsible for only a small proportion of the improvement. Barrabee et al. (1956) confirmed the good therapeutic response to 1-glutavite.

So far I have seen no studies using a combination of monosodium glutamate and adequate quantities of nicotinic acid, i.e., 3 grams per day. A combination of these two nutrients plus smaller quantities of other water-soluble vitamins ought to be a very useful antisenility preparation. 1-glutamine probably should have been used since it crosses readily into the brain while glutamate does not.

A Prescription to Delay Senility

Based upon a review of the literature and my own experience in dealing with senile and presenile subjects for the past 20 years, I recommend the following program to prevent or markedly reduce the ravages of senility.

1. DIET

This should be low in sucrose and sucrose-enriched foods, and low in saturated fats but not carried to the point that nutritious foods such as eggs are eliminated. Protein of high quality should be consumed. The daily food should be divided between three meals with in-between snacks. Whole grain cereals should be used rather than refined cereal products in order to provide adequate bulk (fiber).

2. SUPPLEMENTS

When diet alone does not control or prevent senility, one should use adequate doses of specific nutrients. Of these, the best is nicotinic acid for most subjects, but some may need other nutrients such as other vitamins and monosodium glutamate. Unfortunately, there are no simple methods for determining which nutrients will give optimum results. However, the most practical way will be to use trial and

error, increasing doses of several nutrients one at a time or in combination until the desired response is seen. I suggest that the nutrients should be tried in the following order: nicotinic acid, Pyridoxine, ascorbic acid, thiamine, vitamin B12, vitamin E, 1-glutamine. For many, one will need nicotinic acid 3 grams, ascorbic acid 3 grams, Pyridoxine 250 mg, thiamine 250 mg, vitamin E 800 i.u., with some vitamins A and D. At least this is the mixture I have been taking for several years with no undesirable effects.

Ascorbic acid, a powerful reducing substance, should prevent or reduce cross-linkage formation and therefore might be expected to have anti-aging properties, especially in tissues most likely to suffer cross-linking changes. Collagen is such a tissue. It is the most important supporting tissue, and aging will interfere with function of all tissues it supports. Collagen shows characteristic aging changes which is evident clinically when one looks at an aged person, and biochemically aged collagen becomes inelastic, loses ability to swell, is less soluble in acid, and is less readily digested by collagenase. In 1948 McCormick, an early proponent for using large doses of ascorbic acid, "recommended using ascorbic acid to reduce aging. He stated, "the young women of today will be able to have recourse to a veritable interval cosmetic, a dietetic measure, at the same time practical and pleasant to avoid premature loss of elasticity of their still youthful tissue."

Ascorbic acid should also be helpful in preventing and controlling other degenerative diseases such as arthritis, although only megadoses ought to be researched. It has recently been shown it can normalize cholesterol metabolism which surely ought to be useful in protecting us against senile changes. Stone (1967, 1972) has adequately summarized ascorbic acid's role in treating and preventing senility.

There are two lines of evidence which support the theoretical position that vitamin E is an antisenility factor. Harman's (1969) report suggests that it does prolong life in some

animal species. It also is involved in deposition of old-age pigment formation. Reichel (1970) found higher quantities of lipofuscin in aged tissues in rats, in two children with progeria, and in presenile dementia, Wilson's disease, and a few other degenerative diseases. In vitamin E-deficient rats the adrenal gland contained much more lipofuscin, evidence that vitamin E protects animals against excessive deposition of lipofuscin. He suggested that vitamin E deficiency and senescence may share common mechanisms; for example, the auto-oxidation of cellular membranes secondary to antioxidant deficiency.

Pryor (1971), in reviewing the relationship of free radical pathology and aging, noted that natural antioxidants like vitamin E are essential to trap excess free radicals. Aging would then be accelerated by either an increase in peroxidation, a deficiency in antioxidants, or both. Membranes directly involved in oxygen transfer would be most susceptible to aging, and lung tissue should be particularly susceptible.

Hirai and Yoshikawa (1970) reported (1) increase in brain lipoperoxide with age, (2) this was prevented by vitamin E, (3) lipoperoxide concentration in the brain was much higher in vitamin E-deficient rats compared to animals fed diets enriched with vitamin E. They also observed changes in the dorsal column of the medulla in vitamin E-deficient rats which was almost identical with histochemical changes in the medulla of aged persons.

3. Psychiatric symptoms will require specific treatment as well. Certain minerals will be as important as vitamins, but I will not deal with them.

Role of Subject

Each person must examine himself very carefully and determine what stage of senility he is in. He may not show any evidence of senile changes whatever, but if he is aware of changes in vision, in his hearing, and in other senses, if his memory is ailing, and if he

shows any evidence for any of the degenerative diseases, he must assume the process is underway. He may require a proper examination from a gerontologist.

He should embark on a program of orthomolecular living (Meiers, 1972). This means he must consume an optimum balance of protein, fat, and carbohydrates by increasing his intake of high-quality protein which can be of vegetable or animal origin. He should decrease but not eliminate his intake of animal (saturated) fats such as milk, butter, etc., and markedly decrease his consumption of carbohydrates. He should eliminate sucrose or sucrose-enriched foods and whenever possible use whole foods rather than refined foods, whole grain bread rather than white bread, whole rice rather than white rice, and so on.

This may be sufficient to slow down the senile process, but as megadoses of certain nutrients may be required he should by trial and error determine his own optimum dose of the vitamins, thiamine, riboflavin, B3, Pyridoxine, and, with the aid of his physician, folic acid and B12. He should increase his intake of vitamin E by consuming vitamin E rich oils or vitamin E capsules. It may take many months and years to work out a proper regimen, but as there are as yet no chemical assays which will help, there is no other way.

Role of the Physician

He must accurately determine how much senility is present by considering every sign and symptom of any of the degenerative diseases, including cancer. When present, he should advise his patient about Orthomolecular treatment to reverse senile or presenile changes already present, and when this is not possible, to slow its further progression. His patient is his active collaborator in this joint attack on his patient's senility.

In addition he should try to reverse degenerative changes already present by correcting anatomical defects and by providing megadoses of specific nutrients such as vitamins and minerals, and he should

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try to detoxify the body of old age debris (clinkers) already present.

Conclusion

I have adopted the hypothesis proposed by others nearly 20 years ago that senility is a manifestation of chronic malnutrition. This is supported by evidence referred to. Coupling this hypothesis as a reasonable approximation to the truth, I have recommended that an Orthomolecular approach be used to treat and prevent senility. This includes use of proper nutrition plus reinforcement with megadoses of vitamins as required.

ADDENDUM

Since this manuscript was completed, the results of a national survey in Canada were presented (Sabry, 1973, "Nutrition: a National Priority," Department of National Health and Welfare, Ottawa, Canada). This is one of the most thorough nutritional surveys. Over 27,000 subjects across Canada were examined. From the data in this report, I have estimated the percentage from various age groups whose intake of nutrients was considered inadequate or less than adequate. This is shown in the following table:

		Relation Between Age And Inadequacy of Nutrient Intake Age				
		5-9	10-19	20-39	40-64	>65
Vitamin B3						
Male		1.8	3.0	1.9	4.6	8.8
Female		1.8	10.3	9.3	11.0	18.8
Riboflavin (B2)						
Male		10.3	22.0	32.2	30.2	41.1
Female		10.3	32.0	41.8	48.5	47.6
Thiamine (B1)						
Male		23.2	28.3	42.5	40.4	40.6
Female		23.2	38.1	47.8	49.8	52.8
		Age 5-9	10-19	20-39	40-64	

Ascorbic Acid (Vitamin C)					
Male	14.5	13.7	14.5	13.7	16.8
Female	14.5	17.9	20.6	16.6	13.1
Vitamin A					
Male	17.7	28.7	27.2	30.3	46.0
Female	17.7	48.6	46.8	54.8	53.7
Calcium					
Male	43.7	50.8	21.8	22.8	32.3
Female	43.7	62.2	39.6	43.9	47.8
Iron					
Male	35.5	46.4	15.3	18.3	34.9
Female	35.5	78.2	76.1	66.8	55.9
Protein					
Male	3.0	6.3	9.0	12.8	27.3
Female	3.0	14.2	18.0	27.0	37.7

There is a progressive increase in the proportion from each age group who are deficient in intake of nutrients with increasing age. This applies to vitamin B3, riboflavin, thiamine, vitamin A, and protein. There is no drift upward for ascorbic acid nor for calcium, while iron needs depend upon growth and on menstruation. What is surprising is the high percentage of the over-65 group who are deficient in these nutrients. About 25 percent lack vitamin B3, about 50 percent lack vitamin B2, B1, and A, and over one-third are short of protein. The estimates are based upon generally accepted Canadian standards which, in my opinion, are probably low and should be revised upward. If more modern standards aiming at optimum health had been used for the base line, the percentages tested in this table would have been much worse.

In any event, it is clear that malnutrition and old age are practically synonymous. This survey adds weight to the argument that malnutrition is a key factor in the etiology of senility.

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