LONGEVITY, 2

PAST • PRESENT • FUTURE

by

JOHAN BJORKSTEN Ph.D.

Associate Editors:
Michele Buis-Dulin
Deborah Nieto

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DEDICATION

This book is dedicated to everyone who has aided me by friendly criticism, wise counsel, and with financial support in critical times during the half century of study and struggle that this book represents.

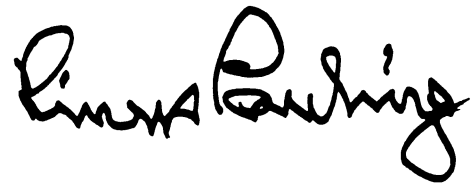
In particular, I wish to express thanks to:

Dr. Herman Adlercreutz, Mr. Fred Andrews, Mr. Peter Benoliel, Mrs. Mertie W. Buckman, Mr. Lucius Burch Jr., Mr. and Mrs William Cameron, Dr. Myron A. Coler, Mr. Tulio Cordero, (the late) Dr. Floyd Eberly, Dr. Elizabeth Roboz-Einstein, Dr. John D. Ferry, Mr. Claud Fincher, Ms. Janet Fleisher, Mr. W. Freeland, Mr. Paul F. Glenn, Dr. K. H. Gustavson, Dr. and Mrs. Franz J. Haromy, Dr. Henry B. Hass, Mr. and Mrs. Martin Hilby, Mr. Björn Holmstrom, Dr. Amos Horney, Ms. Constance Kamberos, Dr. L. V. Komarov, Mrs. F. B. Korsgard, Mr. Frank B. Kozacik, Mr. Edward Lamb, Dr. H. Le Compte, Mr. Jeremiah Milbank Jr., Mr. Robert S. Morrison, Dr. Michael Mulinos, Mr. and Mrs. James L. Neal, Mr. Carl Pacifico, Mrs. Dorothy Petersen, Mr. Gerard Pucci, Mr. Angus Ray, Dr. Aryeh Samuel, Mrs. Laina Sarsila, Dr. Richard Schreiber, Mr. and Mrs. M. A. Self, Mr. and Mrs. Willard Sparks, Dr. Peter Stamm, Dr. Francisca Sundholm, Dr. Thomas Tallberg, Mr. Heikki Tenhu, Mr. Henry Tovey, Mr. Bo Westerberg, Mr. Jan Westerberg, Dr. Donald Wetlaufer, Mr. Timothy Wuliger, Mr. and Mrs. Luther L. Yaeger.

FOREWORD

Dr. Johan Bjorksten is one of the most active and effective students of longevity in the world. For many years he has carried on scientific studies relating to longevity. Forty-four years ago he formulated the biochemical crosslinkage theory of aging. This theory consists in part of the idea that with the passage of time some of the large molecules in the human body are linked to one another by covalent bonds that resist disruption, so that the substances, mainly proteins, become insoluble and resistant to attack by enzymes. The cross-linking changes the nature of the structures constituting the human body in a way characteristic of aging.

In his book "Longevity, Past, Present and Future" Dr. Bjorksten now presents a penetrating discussion of the process of aging and its relation to longevity, in a manner appropriate to the lay audience for whom the book is written. Reading this book should be of value to every person.



Linus Pauling Institute of Science and Medicine
Palo Alto, California 94306

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LONGEVITY, PAST, PRESENT AND FUTURE

INTRODUCTION

The progress of mankind toward better health and increased longevity has been traversing levels. For our purposes, these levels will be called Epochs. The Epochs are characterized by the main causes of death for each time period.

The first epoch was the Stone Age, where the principal cause of death was big carnivorous beasts. The life expectancy was below ten years. The second epoch was disease caused by the microorganisms of contagion. Examples of these are the plague and smallpox. In the third epoch, the primary cause of death is heart and sclerotic disease. Three epochs of existence are behind us. We are able to see two future epochs which will be discussed in this book, but there may be more. The ultimate epoch of existence in a remote future is when the only causes of death are accidents, suicides and violence.

Each epoch is followed by a period of transition. Each transition zone is characterized by the fact that those living in it still cannot see the following epoch, nor reap its benefits of longer life and better health. We are currently in the transition period between Epoch III and Epoch IV.

The Stone Age persons would have disbelieved anyone who had told them that their descendants would have no need to fear big beasts, but instead would be killed by beings so tiny that they could not be seen. If someone would have told even a physician in 1884 that a hundred years hence very few would die from bacterial diseases, but that the principal causes of death would be cancer and strokes, he would have been considered a naive visionary. Today, circulation diseases and cancers kill three out of every four persons in the USA. Yet, very few realize that we have already the means not to cure, but to prevent 90% of these diseases. Eventually, as increasing numbers of people take advantage of this knowledge, as well as the benefits of longer and healthier life that accompany it, we will be ready to leave Epoch III behind us and face the challenges of Epoch IV.

The degeneration of the central nervous system - Alzheimer's Disease and Senile Dementia - will be the killers of the next epoch. This book will endeavor to present solid proof of this and practical methods of prevention where such are available. Anyone wanting to avoid what will eventually be the fate of everyone in the next epoch, will find this information of practical value.

SECTION I

FOLLOWING THE THREAD OF LONGEVITY

AN OVERVIEW

The Epochs which mark the progress toward longer and more healthful life and the transition zones which unite them are shown in the following figure. Even though each Epoch has its' separate predominant causes of death, those who live in a transition zone hardly ever notice this until the following Epoch is far advanced. In the past, the transitions have taken several generations. Perhaps advances can come faster in the future. Each transition period has brought a way to either cure or prevent the earlier main cause of death and with this knowledge came an increase in life expectancy for the average person.

FIGURE 1 - ILLUSTRATION OF EPOCHS

Progress in longevity is in plateaus which we will call "Epochs". These are shown in Figure 1 as rounded platforms. Each Epoch is recognized by the then prevailing main cause of death. The Epochs are connected by transition zones which sometimes lasted centuries.

The first Epoch was the STONE AGE which is shown at the bottom of the figure. Most people were killed by big beasts; and child mortality was tremendously high. The second Epoch was CONTAGIOUS DISEASES. It began when most people died from the plague, small pox, malaria, leprosy, TB and so on. It entered a transition zone about 1660 when the microscope showed us the microworld and ended in 1950 when penicillin hit mass production. Epoch III followed with environmental and deficiency diseases (heart, blood circulation, cancers).

We are now in a transition period. We know enough to prevent 90% of the diseases of Epoch III but do not yet apply this knowledge generally. Epoch IV, in which brain and nerve diseases will be the main cause of death, will have arrived when more than 50% of our hospital beds are occupied by mental cases. The nature of Epoch V is also shown.

Even when an Epoch is past, some, maybe up to 5-10% of the population will still die of its main cause of death. The accidental death by wild beasts of Epoch 1 is analogous to fatal automobile accidents today. Persons with impaired immune systems still die from contagious infections such as the flu. Each past Epoch will still take its toll on the population and together they will form the final Great Barrier which has kept us from experiencing healthful life beyond the age of 70-80 years. Far, far in the future (at the top of Figure 1) we can glimpse a time when disease and aging are no more, and the only causes of death are suicide, violence and accidents.

(The names mentioned in the figure are a few of those who, in my opinion, made important contributions to progress. Due to obvious space considerations, only a few could be listed. In the margin of Figure 1 are listed estimates of longevity in the Epochs. The gap between women and men has widened, and will continue to do so with increasing longevity.)

HOPE

When all remaining problems have been solved and every needed atom is automatically renewed without loss of memory or personality, there will be no Aging nor Disease. For our late descendants, let's hope that people then will have the maturity to live in PEACE.

↑

EPOCH V

Longevity limited by random, non-programmed cross-linking, damaging all kinds of vital molecules, then causing fluids within cells to gell.
Average life span:
Women — 200 years
Men — 150

↑

EPOCH IV

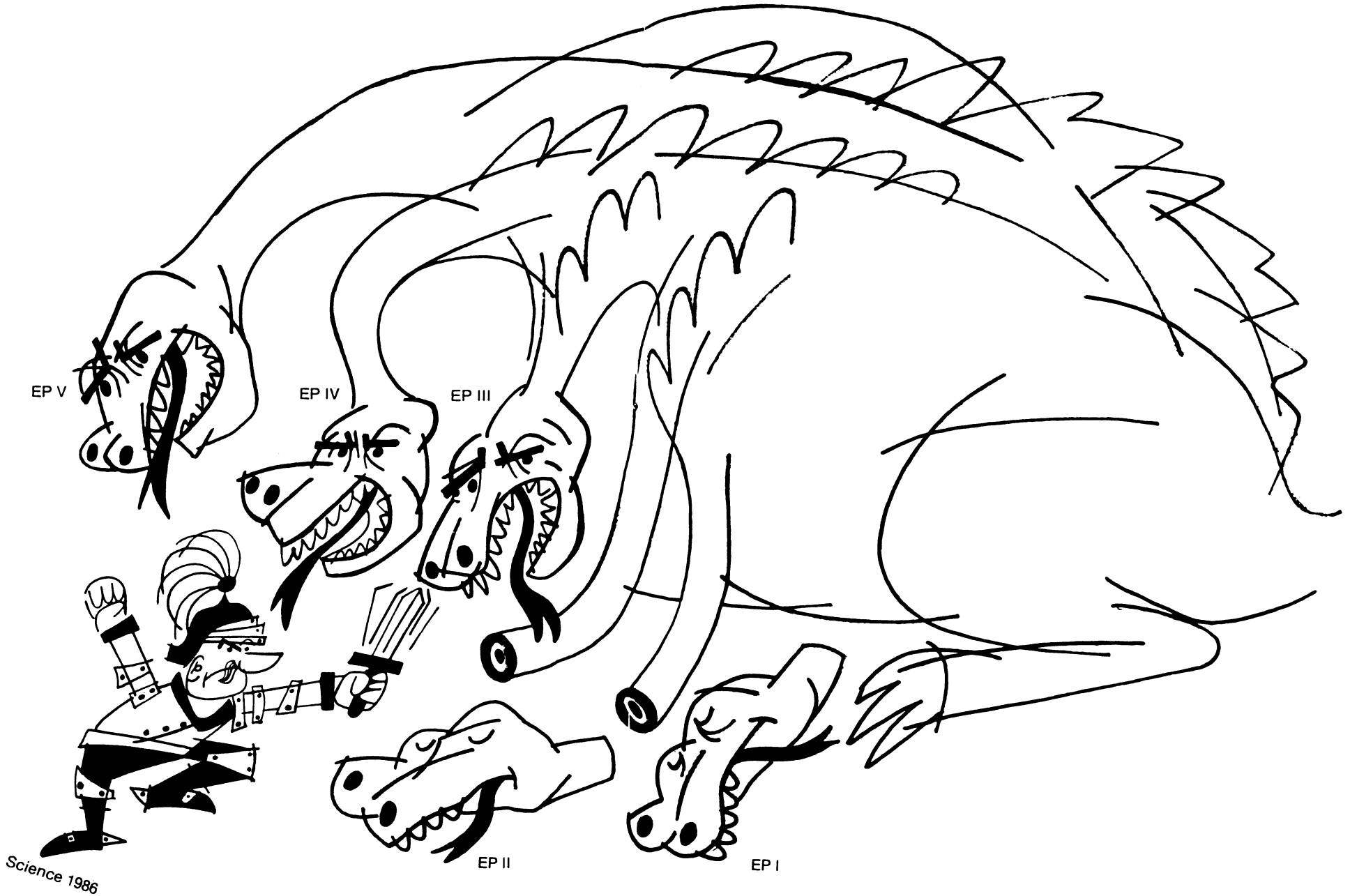
Longevity limited by Brain- and Nerve- diseases.
Lifespans W. 100 years
M. 80
This Epoch may be over by

We are now in year 1986
Transition Ep. 3 to Ep 4.
Lifespan W. 77
M. 70

EPOCH III
Longevity limited by
Deficiency & Environmental
diseases (Heart, Cancers)
Average Lifespan 40 — 60.
Duration 1848 — 1950.

EPOCH II
Longevity limited by
contagious diseases:
Plagues, Pox, Malaria, TB,
Diphteria, and others.
Average Longevity 20 — 40.
Time: ~3000 BC to 1660 AD.

EPOCH I
Stone Age.
Main Cause of Death:
Being eaten by big beasts.
Average life span < 10 Yrs.
Infant mortality was huge.


EP V
EP IV
EP III
EP II
EP I
Science 1986

CHAPTER 1

EPOCH 1 - THE STONE AGE

Our knowledge of the Stone Age is limited by the total lack of written information. From scattered finds of tools and bones we can form a picture, though a very sketchy one, of the time when our remote ancestors began the slow and difficult climb to higher levels of knowledge. In the Stone Age, life was a hazardous, uneven struggle against stronger and faster enemies.

The Stone Age lies 5,000 to 50,000 years in the past. It began first in the warmer climates of the South, before spreading northward.

A woman of twenty-five thousand years ago might have made the following statement, had we been able to contact her:

"I am a cave-wife, and a mother of four, of whom one is still alive. I am now 4 months pregnant again. I have seen 14 summers. When I was mature 5 summers ago, a man attacked me. He was a good hunter so I followed him. We found a good cave and rolled big stones to close the opening so the biggest beasts couldn't get in."

"But a fox came in when we were hunting and stole our first child. The second child is alive. He is very quick and can help catch fish with a pointed stick. The third child died from a snake that came into our cave when I slept. The fourth child was taken by a big bird which came suddenly when all seemed so peaceful."

"My man killed a deer with a stone and was carrying it home when he met a bear. He did not want to give up his deer and fought the bear, but was slashed and died that night. I hunted alone with my boy but then found a man whose wife had been killed by wolves. He came to my cave and was good to us. But he is an old man, nearly twenty summers, and he is now so slow that I worry about losing him too. He went out hunting two days ago and has not come back yet."

Comment:

This description may not be exact but the essential facts will stand: An average life-span well below 10 considering high infant mortality, and the principal cause of death was large meat-eating animals.

CHAPTER 2

CONTAGIOUS DISEASE

Thousands of years went by. Weaponry was improved as metals were taken into use. People now joined in larger communities for mutual defense. The big beasts were no longer a constant menace - or even an important cause of death. Yet, the increase in average longevity was not substantial. Instead of the large beasts, only too visible to all, people were attacked by countless new enemies against which they were defenseless. The viruses, microbes, and bacteria were invisible and unsuspected. Through millennia of this uneven fight, mankind managed to survive, thanks to its immune system. Important components of this system are: white blood cells, the leucocytes of the blood, the lymphocytes, the killer or "T cells" from the Thymus, and the antibody producing n-cells from the bone marrow.

No matter how severe the epidemic, there were always some survivors.

To give some idea of the violence of contagion, the following example may serve.

Epoch II - The Black Death

A contemporary account of one of many plague epidemics.

The 14th century was replete with epidemics of which some were spectacular. The Black Death swept the continent, killing from half to 3/4 of the population where it spread.

In order to get the feeling of the horror of these epidemics, we need to speak with someone who has experienced one. A time reporter has just returned from his interview in the middle of Epoch II. He visited Florence, a principal political and cultural center in Italy, soon after the passage of the Black Death in that city in 1348. He tells us:

"I did not want to materialize in the city proper. Such a sudden apparition might have risked arrest for magic and even summary execution. My dress as a young nobleman was copied from historical pictures.

"I chose for arrival a rural road, about a day's walk from Florence. It was the kind of place and distance where I might meet persons who had fled from the city and were now beginning to return. At a roadside inn I got into conversation with an intelligent-looking man of about my own age and assumed status."

"I told him I had just arrived from a distant city, and was

on the way to Florence and asked him if he thought there was still a risk of catching the plague? He said: "I would not go there myself if I thought it overly dangerous still - but after a miraculous survival by God's grace I believe I would have died already, had it been so written."

"I worked in Florence as an architect's assistant. The Plague was suddenly among us. People were getting sick and dying everywhere. Our physician could not be found. Other physicians were swamped. Besides, what could they have done when God's will was to punish the city for its sins? I thought of going to the church, but it was already packed with sick and dying people. The smell of death was heavy."

"So I felt an urge to get away from there as fast as I could! I put some food and wine into my sack and started out. People were falling over and dying in the streets. Nobody seemed to care. Some children were crying. Many were sick. I almost slipped on the vomit of a dying child as I crossed the street."

"Houses were locked; barricaded. Nobody knew or cared if the people inside were ill, dead, or about to die. Some devoted monks and priests were walking among the sick, administering the last Sacrament. Some of them fell ill too. If this was really a punishment by God, there was not any justice that one could understand. Holy men and charitable persons fell ill, while good-for-nothings survived. Even thieves and scoundrels went about, apparently untouched, to rob homes where people were unable to defend themselves or their property. Law and Order were gone. It was like the Hell which our Florentine poet Dante Alighieri described some 30 years ago."

"But how did you survive?"

"By God's special Grace, of which I feel most unworthy - but who can question His ways? Somehow I got out of this inferno and was soon walking away on a country road. I did not feel like sleeping in any shelter with so many sick and dying around me - even a good distance from Florence. I took a small side road to get away from the main stream of fugitives. I slept a few hours under a tree and then walked on."

"On the second day I found myself in a surrounding which in other circumstances would have been pure joy - a sloping mountainside, with many little brooks cascading - fresh air, no crows or vultures but small birds singing, no bodies, and fresh clean water. Instinctively I had been refraining from drinking anything but rainwater, but now I could drink my fill. Then the sun came out from the clouds. As I walked by an isolated house, I heard gay voices."

"A group of 7 women and 3 men were sitting around an outdoor

table having their midday meal. One of the women hailed me and asked if I had any news from Florence. I said I lacked words to describe the situation there and that this was like another world in comparison. They offered me some food and I reciprocated with some good wine. These people had left Florence well before the worst horror and were now waiting at this secluded place. To pass the time, each of them would tell the others a story every day. The girls asked me to sit down with them and perhaps tell some story too, and I was delighted to do so for a while."

"The stories they told were very earthy, but they all had a good point and were well told. I noticed that one of the men now and then wrote some notes with a stick on a wax tablet. I commented on that to the woman next to me. She said: "Oh, you mean Giovanni Boccaccio? He's a nice person, likes to write stories though his Dad wants him to become a businessman. I guess he might use some of our tales in his stories."

"And you don't mind?"

"Not at all. He wouldn't use any of our real names."

"They wanted me to stay, but I felt that I might have trouble with the men. I thanked them for the pleasant interlude, and moved on." So do we.

Large plague epidemics occurred several times in each century. About 40 years after the Florence epidemic (which went all over Europe), the Plague hit London. Seventy thousand dead were counted and many more uncounted. As late as 1896 a severe plague tormented the cities of Hong Kong and Kanton, and spread with traders and travelers all over the world. The total number of deaths exceeded ten million.

These spectacular epidemics were, however, less devastating than smallpox, tuberculosis (TB) and malaria, which only in the present generation have been brought under control.

For hundreds of years more, this fight against contagious disease went on. The mindless but innumerable microbes, protected by their invisibility, took their heavy toll of lives from an unsuspecting humanity. Those who survived were those with the best immune system, the best balanced diet, and the best luck. The average human longevity was still below 30 years.

This thousand-year deadlock was broken when Antonie van Leeuwenhoek succeeded in making the microscope lenses which made the microbes visible. Now we could see our enemies. True, Leeuwenhoek did not think in those terms, nor did he realize the vast importance of the microworld. However, it was now inevitable that mankind would win its fight in only a few more generations.

Antonie van Leeuwenhoek

In 1648, when Antonie van Leeuwenhoek's stepfather died in Delft, Holland, the 16-year-old boy was apprenticed to a linen draper in Amsterdam. At the age of 20 he moved back to Delft and established himself as a draper and haberdasher. Somewhere along the line he became fascinated by a magnifying glass. From a maker of eye-glasses he learned the rudiments of lens grinding and from there went on; driven by an insatiable curiosity. At the age of 28 he obtained a modestly lucrative job as a book-keeper for the sheriff's office in Delft. He spent most of his salary on buying glass and grinding abrasives. As he went on with infinite patience and much skill, van Leeuwenhoek began to glimpse a new, totally unsuspected world. He could now see "very little animalcules"; some still; some moving briskly under his lenses. He found these animalcules in virtually anything he looked at. At first, nobody believed his "wild tales". A friend put him in touch with the Royal Society in London. A demonstration was arranged. After that van Leeuwenhoek was accepted, though gradually, by the scientific community. He was then 41 years old.

From 1673 until his death in 1723 van Leeuwenhoek communicated his observations to the Royal Society in informal letters. His discoveries were for the most part made public in the Philosophical Transaction of the Society, which in 1680 elected him a Fellow.

With his lenses van Leeuwenhoek reached a magnification of about 300 times. This was enough to see many bacteria and protozoa, to describe in detail the mouth parts of many insects, the entire life cycle of the weevils in the granaries (which were then supposed to be formed somehow from the wheat), and of the flea (which was also believed to be formed from dust and dirt). In 1677 he described the spermatozoa from insects, dogs and man. Van Leeuwenhoek continued his studies with unabated enthusiasm until his death. He was then 91 years old.

Even though van Leeuwenhoek never connected his "very small animalcules" with disease, he gave us the tools for exploring the microworld. It was now unavoidable that somewhere, someone would make observations at the critical time and place, and would find diseased organs teaming with microorganisms not normally present.

Progress comes slowly.

One hundred seventeen years passed before the anatomy professor Friedrich G. J. Henle wrote "The material of contagion is not only organic but a living one and is indeed endowed with a life of its own, which is, in relation to the diseased body, a parasitic organism."

Among those who attended Professor Henle's lectures in Göttingen was a young medical student, Robert Koch. In 1870, Koch was to furnish the conclusive proof that what Henle had said was true. He also created methods for isolating, culturing, and identifying bacteria.

In the years between van Leeuwenhoek and Koch, the medical profession underwent a transition from a largely tradition bound duplication of inherited procedures to a much more open attitude.

Empress Maria Theresa (1717-1780) and her medical adviser, Gerard van Swieten, M.D.

Empress Maria Theresa, Queen of Bohemia and Hungary and wife of the Holy Roman Emperor Francis I, had complete power over one of the mightiest empires of her time. A highly respected Dutch physician, Dr. Gerard van Swieten, was appointed personal physician to the Empress. Dr. van Swieten was given considerable authority over medical activities in her domains.

This was 10 years before the Empress gave birth to her eleventh child Marie Antoinette, who was destined to marry the King of France, and to be beheaded in the French Revolution. (The Empress had 16 children in all, 10 of whom reached adult age.) On arrival in Vienna in the spring of 1745, Dr. van Swieten was shocked by the mortality figures. Three out of four who entered the city hospital died there. Many of those who entered the hospital for one disease, contracted others.

Dr. van Swieten quietly collected the hard data, and placed them before the Empress.

"My God!" she exclaimed. "I had no idea that things were this bad! What can I do?"

Dr. van Swieten seized the moment. He said: "Your Majesty can command that henceforth a death certificate must be issued for every person who dies in one of our hospitals. This certificate must be signed by the physician in charge, and it must state the cause of death based on necropsy by a qualified physician, if not otherwise completely clear." (The term "necropsy" may be better known as autopsy. However, autopsy is a misnomer. "Auto" means self while "necros" means corpse. An autopsy would actually mean an operation on oneself while necropsy is an operation on a corpse.)

"Draw up the necessary orders", said the Empress, "I want to sign them today." There were no committees, no arguments, no appeals. The will of the Empress was the highest law.

So it happened that Austria-Hungary alone of all countries

gave its physicians the opportunity - nay, forced it upon them - to follow through after the death of the patient. Only necropsy could give them the best possible knowledge of what had been the course of the disease, and if a medical error had been made, to recognize it and do everything possible to prevent it from happening again. Vienna soon became the gathering place for physicians from all over the world, striving toward perfection in their high calling. The importance of therapy based on actual observation and the freedom to improve on old practices cannot be overestimated.

I have been told that her decree about compulsory necropsy is the only law from that time that has persisted unchanged through all the subsequent governments of Austria.

A Tribute to those who spearheaded the victories over contagion

The beginning of modern medicine, and the conquest of the contagious diseases fills the time from Pasteur and Koch until Fleming and the technological breakthrough of antibiotics during World War II. If I were to do justice to the great names of that period, there would not be space nor time to follow the thread of longevity through the ages and into the future. Therefore, I refer the reader interested in this important period to the many excellent books that have been written on this. In particular, I recommend "The Microbe Hunters" by Paul de Kruif.

The thought I hope to convey to the reader is that progress in Longevity has been a series of epochs, each of which has lasted a long time. A transition period has then followed, leading into the next epoch. In the past, these transitions have lasted from a hundred to a thousand years, but now the trend is toward somewhat more rapid change as the means of communication have improved. However, even now, those who live in a transition period have been slow to recognize the significance of the following epoch until it was upon them.

The cave dwellers had no concern about enemies they could not see. Those who were threatened most by contagious diseases like the Plague had little concern about the non-bacterial "degenerative" deficiency and environmental diseases which affect our society now. Likewise, we now possess the information which would enable us to prevent 90% of these diseases but we are still beating our heads against a wall in trying to cure diseases which could and should have been controlled by known methods of prevention.

This is an insight I hope to convey to you, and then to suggest what each of us can do individually to live longer, better.

Therefore, no more personal histories from the past - we go

Therefore, no more personal histories from the past - we go on to where we are now - and beyond.

DEFICIENCY AND ENVIRONMENTAL DISEASES

When contagious diseases were no longer a major cause of death, other diseases took their place. These were not caused by invading life forms, like the bacteria, but by our own faulty or insufficient maintenance, or mismanagement. The common term "Degenerative Diseases" does not fit our present knowledge. "Deficiency and Environmental Disease" is the name we shall use.

The microbial diseases have been largely replaced by atherosclerotic disease and cancer. "Atherosclerotic diseases" is used here as a broad term which includes circulatory diseases (heart) and blood vessels. It is now that we shall turn our attention to the major causes of death of the present epoch - Epoch III, Deficiency and Environmental Disease.

CHAPTER 3

EPOCH THREE - THE DEFICIENCY AND ENVIRONMENTAL DISEASES

Today, the diseases collectively known as deficiency and environmental diseases account for three out of every four deaths in the United States. The diseases which comprise most of this category are heart disease and cancers. Heart disease is especially prevalent in the United States. One out of every three persons in the U.S. can expect to die from heart disease, while one out of every nine will die from it in Japan. Such great differences between different countries spell out clearly that heart disease and diet are related. Being deficient in certain substances will heighten one's chances of developing heart disease, as will imbalances in nutrition.

With a properly designed and supplemented diet it is possible to reduce the incidence of these diseases so greatly that they will be no more of a threat to life than contagious diseases are today.

The classical deficiency diseases, Pellagra, Scurvy, and Beri-Beri were easily defined because they were each caused by one single, easily recognized deficiency. Cancer is now believed to depend on several simultaneously present deficiencies, with variations for different kinds of cancers. Heart and circulatory disease are much more likely to occur when there is an insufficiency of choline (a B vitamin) or lecithin, and of antioxidants. Under such circumstances serious disease would be likely to result from toxins, irritations, or other stresses which would normally be tolerated if choline, lecithin and antioxidants were present in the body in the right amounts.

To explain this in further detail, I shall treat heart disease and cancer separately.

SCLEROTIC DISEASES OF HEART AND BLOOD CIRCULATION

Continually exposed to several crosslinking agents normally present in the bloodstream, the innermost thin layer of the arteries, the endothelium, gradually loses it elasticity. Then it cannot move or expand with the pulse wave. Instead, it cracks, usually at a bend or fork of an artery. Blood liquid will eventually ooze through these cracks and carry with it many elements which start the deposition of cholesterol and other degenerative changes. As this "muck" increases, the entire area may calcify, thereby blocking the arteries completely.

Before going further, one basic question has to be answered: Is the hardening of arteries at all reversible? Only recently this question was conclusively answered by the study of D. H.

Blankenhorn. A serial comparison of carefully defined areas of the upper thigh (Femur - where there is a suitable area of small arteries) was marked and recorded so that any fluctuations could be observed. Eight hundred twenty-eight patients were visualized on femoral atherosclerosis, covering 2140 man-years. These studies of fine detail give a much more reassuring picture than previously available data on far progressed disease.

Measurements of angiograms from these carefully defined areas show many changes alternating in both directions. Blood lipid (fat and oils) levels alter the plaques of beginning atherosclerosis. Lower lipid levels reduce the apparent damage, but the gain is often lost in a following period when blood lipid was higher. Among smokers who try to quit smoking without wholly succeeding, there is good evidence that the damage decreases during the non-smoking periods. In studying the ample data of Blankenhorn, one comes to the overall conclusion that in the early stages, before the arteries are permanently destroyed by secondary damage, it is possible to reverse sclerotic changes.

Looking back to Epoch II, we note that the enormous 95% reduction of tuberculosis (TB) deaths did not come by healing of far gone destruction of the lungs, but by effectively stopping the progress of the disease at an early stage. Based on Blankenhorn's studies, I predict that Atherosclerosis is headed for the same course of development and that we shall see the fruits from it in the next decades as we complete the transition into Epoch IV. The means to do it are now within our grasp.

It is possible for us to avoid these diseases by modifications of diet and some endurance type exercise. Circulation failures are connected with deficiencies of lecithin, (of which choline is a part), Vitamins A, E and C, selenium, dietary insight, and proper, consistent exercise.

THE IMPORTANCE OF LECITHIN

Since heart disease is often caused by cholesterol esters blocking arteries, many people believe that they can avoid developing atherosclerotic disease by adhering to a low-cholesterol or cholesterol free diet. This belief is so firmly entrenched that even advertisers have jumped on the bandwagon by touting their cholesterol-free products.

Several studies have confirmed that this emphasis on low cholesterol diets is wrongly placed. Experiments have shown that a high level of high density lipoproteins (HDL) in the blood go farther to prevent atherosclerotic disturbances and should therefore have a high priority when taking preventive dietary steps against heart disease. Lipoproteins, which carry water-insoluble substances including cholesterol in the bloodstream,

come in two forms: low density and high density. High density lipoproteins bind to cholesterol and carry it away, while low density lipoproteins are responsible for the deposition of cholesterol. The characteristic which distinguishes the HDL from the LDL is its 100% higher Lecithin content. Hence, this establishes the importance of Lecithin in the diet to ward off atherosclerosis.

Lecithin is a phospholipid (see glossary) and a necessary ingredient in every lipoprotein. Lipoproteins are the carriers which make it possible for the blood to carry water-insoluble substances, such as vitamins A, E, and D, many prostaglandines and several hormones.

All this becomes possible because lecithin is a double-acting compound. One end of it is "water-loving" while the other end consists of fatty acids like in soap, and therefore binds to fats. This two-fold nature, in addition to its' other properties, makes lecithin very useful and versatile. Let's consider the evidence below.

The National Heart, Lung and Blood Institute of Bethesda, Maryland spent an enormous sum of money, (150 million over a seven year period), to test the relationship between blood cholesterol levels and atherosclerosis. Three thousand eight hundred six white men in the age range of 40-49 were chosen for the experiment. Anyone having a history of heart disease or several other diseases was excluded. All of the men had a relatively high blood cholesterol level (265 mgr or more). Of these men 1906 were given up to 24 grams of cholestyramine resin and 1900 men were given a placebo. The resin treatment lowered the experimental group's cholesterol levels by 13-20%.

The results after seven years were not significant. Sixty eight men of the resin group had died and 71 of the placebo group died. Why were only three lives saved when the cholestyramine resin treatment lowered the blood cholesterol level by 13-20%? Obviously, if the blood cholesterol level appears to have been the major factor in developing heart disease, more lives would have been saved than just three. The major beneficial effect of the resin was to raise the level of high density lipoproteins by 4%. As you will recall, high density lipoproteins are responsible for binding to cholesterol and removing it from the body. This rise explains the slight reduction in the death rates of the resin group. The report's conclusion stated that the favorable effect of the resin was to raise the level of HDL (high density lipoproteins) and not the lowering of blood cholesterol levels.

Another study done by I.D. Frantz in the Minnesota Coronary Report showed similar results. In this study, Frantz had 4000 patients on low cholesterol diets and 5500 patients on a normal diet. Death rates were higher for the first group and not for

the second as was expected. Similar results were obtained by J. Brown et al in the Irish Brothers Report.

In light of the above evidence, the best course of action to take would be to raise the level of high density phospholipids such as lecithin. It is true that unsaturated fats are better for human nutrition than saturated fats, provided that this diet is supplemented with the proper amount of antioxidants. The reason for this will be discussed in the chapter "Nutrition and Oxidation" in section II.

The following diagram was presented by D. M. Small at the International Atherosclerosis symposium in Houston, 1979 (Springer, Publ. 1980). This is still the best overview of the interplay of the various factors in atherosclerosis. We note, (right margin) that the lipid fat content of the intima, (inner layer of the arteries) of children contains about 70% lecithin. This is why Children under 5 do not have atherosclerosis. This lecithin percentage keeps cholesterol and its esters dissolved and safe.

FIGURE 2 - D.M. SMALL

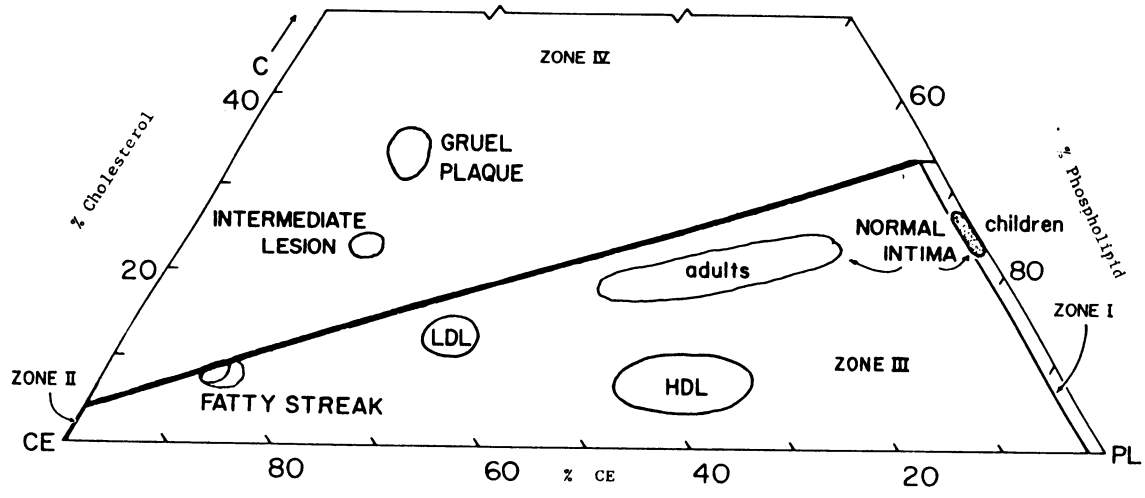


Figure 2 shows the action of different fats and lecithins in aging. It covers very much in one picture, which could make it confusing, but it is the best I have seen. In addition to showing the lecithin content of children's arteries, it also shows that the High Density Lipoprotein (HDL) contains more than twice

as much lecithins as does the Low Density Lipoprotein (LDL). This explains why the LDL easily dumps its load of cholesterol anywhere, including the arteries, while the HDL can pick up cholesterol and carry it away. (In the picture, the content of lecithins is expressed in the distance from the HDL and LDL "islands" to the thick line which goes across the figure).

We note further from this Figure that the LDL which is responsible for depositing cholesterol has only about half the lecithin content of the HDL (high density lipoprotein) which carries cholesterol away. The lesions (damage) shown in this figure are all on the left side of the diagram, where the lecithin contents are low and the cholesterol esters (CE) are high.

Be the details of the process as they may, it is evident that cholesterol is carried in the blood by a lipoprotein. It is readily deposited in the tissues if this lipoprotein had a relatively low lecithin content (Low Density).

Lecithin is not only important as a binder and neutralizer of cholesterol. An even more important function of lecithin is that it participates in the transport and exchanges of ions and electrons in the brain and muscles. It helps particularly in coupling reactions together to get the split second timing that is essential for brain and nerve functions, as well as many other vital muscular functions. (Green et al., Blondin and Green, 1975-1978.) Choline-lecithin is thus necessary for proper heart function. The very high content of lecithin in the brain shows that lecithin is a versatile key chemical, and essential in human nutrition.

Lecithin can carry metal ions through membranes up to ten times faster than the metal could be transported by any single kind of salt forming substance. Moreover, the active ion carrier can be a whole set of lecithin molecules working together. In a series of remarkable studies, the late Dr. David E. Green and G. A. Blondin at the University of Wisconsin elaborated and applied this remarkable mechanism which seems to explain the enormous use of lecithin and the very similar cephalin as major constituents of the brain. Their work was perhaps twenty years ahead of its time, we shall hear more about the consequences of it as the years go by.

Virtually no effort has been made to commercially emphasize the importance of lecithin, and why not? It's not patentable because it has been known for so long, the recommended dosage of 10 grams daily is inconveniently large, and the consistency is unpleasant to some.

Sources of Lecithin

In the body, lecithin is made by at least three different processes, which indicates its importance. However, all these processes require choline (a B vitamin) for the syntheses.

The choline part of lecithin occurs in eggs and cereals as follows. The figures are rounded off for simplicity:

Occurrence of choline in foods:

milligrams per 100 grams:

Cereals:	
Corn	60
Wheat	94
Barley	130
Rice	110
Oats	150
Milk	15
Butter, Margarine, Vegetable Oils	5
Cheese	50
Egg White	2
Egg Yolk	1500
Brain	2200

It is thus seen that egg yolk and brain are by far the largest source of choline, or the equivalent amount of lecithin, of all sources in the western world.

If for any reason egg is restricted to less than one daily, some other source should be found for either lecithin or choline. Deficiency of lecithin-choline can have dire results. Lecithin can be made in the body if choline is present.

Calf's brain is an even better source of lecithin than egg yolk and you would do well to consider adding it to your diet. One approach is to follow one of the French recipes for using it as filling in an omelet, or with a sauce of morels, or some other tasty mushrooms. The French proverb says: "With a good sauce you could eat your grandmother". This should apply to calf's brain as well.

A French recipe for the preparation of brain for a meal is as follows: mix cold water into the brain until the consistency is as you want it. Then add salt, pepper, and other spices to your taste. Heat it to the boiling point for two minutes. Let it cool and eat it with your favorite sauce or condiment. Calf's brain is not only the richest natural source of lecithin, but also a source of growth hormones.

An alternative to calf's brain would be to use technical soya lecithin. This is used in industry as a food emulsifier. The inexpensive technical grade consists of 70% lecithin and 30% soya oil. The 4 grams of soya oil contained in 14.3 grams of technical lecithin is not objectionable in this context because it keeps the lecithin fluid at body temperature. The product has about the consistency of butter or of a soft cheese. It could be compounded with other cheeses, like Brie and Camembert. The lecithin should not be heated to a higher temperature than what your fingers can stand as already mentioned. Lecithin contains choline, and satisfies the need for this B-vitamin as well. Technical soya Lecithin can be purchased in big tubs from companies which use food processing, especially with chocolate coatings.

DIET

As for diet, the "Pritikin diet" is perhaps the most detailed and easily understood so far as it goes. It stresses basic natural foods and exercise, requires a hard self-discipline and stimulates its adherence. It also stresses endurance type exercise. Without a doubt the Pritikin Diet has done a great deal of good for many persons.

Its drawback is that it may be more stringent than is necessary, and thus more difficult to follow. For example, eggs could well be tolerated in moderation, for their lecithin should suffice to offset such disadvantages as their cholesterol content would otherwise bring.

Cholesterol occurs in nature together with lecithin. Where it is so combined it does not tend to get out of hand. Cholesterol in eggs, where it occurs together with lecithin, does not build up in the blood at all like the same amount of cholesterol in meat would.

ISCHEMIC DEMENTIA

Mental functions depend on a constant blood supply. When this supply is reduced, by scleroses, thrombs or whatever, the mental functions are reduced locally in proportion to the reduction of the blood supply.

Such mental impairment is easily recognized by the physician from both the pattern of the mental damage and from its localization. Functions which are dependent on other arteries for blood supply are generally functioning normally. Since certain areas of the brain are responsible for specific functions, the physician can pinpoint where the damage is in the brain by which functions the patient is unable to perform.

Reduction of the blood supply of the brain by atherosclerotic changes impair those mental functions which depend on that area where the blood supply is diminished. This type of dementia is clearly distinct from the neuronal diseases of Epoch IV, in which all neurons in large areas are affected and no dependence on blood supply is apparent. The same type of diet which prevents atherosclerotic disease will prevent Ischemic Dementia. Ischemic Dementias are not presently a major cause of death.

CHAPTER 4

CANCERS

In normal growth of multicellular organisms, cells cease growing when they have reached a certain position or state. If even a single cell fails to stop its growth, that cell and the new cells formed from it will continue to grow and divide at the expense of all other cells. As in many cases of cancer, this growth goes unabated until the parent organism dies, unless they are killed by the immune system's defenses: phagocytes, T-cells and other members of the host's immune system.

In the United States, 16.7% of all persons are now destined to die of cancer, and the trend is upward.

Cancer is so deadly because cancer cells stem from normal cells and are therefore not recognized as enemies by the immune system. They belong to the family, so to speak, so they are allowed to go on growing and dividing even if this means the death of their host. How can we wake up the immune system, show it what is going on and bid it do its duty? The answer is now at hand as will be described below.

Chemotherapy

Since cancer cells grow faster than normal healthy cells, they use more nutrients. If the food is poisoned, the cancer cells may get a dose of poison that kills them, while the normal cells might survive - though just barely. This is a cruel thing to do, for the patient will be very sick, but death from cancer is even more terrible. These clinical applications may be achieving cures indirectly through their metabolic effect.

The greatest disadvantage of chemotherapy is that the immune system is damaged and possibly even destroyed. The immune defense cells have to multiply very fast in order to keep ahead of any infection. Since they, like cancer cells, need more nutrients for this rapid growth, they also fall prey to the cell poisons and X-rays. The death of the immune system together with the cancer cells leaves the body defenseless if any cancer cell happens to survive, or against any new cancer or new infection.

Apart from the success with Hodgkin's Disease, childhood leukemia and perhaps a small number of less frequent cancers, it is not possible to detect any sudden change in death rates that could be credited to chemotherapy.

The well known oncologist Dr. John Cairn estimates in a 1985 article in Scientific American, that 5,000 to 10,000 lives yearly

are saved by chemotherapy. He goes on to point out that this should be viewed from the perspective that 100,000 lives are lost completely unnecessarily each year due to lung cancer caused by smoking. Dr. Cairn suggested that this saves the U.S. Government some $10 billion yearly in social security cost. Each smoker, he states, saves the U.S. Government $35,000 "simply because they will on the average die sooner than non-smokers; most of these deaths occur after retirement..."

At the 21st annual meeting of the American Society of Contemporary Medicine and Surgery (1986), Dr. George C. Crile, Jr., Oncologist (physician which specializes in cancer treatment), Cleveland Clinic, Cleveland, Ohio spoke on the subject of:

Changing Trends in the Treatment of Cancer

Dr. Crile indicated the value of self-examination by patients as a means for early detection. Eighty percent of early detection of mammary cancer resulted from self-examination. If these patients had waited until their next annual or semi-annual examination, the prognosis would have been much less favorable.

Dr. Crile conservatively, though quite clearly, indicated that the trend is toward lesser reliance on chemotherapy, and greater reliance on methods which entail action by the immune system. He noted that the disease of President Reagan which has been in the public eye, particularly brought out that President Reagan did not have chemotherapy.

The prognoses are better when a cancer has been treated with X-rays than when chemotherapy has been used for the same purpose; to destroy cancers not safely removable by surgery. The inference seems to be that when the cancer cell which is killed by X-ray radiation remains in the body, it then constitutes an antigen which helps stimulate the immune system and awaken it to action.

Evidently the effect of the X-ray radiation expertly used is a much safer and more sophisticated way of causing the positive effect which Dr. Crile repeatedly achieved with cancer patients.

THE IMMUNE PROCESS OF THOMAS TALLBERG

The trend which becomes discernable is thus away from chemotherapy and toward increased reliance on the immune system. The most advanced immune development is probably that of Thomas Tallberg, M.D., and professor of immunology at the University of Helsinki, Finland. Tallberg approached the problem of bringing the immune system to react against cancer cells even though the cancer originated in the patient's body, and thus escaped immediate recognition.

Tallberg's technique entails finely grinding the cancerous tissue sample so that no living cancer cell remains. Then by a crosslinking (linking them chemically) process, he prepares aggregates of these ground cells which are much larger than any individual cells but still small enough to be injected. The immune system will then attack these aggregates because their size marks them as definite strangers to be removed. In the process of removing the larger aggregates, the immune defense cells learn to recognize the cancer "scent" so that they then attack all cancer cells and remove all metastases.

We may think of the Tallberg process like this: You have a good sturdy watch dog who loves you and wants to protect you. You also have a couple of little poodles, which the watch dog knows and never bothers. Now in some magic way the poodles begin to multiply so that there are hundreds of them. Your good watch dog will be confused, but he will not bark, nor attack the poodles. If now again by magic you can merge hundreds of the little poodles into one elephant size poodle, your watch dog will surely bark and probably call on his friends to attack and expel the giant intruder. But when the giant intruder is done away with, your watch dog and his friends will have noticed that the swarm of little poodles have the scent and taste of the giant enemy, and will do away with them too.

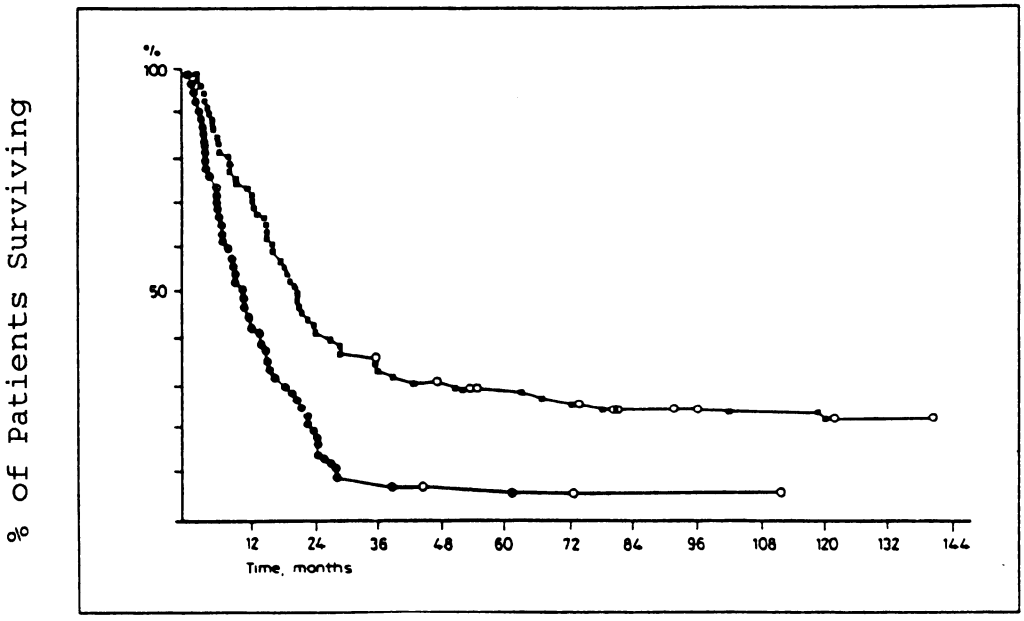
This may sound like a tall tale to you, but it has worked. The magic in making the "giant poodle" is the magic of chemistry. Dr. Tallberg got the tumor from the surgeon who had operated on desperate cancer cases. These cases were considered hopeless because it was impossible to remove all of the cancer since it had spread throughout the body. The full details of Dr. Tallberg's procedure are given in his 1979 paper, supplemented in 1985 and 1986 papers.

The following Figure illustrates the data from 12 years of comparison between cancer patients with metastasizing (spreading) cancers of the kidney. The experimental group (designated by the upper line) was treated by the Tallberg immunity method and a matched number of similar patients (lower line) were treated conventionally to serve as the control group. The left axis refers to the percentage of patients still alive. These patients were at the University Hospital in Helsinki. They were diagnosed and treated by the same physicians and staff, one group according to the Tallberg procedure, the other according to the best conventional procedure.

At the 24 month mark, notice that only 10% of the group treated conventionally through chemotherapy and radiation were still alive while over 40% of the Tallberg group survived. The most important point that the graph does not make is that those persons who survived the first two years after Tallberg's

immunological process and follow-up treatment could anticipate a **normal** life expectancy. This can not be said for those persons who survived the conventional cytotoxic treatment (Cell poisoning). On the contrary, the destruction of the immune system left these persons unprotected from any other life-threatening disease or new cancer.

FIGURE 3 - RESULTS FROM 12 YEARS OF WORK WITH CANCER PATIENTS WITH METASTASIZING CANCERS Tallberg



Tallberg Immunity Therapy - Upper Line

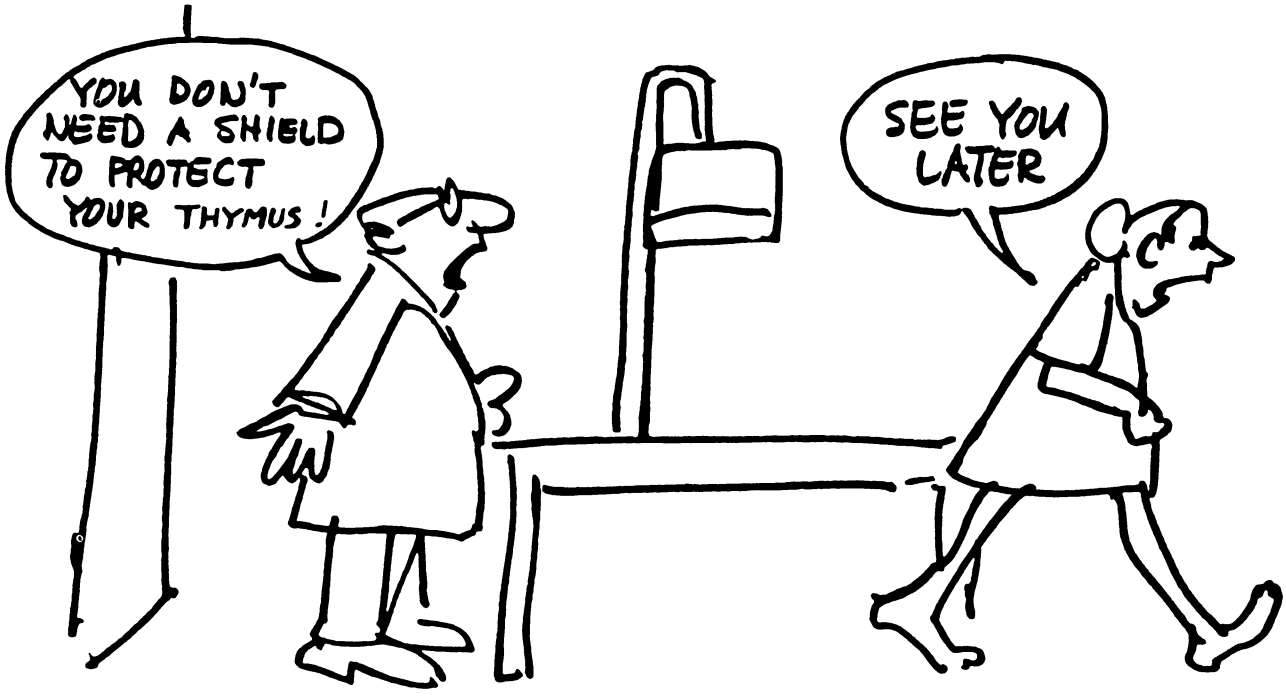
Conventional Cancer Therapy - Lower Line

Whichever way we count the results, the immune therapy has at least three times more cures than the conventional cytotoxic treatment. Tallberg's results have now been confirmed in the United States by J. A. Neidhart et al at the Ohio State University Comprehensive Cancer Center, Columbus, Ohio.

To obtain results like those above, it is essential that the immune system is functional. Cytotoxic treatment, or X-rays in excess of a few photographs are highly detrimental to the immune system. If X-rays must be used for more than a few photographs, and particularly in whole body irradiation, it is of vital importance to protect the thymus gland from radiation damage. The immune cells multiply about as fast as cancer cells, and are

therefore as sensitive to X-rays. If any cancer cell survives the treatment, the T-cells (T for Thymus) could save your life, wear a lead shield. If complications should arise, the health and vigor of your thymus could tip the scales of life and death for you.

FIGURE 4



The leucocytes (white blood corpuscles) are the "police force" of the immune system and should be maintained in strong condition. They should never be jeopardized by needless use of chemotherapy, cortisone or X-rays. They can be aided by Vitamin C and possibly also small amounts of copper and/or iron which are the catalysts for the ORD (Oxido-Reductive Depolymerization) reaction which the destroyer cells of the immune system use.

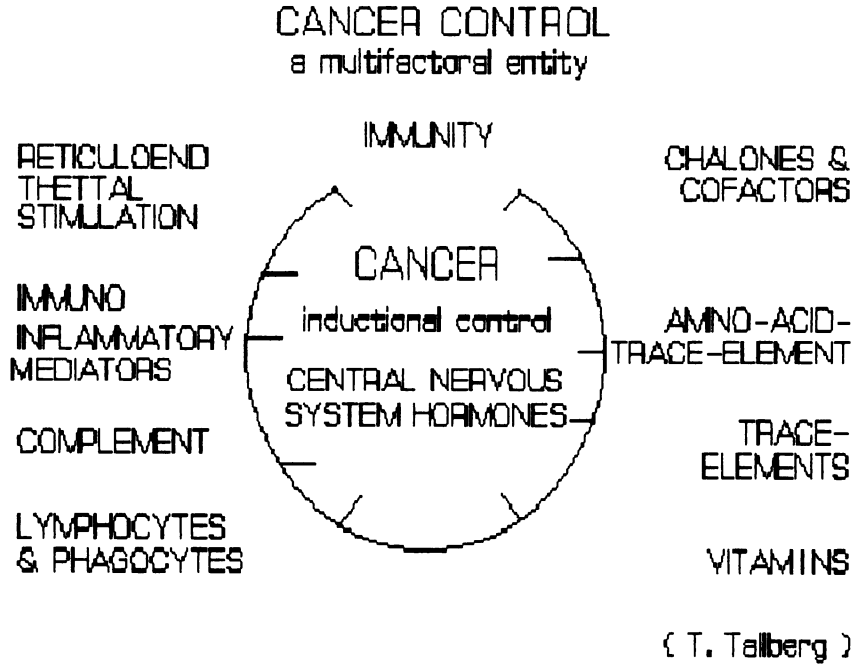
The success of the immunological process depends greatly on the follow-up diet. We can logically expect that a diet which gives the highest rate of survival after treatment will also be the one which makes it most unlikely for the disease to start at all.

Dr. Tallberg emphasizes the importance of a regime of vitamins, and trace elements to support and enhance the immune system. A haphazard high dose of everything is not advisable. Any unnecessary excess of desirable substances could be absorbed by the cancer cells, thereby enhancing their growth and lowering the patient's chances for survival. However, this does not apply to Vitamin C which is essential for the production of free

hydroxy radicals which are used as ammunition by the immune system. Dr. Linus Pauling recommends a dose of 10 grams daily, as basic, with much larger doses tolerable. Dr. Tallberg recommends the use of Vitamin C in the highest dosage officially approved.

Dr. Tallberg considers cancer a multiple deficiency disease, and many observations confirm this conclusion. The following diagram illustrates the concept of cancer as a disease brought about by deficiency in growth control factors. Each of the factors shown has an influence on the loss of growth controls. If all of these known growth controlling factors are at hand, cancer is unlikely.

FIGURE 5 - GROWTH CONTROL FACTORS TALLBERG



Dr. Tallberg's working hypothesis is that the factors shown in Figure 5 control cell growth, and that deficiency of more than one of these can open the way for the uncontrolled cell growth which is cancer.

I shall now briefly discuss some of these factors, referring to Figure 5. These results weren't proven in double blind tests with humans, but with experimental animals. Dr. Tallberg's overall result with metastasized human cancers (Figure 3) commands respect for his working hypotheses.

FREE AMINO ACIDS WITH CHROMIUM AND MANGANESE

Promising results in the control of experimental leukemia (blood cancer) were obtained by combining three free amino acids with the metals chromium and manganese. The tests were made with rats using a very malignant cancer strain known as Chloroma. Five to ten million of these deadly cancer cells per 100 grams of body weight were injected into the bloodstream of these rats. They also received a specific combination of the amino acids and two metals before and after their cancer cell injection.

Normally, such an injection of cancer cells would kill every rat within fourteen days. However, because of the combination of amino acids and two metals given them, 50% of the rats overcame the millions of cancer cells and got completely well. This success rate of 50% fell into a narrow range. When the combination of amino acids and metals was varied even slightly, the survival rates were much lower. The nearest of a considerable number of tests using just a slight variation of the remedy had survival rates of only 6.6% and 4.3%.

Dr. Tallberg bases his optimism concerning cancer control on his animal experiments. The particular combination of the amino acids and two metals could be used in leukemia patients to support and supplement other treatment.

In the 1940's, Dr. H. H. Beard injected all of the three basic amino acids (arginine, histidine and lysin) into rats bearing a normally fatal cancer (Emge Sarcome). Surprisingly, the result was total regression of the cancers, in other words, a total permanent recovery.

A few years later, others tried to duplicate this result, but all attempts failed, so the matter was forgotten by most. However, Tallberg recalled that shortly after Beard's work, the chemical manufacturers proudly announced that they had adopted a new manufacturing method for these basic amino acids. This enabled them to get a higher purity than before. The "impurity" they had removed was the rare element "Tungsten" and it turned out that this was essential to achieve the original good results with the amino acids. When it was added, the process worked again. Much study is still required before all details and safety tests have been worked out with rats, and then with humans, but this is one of the most promising recent developments.

TRACE ELEMENTS AND SOME OF THEIR CRITICAL RATIOS

Zinc, an essential metal, is a component of several necessary enzymes. It has been found to stimulate the growth of cells in general and is an essential metal both for growing children, and for athletes to increase their muscle strength.

However, it could be dangerous for cancer patients for the same reason. Cancer patients must avoid such growth stimulants since it would increase the speed of cancer growth. This caution is based on a preliminary clinical study where in every one of eight cases the tumor of the patients increased when zinc was supplemented to the diet.

Selenium, in water soluble compounds, is particularly valuable as an antioxidant. It counteracts the metabolic formation of substances like lower aldehydes, peroxides and quinones, which are crosslinking agents, and carcinogens (crosslinking will be discussed in chapters 6 & 7). Areas with high selenium content show a reduced incidence of cancer.

THE GRANULOCYTE CHALONES

These elusive components are highly effective in stimulating some of the key steps in the immune system. The addition of these chalones can increase the activity of the enzymes which build RNA. These syntheses can be stepped up as much as 1500%. There is a good analytical method to follow this which, although time consuming, is accurate and workable. It consists of determining the speed with which radioactive (H3) thymidine, a building block in RNA-syntheses, is being taken up by the bone marrow of mice. This speed is a good indicator of the efficiency of an important part of the immune system.

These chalones are tantalizing substances. There have been phenomenal beneficial effects in animals, and there is no reason why they should not work just as well in humans. The problem is that we don't have available a good, dependable source of these chalones. In due time, this factor will probably be brought under control and will then be a valuable addition to our cancer preventing capacity. Chalones are presently on the forefront of current cancer research and will be discussed in more detail in section II.

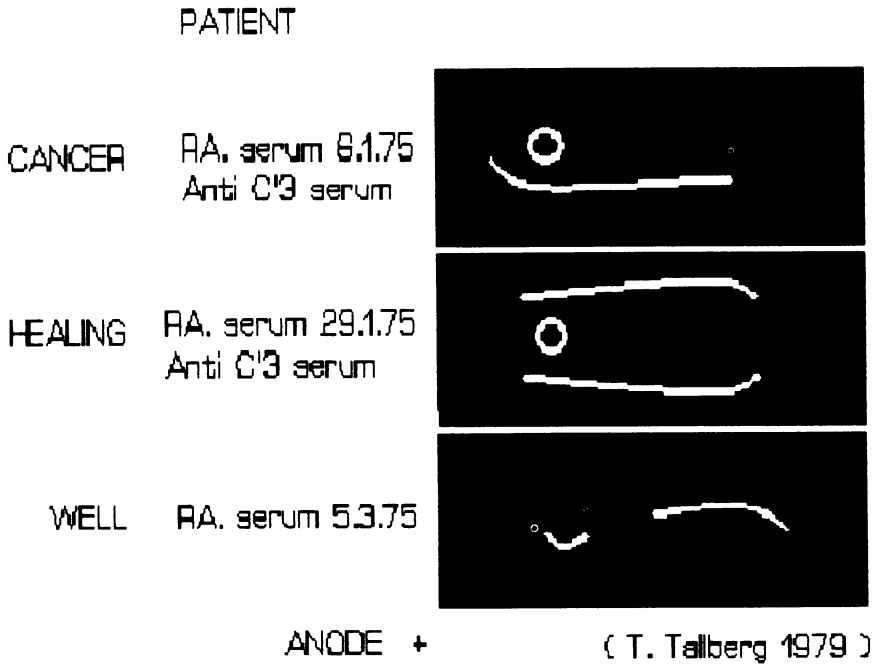
COMPLEMENT C3

In a tumor patient's blood serum, there is a measurable substance named "Complement C3". The motion of this can be charted in an electric field. When Tallberg's immunotherapy was applied, as already described, the substance Complement C3 underwent a modification and changed its behavior in the electric field. After the patient's condition had been improving a month, the blood serum contained about equal amounts of both activated and inactivated forms of C3.

After two more months the change was complete showing only activated C3 when at the same time the tumor had completely disintegrated. This was seen in 1977, and the patient is still well after eight years. (Tallberg)

This experiment proves that the Complement C3 can be activated by immunotherapy to form a tumor dissolving sub-unit called Complex C3b. The electric field method to analyze this is rapid. It has also been shown that C3b kills leukemia cells in experimental studies.

FIGURE 6 - COMPLEMENT C3 MODIFICATION Tallberg



VITAMINS

A few years ago I was for the third time re-reading Roger Williams' basic book on nutrition, and stopped at a small paragraph about riboflavin, Vitamin B2. He mentioned an experiment wherein rats were given riboflavin before getting a normally fatal 100% dose of carcinogen. Three percent of those rats survived. The 3% was not much, but it was enough to make me concentrate on the following.

If these rats were given a teaspoon of casein, (the main protein in milk), in addition to the riboflavin, then there was a substantial increase in the number of survivors (30%). This seemed an exciting lead. I telephoned my friend, a professor of Oncology (cancer science) and asked him if there had been any follow-up on this and if it applied to cancers other than those caused by the azo dyestuff "Butter Yellow" (no longer used in foods). He said: "This has been thoroughly studied. We know

the biochemistry of that cancer. The riboflavin effect only applies to the cancers that are caused by azo dyestuffs. But if you are interested in cancer prevention, why don't you look at Vitamin A? I will send you some reprints of those studies." He did. I read them and phoned him back:

"I have read the reprints you've sent me and if I understand them correctly, a dose that would correspond to about 50,000 I.U. of Vitamin A for humans should give almost complete protection against epithelial cancers. Is that right?"

"It would seem so."

"Then, what percent of all cancers are of epithelial origin?"

"About 90%."

"90%!! ??"

"About that, maybe between 80 and 90% but I think closer to 90. The epithelial cancers include all lung cancers, all skin cancers, most brain cancers, most cancers of the digestive tract and many glandular cancers. That will add up to what I said, near 90%."

"If this is so, why have we not heard more about it? Why has no action been taken?"

"We oncologists have done our job when we publish the facts. We know from experience that it takes different thinking, different politics, to get anything done for humans. In due time it should filter through."

"One more question. I understand that about 300,000 I.U. (International Units) are poisonous. Some people could then be hurt by as much as 50,000 units of Vitamin A. What do you think is the risk of taking 50,000 units?"

"I do not know. The highest dosage approved by Food and Drug Administration is 10,000 I.U."

"If one were to take a toxic dose, what would happen?"

"An early symptom would be severe, persistent headaches. If your doctor did not know that you had taken Vitamin A in excessive quantities, he might suspect a tumor of the brain."

Any headache which does not yield to aspirin or pass quickly should be taken as a warning sign that Vitamin A intake may be too high for you. Every person is different.

A high Vitamin A level not only has a great protective effect against epithelial cancers in animal tests, but also stimulates the immune system (Nauss) and has in humans caused regression of still benign skin tumors of types which otherwise frequently develop into cancers.

The mode of effect of Vitamin A is to rejuvenate the epithelial tissues. These tissues then show a change to a more youthful condition which is more resistant to cancers. Vitamin A is not effective with other types of cancer, yet the protection from epithelial cancers alone should greatly reduce the overall cancer hazard since epithelial cancers comprise 80-90% of all cancers.

Vitamin C, ascorbic acid, has many functions. Although it hasn't been shown to be a cure for cancer, it is essential for the function of the immune system. It is immediately transferred to the leucocytes and is used by these to fight infections. It is necessary to increase the dose several times over when one is suffering from colds or infection of any kind. There is no practical dose restriction. Doses up to and exceeding 10 grams/day are well tolerated. The acidity of very large doses is easily controlled with some baking soda as Pauling suggests, or with natural skim milk.

The already adequate safety margins are further enhanced if a few milligrams of Vitamin B6 (Pyridoxin) are taken together with the Vitamin C. When in good health, take at least 500 mg if you are a woman. If a man, take 1,000 mg in several small doses in the course of a day. This suffices for normal health.

Vitamin C is an essential part of the ammunition the immune system needs in fighting for you against infection or anything it senses as not normal, and possibly dangerous. Tauber and Babior showed that white blood corpuscles release bursts of free hydroxy radicals to kill invading germs. It is a powerful weapon of general destruction which the immune system has mastered.

The facts on which this knowledge is based have been marshalled and proven step by step by G. von Ritzel, Stone, Pauling, Babior, Tauber, Pigman, Daubenmerkl and many others. Particularly C.W.M. Wilson and co-workers have followed the movements and changes of Vitamin C in the body.

A deficiency of Vitamin B2 (riboflavin) in the diet can cause a weakness in the corners of folds, such as the edges of the mouth. This condition is known as Angulostomatitis. Such irritations can develop into cancers. Vitamins B1 and B6 have been reported to have some cancer protective effect, either in concentrate or in multiple B sources, such as brewer's yeast. Some anti-cancer activity have also been ascribed to Folic Acid and "Vitamin H".

COLON CANCER

In tests conducted by nutrition researchers, the poorest of all carbohydrates, (so far as digestion is concerned), is the unboiled starches. This was somewhat surprising because the boiled starches were the best of all and quite a great deal of literature, and authorities teach that we boil too much and would be better off if we ate more raw food. It is true of course that boiling destroys some of the vitamin content and is particularly bad for vitamin C, but none of the rules applies to everything. To serve nutrition well it is important that the product be taken up by the body for further processing. Unboiled starch is not dissolved in the intestine or the stomach, but comes pretty much unchanged to the colon at the end of the digestive tract. But even for those food substances which are processed earlier in the digestion, the physical form and composition may make for great differences.

Already Dr. Maimonides, one of the great physicians about 1200 A.D., had a lot of common sense to say about nutrition which applies even today. In order to be properly processed the food should provide a certain amount of bulk. In moving the food through the intestine it should have a loose and bulky consistency. This makes it easy to form and move forward with such waves of contractions and relaxation as smooth muscles of intestinal walls provide. The consistency of the food moving from the stomach is quite fluid. It permits thorough and easy mixing with the digestive fluids from liver and pancreas. Towards the end of the small intestine, most of the digestible nutrition has been absorbed. The water is absorbed toward the end of the small intestine so that the remaining mass thickens. The consistency at that point should not be so stiff that the flow stagnates. This stagnation could, in turn, lead to infestation by various intestinal bacteria. A balance of fluffiness, binding fibers, and bulk is necessary to ensure smooth and early enough clearance of the way.

Dr. Maimonides knew that if the excrements were hard and lumpy, so that they did not move well, this condition was conducive to ill health. He had certain herbs which he used as laxatives, but the effectiveness of these herbs was probably in part due to the hot water the herbs were boiled in.

Modern medicine and nutritional science have gone into more detail. There are many ways in which digestion can be helped, thereby preventing stagnation in the colon or elsewhere. Particularly mentioned are:

1. The patient should drink more water. Most people would benefit from drinking more liquids than they do.

2. Add fiber. This fiber could be bran, fibrous vegetables, unsifted rye, or cellulosic micro-fibers. Anything fibrous would do as long as it is soft and pliable, and does not dissolve. These fibers will act to keep together the masses moving through the digestive tract so that they do not lump, but stick together in a larger mass which can be moved forward.

Comparisons of causes of deaths sometimes reveal unsuspected facts. In many cases, differences in death causes could be linked to differences in diets. It is quite understandable that the Japanese have about 9 times less circulatory troubles, including strokes, than Americans because of a lower fat and more varied diet. What seems more puzzling is the comparison between groups of similar diets, which show very wide differences in some specific regards.

As an example of this: in the city of New York, and the city of Kuopio, Finland, the diet of the average citizen is in both cases a high fat diet with roughly similar proportions of protein and carbohydrate. How then could we explain that two particular forms of cancer are two to three times more common in New York than in Kuopio, namely cancer of the colon and cancer of the breast. Why only these two forms of cancer? It could hardly be any of the usual environmental carcinogens- they would not have made this strange selection. What could these two seemingly so different cancers have in common? Sometimes it pays to be curious, particularly when the same mystery is observed in two seemingly unconnected situations.

The most apparent difference between the diets in New York and Kuopio is that although both consumed the same amount of fat, the typical feces (stool) of the citizens of Kuopio were much smoother and bulkier than New York feces. Upon dilution and screening, several percent of long fibers were obtained from the Kuopio feces. The New York feces typically were smaller, harder, fragmented. What remained on the screen was essentially non-fibrous.

The role of the fibers was apparently to produce a smooth, bulky mass which would move easily through the intestines. This explains the relative absence of edges and sharp corners which might scrape or abrade the intestinal wall, and induce cancers, particularly in the colon. The fibers provide a better structure for aeration of the mass, and thus for the development of a more aerobic bacterial population. This includes Lactobacillus acidophilus, and some Clostridium-type organisms which are quite different from the bacterial population in New York.

The clinical results of adding fiber to food have been excellent. It has been found that adding fiber substantially reduces the frequency of cancer of the colon and surprisingly also similarly reduces mammary cancers. This seems a strange

connection, but we have to accept it as a fully established fact. Why the incidence of cancer in colon and in breast should have this similarity was a riddle, until Adlercreutz and co-workers found the explanation in the connection between the function of excretion, and the recovery of building blocks from which the female hormones, estrone and progesterone, could be synthesized in the liver. When the substance in the colon is porous and fluffy, the recovery of the building blocks functions well, and with this addition, the amount of estrogen in the blood increases.

This estrogen has an anti-carcinogenic effect, which explains why an improvement in the consistency of the stool has a considerable, favorable effect in reducing the risk of mammary (breast) cancers as well as of prostate cancers, in addition to the more obvious beneficial effect on cancer of the colon.

We must sympathize with the dedication of the scientists and lab technicians who undertook this study and with patience and precision pressing large quantities of stools through metal screens to determine their fiber content.

3. To drink carbonated beverages in the evening. This forms small bubbles in the intestines and adds to the bulk and soft masses that are easily moved. However, due to its high sugar content, soft drinks should be avoided. A better alternative would be to add plain soda water to your favorite fruit juice, such as orange or cranberry juice. The result would be a nice bubbly drink which is also good for you.

A recent Russian publication from the Gerontological Institute of Kiev, shows that eating activated carbon in the evening is a healthful practice. The beneficial function of carbon is to absorb and thus bind and remove such toxin (poisons) as the bacteria form in the colon. This was reflected in reduced frequency of cancer of the colon.

4. To drink some distilled or rain water in the evening. This will cause a swelling of colloidal material which leads to the desired soft and movable consistency, and increases bulk.

5. Take Vitamin C tablets in the evening, in the dosage that is right for you, to keep the intestines working. Large quantities will even cause diarrhea, so with a little experimenting you can find the right quantity to achieve any consistency and rate of flow.

6. If milk agrees with you, an excellent procedure is to drink two glasses of milk before going to bed. Buttermilk is particularly effective. Immediately upon drinking, the milk is coagulated in the stomach to a soft bulky mass which is very easily handled.

easily handled.

7. Eat more fruit.

The above gives us a wide choice of methods to normalize and optimize the flow of digestion and regularity of excretion. The main thing is however, to realize that regularity of intestinal functions is indeed important. Any hardening or condition that might cause scratching of the colon, or scratching or irritating of the intestinal surfaces could develop into cancer.

PERSONAL PREVENTION

Oncologists have indicated that a high Vitamin A content in the body is highly efficient in preventing epithelial cancers. These comprise 80-90% of all cancer cases. In view of the entire range of demonstrated prevention with both animals and humans, it seems a safe conclusion that 90% of all cancers are preventable.

What can we do to protect ourselves from cancer:

1. Have a high intake of Vitamin A. I know twelve persons who have taken 25,000 International Units daily for several years without signs of excess. (International Units refers to units of measure agreed upon by the World Health Organization. Bottles of Vitamin A list their content in terms of I.U.) The highest dose approved by United States Food and Drug Administration is 10,000 Units. A higher dose requires a prescription. Daily dosages of more than 50,000 I.U. can be hazardous. The first symptom of excessive Vitamin A is severe headaches which do not yield to aspirin.

The dose is dependent on the patient. Only a physician with full knowledge of the patient's physical condition can make a recommendation. Most physicians will start with a conservative dose, then gradually increase this until either the desired result seems achieved, or some adverse effect occurs.

Carotene, the precursor of Vitamin A appears to be safe, since it is converted to Vitamin A in the body as it is needed. Extremely high dosages of Carotene have been reported being used in Germany. As much as a million units have been mixed with human milk and given to patients. This is mentioned as interesting, but is not recommended. Overdose of Carotene causes a yellow coloration to the skin, which vanishes without observable harm when the overdose is discontinued. Vitamin A is only proven effective in prevention. It is not a cure.

2. Have a high intake of Vitamin C. Take at least 500 mg per day if you are a woman and 1000 mg a day in small doses for a man.

Vitamin C is not a medicine, but is a nutritional supplement and used by the body as a food. The dosage is not critical. This is in great contrast to, for example, Vitamin D or selenium and even to a degree Vitamin A, which are all toxic if taken in excess of the established dose. The details of how Vitamin C works are well known and reproducible in the test tube, but only the immune system has this under control. The immune system does its best, but without nutrient Vitamin C at all times, it is like an army without enough ammunition.

A healthy body needs the other vitamins too. Any deficiency in essential nutrients means a weak spot in the defense. A good fence shouldn't have a weak spot. It doesn't help to make one part of the fence enormously strong - it is the weakest point of our fence that is critical. On the other hand, an excess over what the body can use can also be harmful, as I mentioned above in the cases of zinc, Vitamin A and D.

3. Weigh yourself every morning. Being Overweight is generally bad. Dr. R. L. Walford, a leading Immunologist, recommends periodic fasting. Animals which are fed all they want do not live long. Regarding obesity, it could be a sign that your diet is short of some one essential substance. Not understanding what might be missing, your appetite will tell you to eat more. If such urgent desire for more food occurs, it may be a good idea to consult your physician or nutritionist as to what essential ingredient is missing from your diet. Then take a substantial dose of that daily for a couple of weeks and see what might stop your urge for excess food. In such a search an early thing to try might be niacin because it is a part of over fifty different enzymes and even a "normal" intake might not be enough. Other candidates may be Vitamin B6 or B12.

The bathroom scale combined with common sense is a quite reliable guide. The "Law of Le Compte" is also worth keeping in mind: "The rate of aging is related to the number of deficiencies and to their severity."

4. It is advisable to have a hair analysis at least once a year to be alerted to any apparent deficiency or disproportion. These are easily corrected by diet, when known. Don't let yourself go! Observe yourself and your habits to see if you are working for or against your own survival.

5. Keep stress at work and at home to minimum. Arrange your schedule so work flows smoothly without over straining.

6. Ensure that your digestion system is working properly by following the suggestions in the section on colon cancer, pages 30-33.

CHAPTER 5

EPOCH FOUR - MENTAL AND NEURAL DISEASE

We will have entered Epoch IV when at least 60% of hospital facilities are occupied with mental or neural cases, and no other group is above 20%.

We still linger in a transition zone. We have the knowledge, not to cure but to prevent 80 - 90% of the diseases of Epoch III, the cancers and sclerotic diseases. Historically, transitions have taken centuries, but perhaps we can move faster now.

In an analysis of the present, the incoming century is the most difficult because the cross currents are many and we are already being drawn into their whirlpools. The first task then is to get our bearings. What are the real causes of the mental diseases? Is there a basic stop set for the longevity of mankind, and if so, can we remove or get around it? If not, is it our ignorance which limits us? What should we explore next?

For effective planning, it will be necessary to consider all evidence and follow logic wherever it may lead us, - and intuition now and then.

NON-ISCHEMIC DEMENTIAS

The word "Dementia" comes from "de" = "removal" and the Latin "Mens" = "Soul", thus, "de-souling".

Senile Dementia is a broad term which includes all the age-related processes which cause the loss of the mind. Ischemic dementias are localized, and are due to a blockage of certain specific arteries. These types of dementias belong in Epoch III, where they were discussed on page 17.

This year, a sizable part of the age dependent dementias is due to sclerotic or other disturbances of the blood circulation. This confirms that we are still in the transition between Epoch III, dominated by heart disease and cancer, and Epoch IV, dominated by mental disease.

We are now concerned with non-ischemic dementias, due to broad area damage to large masses of neurons (nerve cells). In these cases circulation can be entirely normal. Non-ischemic dementias are not due to interruption of blood flow. A major cause is neuronal diseases. These dementias are connected with disturbances in the neuron-related substances which we term "Hormones" and "Factors". Hormones carry a chemical message and

are destroyed when the message has been delivered. Factors do not carry messages, but are substances necessary for the continued function and well-being of at least one kind of neuron. Presently, it is believed, though not fully proven, that the most common cause of senile dementia is a deficiency of one or more of the "Factors".

Alzheimer's Disease (AD) will become increasingly common as we approach Epoch IV. At least 500,000 persons in the United States are now suffering from this and related diseases and many more cases may go unreported or not diagnosed.

Alzheimer's Disease (AD) is a poisoning of the neurons. These cells do not normally divide (multiply). AD affects a very broad range of these neurons. It is characterized by the very large areas which the disease acts upon without special localization. In other words, AD affects the entire brain, not a specific area. A principal characteristic is the tangles of proteinaceous substances. These tangles gradually fill the cells, thereby crowding out all the actions or functions which are normal to these cells. What remains of these is only neuronal plaques. These are the tombstones of what was once a neuron. In this manner, cells become filled with various kinds of crosslinked, metabolically worthless conglomerates of substances.

The onset of Alzheimer's is gradual: first, loss of short range memory, then unsteady motions, faltering speech, difficulty in simple mental tasks such as multiplication, and disorientation. Finally seizures result, complete failure of the nervous system, and death. The difference between Alzheimer's Disease and Senility is slight, if any. Usually, when an old person shows these symptoms, he or she is diagnosed as having Senile Dementia. Conversely, if it's a young person, he or she is diagnosed as having AD. Persons as young as in their 40's have been stricken with Alzheimer's Disease.

Characteristics of Non-ischemic Dementias

1. Tangling of fibrils within the neurons - tangles occur in ordinary Senile Dementia, AD and other mental diseases. Two virus diseases (Kuru and "cjd") resemble AD in their symptoms. However, there has not been any evidence to indicate that AD is contagious.

2. Aluminum - Daniel P. Perl, Department of Pathology, University of Vermont College of Medicine in Burlington, identified abnormal accumulations of aluminum within neurons containing neuro-fibrillary tangles, derived from Alzheimer's disease patients. The indigenous native population of the island of Guam who suffer from amyotrophic lateral sclerosis and parkinsonism with dementia have similar accumulations in their brains.

Symptoms similar to those occurring in AD have been provoked in animals by injection of minute amounts of aluminum in a soluble form. AD symptoms were also mistakenly induced in the unfortunate artificial kidney patients who received treatment with water containing more than 80 micrograms of aluminum per liter (about a quart). One liter of water is very nearly 1 billion Nanograms abbreviated ppB. Thus one microgram per liter is the same as 1 ppB. Both are in common use and we will be using the ppB measure when we discuss aluminum amounts.

NEURONAL AGING AND DECAY

The age-dependent decline and final ruin of the neuronal system is illustrated in the following Figures. These are drawn freely to emphasize typical features, and are not claiming accuracy in fine detail. The loss of skills with age, which ends in senility, is due to the loss of nerve cells (neurons) and the withering of their connections with each other. Figure 7 (Schaibel) shows the neuronal connections within corresponding sections of the grey substance of two brains. The one on the left is from a 24 year old, the other from an 86 year old who was not senile. Figure 8 (reading from left to right) shows a high magnification of the fine branches (neurites) of a young, late middle age and a senile person.

FIGURE 7 - BRAIN OF 24 YR. OLD AND NORMAL 86 YR. OLD (After Schaibel)

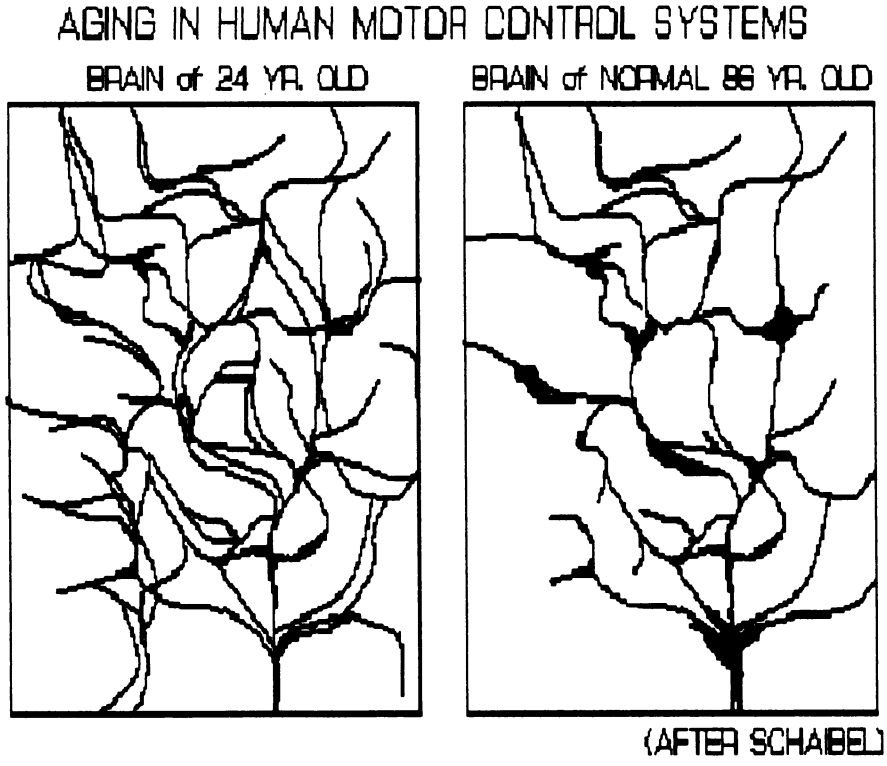
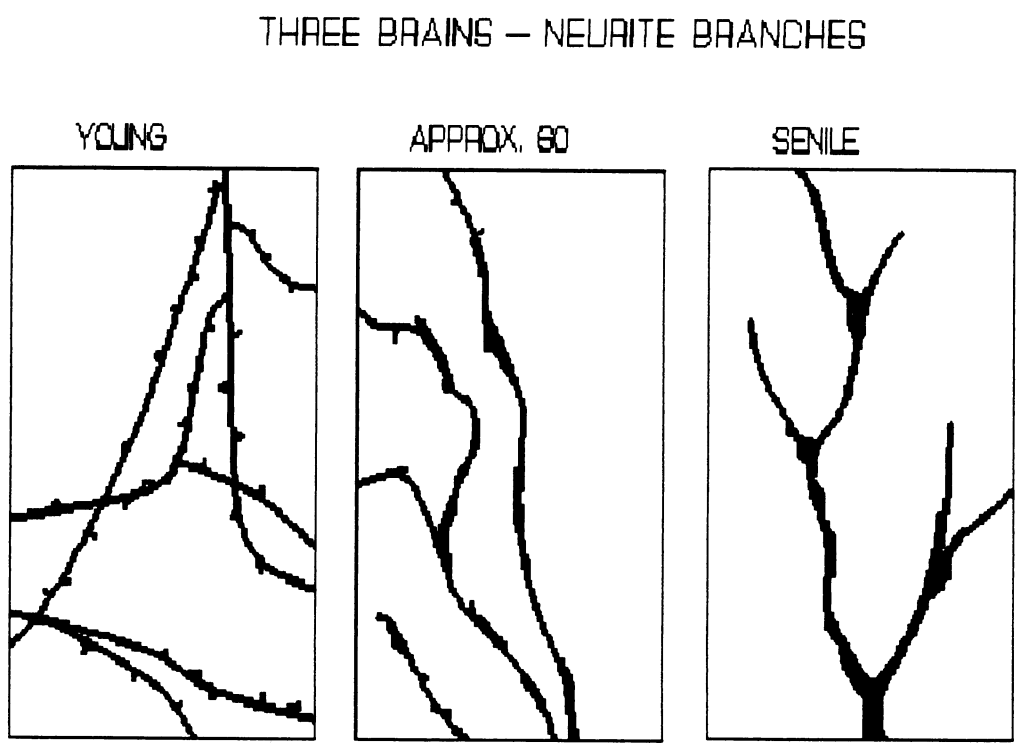


FIGURE 8 - THREE BRAINS NEURITE BRANCHES (After Schaibel)



In Figure 7, the older brain not only shows fewer neurons but a shrinkage and curtailing of the connections between these neurons. The communication and cooperation between the neurons are thus being reduced in the aging process. With fewer paths between the neurons, some of these paths may be crowded, and messages may take a longer time to get through. Decisions, interactions, will become slower, but they will still take place so that the brain continues to function.

Finally, in Figure 8, the neurons of the senile brain only have some stems left, and have lost contact with each other. The brain has then lost most, if not all, of its ability to function normally. What might we be able to do to stop this tragedy?

CAUSES OF NON-ISCHEMIC DEMENTIAS

What is behind these threats? There are at least three lines of development acting together against us. Given enough time, any one of these alone could cause massive destruction.

1. The decline of the level of Neuron Maintenance Factors (NMF).

2. The interference of intracellular transport due to repeated crosslinkage of large molecules. At the earliest stages

of crosslinking, small aggregates (clumps of substances) floating within the cell may close the passages of narrow channels. The neurites, which are the branches which connect neurons to their end organ, could be blocked by these aggregates. Unless the neurites can somehow get the needed Factors from the end organs, they will wither and die.

3. Poisons in the micro-environment. Of these, aluminum has been proven to cause Alzheimer's Disease symptoms. The role of aluminum in aging will be described in detail in the next chapter.

The first of these causes is the most immediately threatening and will be discussed in this chapter. It is nearly impossible to discuss the danger of Aluminum without simultaneously dealing with Crosslinkage. Therefore, the main emphasis of Chapter 6 will be on Aluminum's role in Non-Ischemic Dementias and will include an introduction to Crosslinkage. Crosslinking, which relates to both Epochs IV and V will be discussed in detail in Chapter 7 in connection with Epoch V.

NEURON DEATH OR MALFUNCTION DUE TO LACK OF A "FACTOR"

Orientation

A genetically determined path has been laid out so each nerve cell can find its target organ. In these paths, the nerve growth Factors guide the embryonal nerve fibers so that they grow to the vicinity of their end organ. The organs at the end of the path then attract the nerve fibers with specific Factors they must reach in order to survive.

These Factors are manifold. An apt collective term for them is Nerve Maintenance Factors. There are at least four groups and quite possibly more.

a. The neuron survival Factors.

b. The neurite growth stimulating Factors.

c. The surface bound neuronotrophic Factors (requiring the presence on the neurons surface of either polyornithine or the protein "laminin"). Additional coatings with similar surface characteristics will probably be discovered in future years.

d. Placental Factors which may or may not be as above.

These Factors have been studied by many researchers. Recent assay methods make possible the determination of the presence of some factors in as little as an hour. Knowledge of the quantity of Factors can be determined within a day.

In contrast, almost nothing is known about the role of these or other Factors in aging processes. This is because of the lack of truly representative meaningful animal models, and the very long time and enormous expense of making quantitative double blind tests with humans.

It stands to reason, however, that the Nerve Maintenance Factors (NMF) play an equally important part at the end of life as they do at the beginning. The most rapid way to prove this hypothesis is to solve the problem of supply of the Factors and then demonstrate their efficiency on humans.

One possible cause of neuronal death in old age is that the normal supply of Nerve Maintenance Factors is declining, along with for example sex hormones, insulin, and many others. If this is so, it would not seem unlikely that an artificial supply of selected nerve growth or maintenance Factors from other organisms might substantially prolong the health of the human central nervous system. If they were applied early enough, they might have some beneficial effects in Alzheimer and Senile Dementias, and possibly even in the malfunction of some extra-cerebral neuron-dependent pacemaker mechanisms. There may be some difficulty in bringing such factors into the brain, but these might be solved. In recent years we have learned much about the blood-brain barrier.

Background Information

The existence of Nerve Maintenance Factors was predicted early in this century by the great pioneer in Brain Anatomy, Santiago Ramon y Cayal, the "Don Quixote of the Microscope". The chain of events which led to the identification of the sources of some of these Factors was described by two pioneers in this field in a semi-popular article (R. Levi-Moncalcini and P. Calissano, Scientific American, 240, 44-53, 150 (1979)). Principal sources of the Nerve Growth Factors are mouse salivary glands, sarcoma, snake venoms and human placenta.

A breakthrough in the human Nerve Growth Factor was made in 1978 when I. D. Goldstein, C. P. Reynolds and J. R. Perez-Polo isolated and purified a powerful nerve growth stimulant from human placenta. This is now available to researchers in milligram quantities at a cost of at least four figures per milligram. In this context, it is appropriate to note some of the observations made in the 1960s at the V. P. Filatov Institute, Odessa, USSR, on therapeutic results with placenta extracts and suspensions.

The late Dr. Filatov was a leading eye surgeon in the Soviet Union. Many of his cases required transplantation of corneas,

obtained from healthy eyes of persons dead from other causes. In some cases, transplantations were made to infected eyes and Filatov observed that in some of these cases the infections healed peripherally around the transplant.

This lead Dr. Filatov to study the detailed history of the handling of these corneas while they were in storage to be used in operations later. He found that the best results were obtained with corneas stored about 7 days at temperatures of about +4 degrees Centigrade - cold enough to practically stop bacterial growth and yet warm enough to permit enzyme action breaking down protein and liberating whatever caused the desired effect.

Because of these findings Filatov and his associates began to study possible antibiotic effects of other organs than the eye, when these were stored a week at 4 degrees C. They tried virtually everything, and when they came to placental suspensions or extracts, strikingly favorable results were obtained. In these experiments, Solvieva gave experimental animals an amount of poison which would normally have been enough to kill 50% of those tested. This is known as having a 50% lethality. However, after administering placental preparations to the animals, the results were substantially better; fewer animals died.

Analyses were made in an attempt to identify which substances in the placenta and cornea were giving the positive results. However, none of the compounds identified could explain it. The explanation might be that the results were due to some very potent "Factor" present in minute amounts which did not show up in ordinary analyses. The Nerve Maintenance Factors would meet these conditions. Some of these are active in doses as low as one part to a billion. It may be significant also that the two sources highlighted by the Filatov studies -cornea and placenta- are also two of the sources in the forefront of the latest work with nerve growth Factors in the USA.

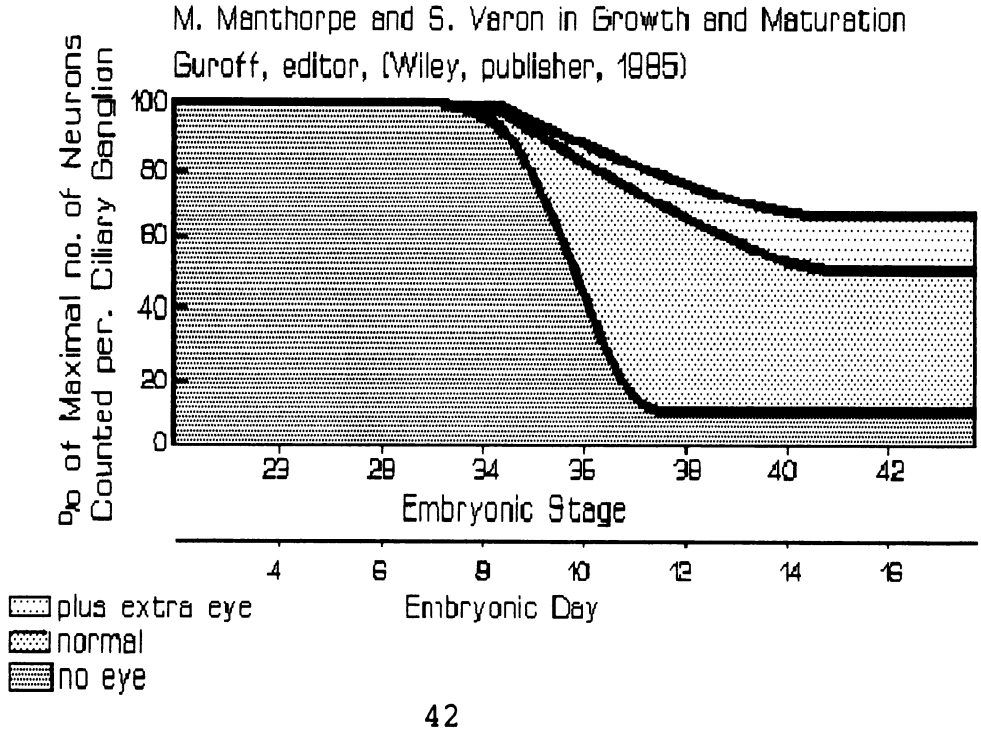
A BREAKTHROUGH IN ASSAY METHODS

"Assay" is the way to find out the exact quantity of the active part of whatever you work with. The miner takes his ore samples to the metallurgist who assays it, and tells him exactly how much gold can be extracted per ton of the ore sample.

The speed of progress in any field is closely related to the speed of judging the results of each experiment. To reliably and reproducibly evaluate an experiment in human aging would require groups under close control for ten to twenty years. Much simpler, faster and less costly is the determination of the effect of various classes of Neuron Maintenance Factors in chick embryos.

The Ciliary Ganglion Assay (nerve tissue responsible for proper function of the chick eye), was developed by M. Manthorpe, S. Varon and their associates in La Jolla. It is based on the fact that to make certain that no precious eye is lost for lack of nerve connection, nature provides a 100% excess of neurons for each chick embryo. Death comes in the 8th - 11th day after conception to 50% of all nerve cells present (since nature had provided twice as many as needed). This death is prevented in whole or in part if more Neuron Maintenance Factors are added. Figure 9 shows such assay curves applicable to Factor assays. In an eyeless chick embryo the neurons which would have provided connections for the eye, had it been there, will all die between the eighth and the 11th day after conception. To survive they need a "Factor" which the eye normally gives them. To find out what this factor might be, or how it could be separated and studied, Manthorpe and his co-workers added possible source materials to these chick embryos in their eighth day. From the number of surviving neurons they could tell in a matter of hours, if there were any survival factors present, and in a day how much of it there was. In the search for new Factors or the study of the known, it makes a tremendous difference if you can tell in a few minutes how much active material you have in your sample, or if it will take a week to find the facts. Notice that for the normal chick embryo (middle line), by the 14th Embryonic day only about 50% of the Neurons are still viable. When an extra eye was added to the material, about 70% of the Neurons remained.

FIGURE 9 - ASSAY CURVES FOR THREE MOST READILY DISTINGUISHED CLASSES OF FACTORS (After Manthorpe, Varon et al)



This ciliary assay permits a qualitative judgment of activity in an hour and a quantitative determination of neuronal Factors in a day.

To make a similar determination of these Factors at the end of life would require large groups of persons under close supervision for many years. Compare the cost of maintaining say 200 persons under surveillance for at least five years, with the cost of 200 chicken embryos for 11 days. If research were carried out according to conventional procedures and requirements, it seems at least very unlikely that the decisive control of neuron death could be achieved sometime soon.

It is tempting therefore to seek a shortcut, to work out the characteristics and properties of the Nerve Maintenance Factors with the egg models, and take a gamble that what we find out with these fast models will be applicable to humans. We can make the bold assumption that as most hormones and Factors decline with age, so will also the Neuron Maintenance Factors. We may also dare to assume that as we can save the chick neurons from death by giving them Factors from a new source, so might we be able to stem the neuronal decline of mankind by developing a large supply of these same Factors.

A Possible Shortcut

On the basis of present knowledge, it seems plausible that the cause of the progressive death of neurons at higher ages has the same causes as similar neuronal withering and cell death at the fetal stage. This jointly shared cause is namely a shortage of one or several of the Nerve Cell Maintenance Factors. These were the same Factors which have been found in Chick embryo.

Longo, Manthorpe, Varon and co-workers found that the liquid oozing from a wounded human brain through a crack in the skull enabled chick embryo neurons to survive without any other Factors.

Such relationships usually work both ways. The Factors from the chick embryos might be the means to save aging persons from becoming senile.

The principal source of human growth Factors has been the placenta. In its first months, the fetus is not capable of making for itself all of the Factors needed to sustain its development. For example, at least one of the growth Factors has a molecular weight of 150,000. Such a large molecule, in which more than a 1,000 subunits are linked together, is apt to be unwieldy and difficult to maneuver. It is understandable that handling these Factors is too difficult a task for a youngster who was not even born, so the most practical solution was to let Mother supply these Factors through the placenta. This explains

why placenta is such a good source of Nerve Growth Factors.

This size and complexity of some of the placental Factors constitutes a major problem for researchers. While some of the Factors are relatively easily made peptides, others, like the nerve growth Factors were found to have molecular weights of about 150,000. This means that they were composed of about ten thousand atoms of carbon, nitrogen, oxygen and hydrogen, each of these atoms being in an exactly determined position.

Even with modern sophisticated instruments in the hands of capable researchers, duplicating this is far from an easy task. You can think of it as a puzzle game in which you have to put together 10,000 pieces, of which 2,500 are green, 2,500 red, 2,500 blue and 2,500 yellow. The pieces of the same color are all alike and different from those of any of the other colors. You have to put all these pieces together to build a watch-like fine instrument in which each piece has its given place in relation to all the others. To make it still more difficult, the pieces are so small that you can only see them with an electron microscope.

If the nerve Factors of chickens should prove valuable in human medicine, this could be extremely important because chicken eggs (or the embryos growing inside) are quite inexpensive, particularly if all by-products are utilized. It seems very possible that the chick Factors will work well with human brains because as previously mentioned the reverse of this has already been found to be true.

So far,the progress in our knowledge of these "Factors" has been dependent on experiments with very young organisms, such as chick embryos and rats. Nonetheless, the mass of available data points to the conclusion that the particular experimental animals used make little difference in the case of Nerve Maintenance Factors. This is because Nerve Maintenance Factors do not appear to be species-specific, which means NMF's from one kind of animal will work on other types of animals.

AVAILABILITY OF THERAPEUTIC NERVE MAINTENANCE FACTORS

We have seen that the Nerve Maintenance Factors can have a far reaching influence on the health and survival of neurons and their connections. The existence of such Factors has been known for more than 30 years. The pioneering work of Rita Levi-Moncalcini expanded our horizons by showing that a family of nerve growth Factors exists and is necessary for normal nerve development and possibly also for some nerve functions.

A principal problem in this research is the very low con-

centration of these extremely potent substances. This makes it very difficult to obtain quantities needed for research or clinical testing in any major way. This is still a difficulty which has, until just recently, retarded research in this field.

To achieve completely comparable results in studying the Factors, it was necessary to move the organism to be tested to a more fully defined artificial condition. The test neurons are then cultured in nutrient liquids. Materials believed to contain additional Factors are added to the liquid. The liquid is then broken up into units to make comparisons easier.

The material containing the Factors is usually obtained from spinal nerves Dorsal root, sympathetic (nerves for involuntary muscle action), or ciliary ganglia. The main groups of Nerve Maintenance Factors are the neuronotrophic, which primarily ensure the well being of the nerve cells, and the neurite growth promoting Factors, (of which there are many variants including the ciliary Factors). None of these materials are sufficiently rich in quantity or concentration of Factors.

The cost of applying present techniques to any of these materials would bring the cost of preparing the Factors somewhere in the range of what the cost of antibiotics were sixty years ago. The task now before us is to do in a shorter time what Waksman and Florey and their numerous co-workers did for penicillin during the 25 years that followed Fleming's initial discovery.

To accomplish the same with Nerve Maintenance Factors the following is required:

1. One or more leaders who are convinced that the problem can be solved, and who are wholly dedicated to its solution. If more than one leader, they must all be wholly dedicated to the problem and work like a unit.

2. There must be a broad public demand for a solution of the problem, to assure all out financial and political support. This support will come when more hospital beds are occupied by mental patients than with cancer and heart cases.

ARTIFICIAL SUPPLEMENTS

Since the cost of the presently available Factors are in the ten thousands of dollar per gram range, some researchers have begun adding low-cost activators to the expensive Factors. A few of the published results particularly tickle my imagination, because they point the way to lowering the cost per experiment which will of course make research more feasible. The following is taken from the data in a paper by S. D. Skaper, I. M. Selek, M. Manthorpe, and S. Varon, Brain Res. 302, 281 (1984).

These authors experimented with the following low-cost activators to see which ones had positive results with chick embryo neurons. The substances listed in the left column are the substances which were added to the culture medium. The second column shows how many ciliary neurons survived out of a thousand after eight days. As you will recall, the ciliary neurons which have not connected with the chick's eyes after the eighth day of fertilization will normally die.

Addition	Survival of 1000
None	0
Insulin	310
Pyruvate + insulin	630
above + serine + iron	900
Pyruvate + serine +iron	0

This table, in its simplicity, shows very great differences in results with little or no continuity. This shows an economically important situation of a type which usually is unattractive to the academic researcher. These substances have already been identified and used in many other aspects of medicine. The academic researcher would rather discover a new substance which would be effective, instead of experimenting with new uses for known substances. It seems probable that even the best of these combinations will be found to be far from the optimum. However, the favorable result with pyruvic acid, an intermediate product in both sugar and amino acid metabolism, is quite suggestive of better things to come.

Summary and Conclusion

The progressive death of neurons of the brain is a principal cause of the mental decline which, at the present time, will ultimately befall everyone who does not die earlier of other causes. At this particular point in time, when we are in the transition between Epochs III and IV, the reason for this progressive loss of neurons has become apparent, and a means for correction is in sight.

The apparent reason is that a broad range of hormones and other vital biochemicals decline in quantity with age, and that Neuron Maintenance Factors (NMF) are among these. The decline with age of endocrine functions, including also sex hormones, are well known. It is entirely plausible that this also will be true of several, possibly all, of the NMF. This would suffice to explain an important part, if not all, of the neuron deaths which is now the major cause of the age-dependent decline of the nervous system.

If this surmise is correct, adding the missing NMF could be helpful in reducing, if not stopping, the progressive death of neurons, and the withering of their outgrowths (Neurites).

It seems probable that the NMF which are necessary to stop neuron deaths in old age are the same Nerve Maintenance Factors which stop the death of neurons in the fetus so they can connect to the right end organs and ensure healthy offspring. (In the chick embryo 50% of ciliary (eye) neurons die between the eighth and eleventh day after conception). Nature usually follows the simplest path, so it is simpler to use a Factor already present from birth than to get another set of Factors for the senile individual, particularly when the latter is on the way out.

POSSIBLE CONSEQUENCES

If some of these positive effects researchers have had with chick embryo Factors can be reconfirmed with human cells, much time could be saved. If this doesn't work with humans, emphasis could be placed on human placenta since it is a proven source of some human nerve growth Factors.

In the near future, we shall probably see broader application of the recent assay methods developed by Manthorpe, Skaper and Varon. This is the key to rapid progress, which will undoubtedly yield many important results in the near future. Next, would then come the possibilities of low molecular activators functioning in synergy with the Factors, and broadening their field of application. The pyruvic acid lead looks particularly promising.

This presentation is predicated on the belief that the decline of NMF is an underlying Factor of neuron death. Neuron death could be the greatest cause of Senile Dementia, and the "normal" mental decline.

YOU AND THE NEURON MAINTENANCE FACTORS (NMF)

The NMF are the latest frontier of medical-chemical advance. Its potential is enormous. Moreover, its present rapid development is assured because we stand on the threshold between Epoch III and Epoch IV, and the mastery of NMF is crucial in the epoch we are about to enter.

Speaking in the terms of epochs, 50 years is still rapid. Human conservatism is great and the resistance to new trends - some call it "stupidity" - should not be underestimated. Nonetheless, Penicillin and its companion antibiotics made their breakthrough into mass production in only 26 years. Now that it's done, it seems like yesterday.

For progress we should look forward, but remember the past for clues and perspective. As we stand now, is there anything that we could apply right now that just might help us some and that would not be risky?

Yes, there are observations which might be used to our advantage, but all of these are built on guesswork and a still very sketchy knowledge of these Factors. We can already form some ideas of their occurrence, and the conditions that support their formation. For example, one of the important Factors which stimulates the growth of neurites is known as PNPF (Polyornithine Binding Neurite Growth Promoting Factor). This Factor can only act on cells which have received a coating of polyornithine. Polyornithine gives the nervous system a way to mark or to designate which of the neurons should send out neurites in some certain direction. This ability seems to be important for the correct construction of parts of the nervous system. Polyornithine is composed of ornithine, a dietary amino acid but not among the most common ones. A shortage of ornithine at a critical time of synthesis might well keep the neural system from developing to its full potential.

Some evidence makes it plausible that the principal time of synthesis of this system is in the first couple hours of sleep. If all this is correct, and a person has less than the optimal amount of ornithine, it could appear that half of a teaspoonful of ornithine before going to sleep could increase the health of at least some parts of his nervous system. Ornithine would be most palatable in the form of ornithine hydrochloride. The pure amino acid has a less pleasant taste.

The chances of something this complex working out in practice is perhaps no more than ten percent, but since the substance is a dietary amino acid there seems to be no appreciable risk in trying it. For some, the improvement could be substantial.

A greater risk would be attached to tests with the Factors themselves, but the present high prices of these minimize the temptation for most of us at the present time. A recent cost estimate was (in U.S. dollars) $1,800 per milligram or $50,700,000 per ounce. However, for human experimentation, probably one milligram daily might indicate something, and this would cut the cost to $657,000 per year.

However, I don't mean to exclude a dietary approach to this problem. So far, we know very little about the effects of diet on the levels of any of the NMF Factors in humans. Clues might be found in the protocols of cures ascribed to cell therapy or to placenta extracts or suspensions.

Thus far, no really rich source of the Nerve Maintenance

Factors has been found that would make mass production possible. With great effort and expense, it has been possible to make a few milligrams of the NGF from human placenta. Similar very small quantities of the three principal groups of Factors from the chick eye and some from a rat tumor have also been isolated.

Though none of these even begins to make possible any large scale clinical tests, researchers could use them to determine their exact chemical structures. Once this is known, the chemical synthesis might be possible on a large scale.

A considerably better bet would be to center efforts on the molecular engineering approach. This would mean using an RNA-Probe to pinpoint the positions of the genes responsible for making the various Factors. After they've been pinpointed, they can then be transferred to some easily managed micro-organism which is good at protein synthesis. In this way, we would be putting the bacteria (micro-organism) to work for us. Given enough time and money this would probably succeed. The initial success with this first Factor would stimulate others to join the effort. In a few years (hopefully) or a few generations (at least) this problem will be solved and then the moment of truth will be near: We will know if one or more of these Factors can keep human neurons alive and healthy so that senility, and decline of mental abilities with age will be things of the past or, will no longer worry us.

With this, and effective control of the environmental factor of aluminum in water and food supplies and/or effective aluminum removal from the body, we should then be able to leave Epoch IV behind us and proceed to face the hazards of Epoch V with good courage and, hopefully, in the process, give our great grand children as grownups the pleasure of knowing their - oh so wise and experienced great grandparents.

CHAPTER 6

THE ALUMINUM HAZARD

That aluminum plays an important role in most cases of Alzheimer's disease and senile dementia has been proven. The evidence includes the showings that:

1. Aluminum compounds applied directly to the naked brain cause severe nervous symptoms.

2. A milligram quantity of aluminum chloride injected a single time into the brains of cats or rabbits causes an illness which in the course of several months progressively destroys the brains and causes death.

3. Persons who have lost both kidneys can only live if they have their blood washed in an "artificial kidney". In this treatment, which has to be repeated two or three times weekly, the patient's blood is bypassed through a very thin walled tubing much like a sausage casing, which passes through circulating fresh water. When this is done the waste products that normally go out through the kidneys pass through the walls of the thin tubing into the wash water which is fifty-five gallons per each treatment. Unfortunately overlooked was that any small molecules in the water also pass through the thin wall into the blood.

In 1972, when this treatment was new, a large number of patients began to stammer and in a month became mute. The condition got worse and in another three to six months they were dead. At first it was believed that this was some infection, but finally Dr. Alfrey at the Veterans' hospital in Denver had a complete analysis made of the brains of the deceased. The only thing that was unusual was a very high **aluminum** content, about three times the normal, in almost all of these patients.

Today this does not happen because strict requirements are made on the permissible aluminum content of the water used for artificial kidneys.

However, little attention has been paid to aluminum in public water supplies, particularly the tap water in cities and other public water supplies. This is one of the most obvious sources of the aluminum increases with age. At the present stage of our knowledge it is not totally impossible that the loss of mental skills with very high age is to an important degree caused by excessive aluminum in our water supplies. Aluminum is deliberately added to our water in many places in order to remove cloudiness in the water.

4. In Alzheimer's disease as well as in Senile Dementia the nerve cells (neurons) are filled with insoluble fibrils. Dr.

Daniel Perl has recently shown by using laser spectrography that these tangles contain aluminum.

5. The Aluminum atom has a very small diameter and a very high surface energy. Therefore, it can penetrate almost everywhere and displace any of the other common metals in the soluble compounds. In particular, aluminum readily displaces calcium, which is present in every living cell. Each aluminum replacement of calcium results in a new branching as shown in the figures on page 62.

The following points have been raised:

A. There are cases in both Alzheimer's disease and in Dialysis insanity in which there was no increase in Aluminum. Aluminum is not the only substance which causes the tangles. As will be shown in detail below, aluminum has this effect because it is a powerful crosslinking agent. Several other crosslinking agents may have the same effect, but to a lesser degree, and are less commonly present. Above all, the organic crosslinking agents are extremely difficult to find, like a needle in a haystack. In the case of aluminum we can burn the "haystack" and locate the aluminum in the ashes very easily.

B. In the Dialysis insanity, the tangles are less regular than in Alzheimer's Disease and they are located mainly in the cytoplasm and not in the innermost "nucleus" (management center) of the neurons. This objection has been raised particularly by anatomists. This difference is entirely expectable when different concentrations are used. In the case of dialysis dementia, there is much higher concentration of aluminum due to the fact that a dialysis patient's "kidney" is washed with about 50 times the amount of water a person would drink. In Alzheimer's disease, the concentration of aluminum is much lower. The disease takes more time to develop so the aluminum has more time to get into the nucleus. To the chemist it is commonplace that any precipitates look different dependent on how concentrated a solution of the reactants you use. I suggest a glance at the pictures on pages 61-62. With very much aluminum present the molecular arrangement may resemble the "messy" structure on page 62 rather than the more orderly lowest figure on page 61.

INSOLUBILITY, A COMMON DENOMINATOR

In all non-ischemic Senile Dementias, the key word is insolubility of cell matter. Anything that is totally insoluble and irremovable will, in a lifetime of 70 to 120 years, accumulate in non-dividing cells (neurons are normally non-dividing) to such an extent that severe disturbances, and finally death will follow. Any researcher equipped with enough advanced instrumentation, patience and persistence who sets out to seek a

particular compound in these insoluble senile aggregations (clumps of substances) will find it. Every one of these polymers, however rare it may be, will leave its trace in the accumulations. Examples of these are amyloids, lipofuscins, hyalins, aging pigments, etc ("Liver Spots" are an example of aging pigments). These examples are merely the "tip of the iceberg". They are all aggregates, or combinations of different molecules.

Aluminum is a dominant reactor in crosslinking because it is commonly found in nature, has a high crosslinking efficiency, and is easily found in analysis because it remains in the ashes when everything else is burned away. Nine thousandths percent (0.009%) of aluminum suffice in one model system to change a polymer from totally soluble to 99% insoluble in any non-destructive solvent. Silicon, which is 4-valent, starts two side chains where aluminum starts one, but is not as reactive, and therefore less common in these diseases than is aluminum. With this background in mind, it is now appropriate too that we learn about the crosslinking mechanism and the role of aluminum.

CROSSLINKING -- A BASIC UNDERLYING PROCESS

Crosslinking of large molecules within cells has been stressed by the author as being a primary underlying factor of all age-related changes in the body. It is also, therefore, a primary factor of senile dementias. As we know from the previous chapter, one of the main characteristics of non-ischemic dementias is the tangles of fibers within the neurons. Crosslinking is a causative factor of these tangles.

The Crosslinkage Theory of Aging (first formulated by the author in 1942) holds as its main premise the fact that crosslinking of large molecules within cells occurs regularly and unavoidably wherever large molecules (having at least two reactive sites) and crosslinking agents co-exist, and they do co-exist in every living cell.

A direct effect of crosslinking is to render once valuable macromolecules into insoluble inert aggregates. These aggregates will accumulate in the cells. Their growth will then cause three major changes in the cell:

1) Create a deficiency of one or more irreplaceable molecules.

2) Form a network which impedes intracellular transport.

3) Create "floating inert islands" in the cytoplasm. These will retard intracellular transport and might plug narrow passages.

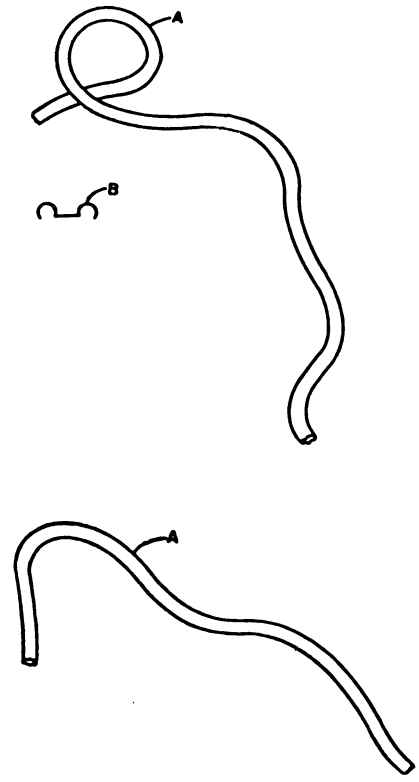
4) Cut down the volume of space available for vital molecules within the organism.

Eventually, these hindrances will lead to death of the cell. In the case of dividing (cells able to reproduce) cells, new cells are created through mitosis to replace those which have fallen prey to crosslinking. However, non-dividing cells such as neurons and large muscle cells can not be replaced. Once, for example, a brain cell is lost, it has been regarded as lost forever, (though recent work with growth factors has indicated that even old muscle or nerve cells may be brought to division). Some large muscles, such as the heart, can counteract crosslinking by its repeated stretch and relax cycle. This "orients" the crosslinkers and therefore keeps the arteries and arterial heart muscle from becoming hard, losing elasticity, or otherwise nonfunctional.

Crosslinking has many industrial uses. Tanning is crosslinking. It is used in the leather tanning industry to turn once elastic, supple, horse and cow hides into the durable, stiff material we know as leather. Carpenters use **cross** beams to strengthen building structures. When the purpose is to make something more rigid and less elastic, crosslinking is the way to do it. However, in the case of our own cells, crosslinking can be catastrophic when it happens without control, by pure chance. We can recognize some of these effects in our outward appearance. For example, the effect of solar radiation on the fats in our skin is to make it combine with oxygen to form crosslinking substances (mainly aldehydes) which then tan the collagen and other protein in the skin, thus making it "age" faster. This is the explanation as to why exposure to the sun will age your skin faster than if you tried to keep sun exposure to a minimum. Unfortunately, the effects of crosslinking "under the surface" go unnoticed until they manifest themselves as diseases which are often irreversible.

Crosslinking agents are substances which induce crosslinkages among molecules. Exactly how the crosslinking agents act, and how crosslinks form, is shown in the following series of pictures:

FIGURE 10 - MACROMOLECULE AND CROSSLINKING AGENTS



In Figure 10, Crosslinking has not yet occurred but the conditions favor it. A is the macromolecular chain. B is the crosslinking agent. There are numerous crosslinking agents, of which many are normally present in every cell of the body, carried around by the motions of the fluids in the cell or in blood or serum. They include, but aren't limited to, oxidation products like aldehydes, free radicals and various metals. The necessary condition is that these crosslinking agents have at least two "hooks", each of which can attach firmly to some point of any large molecule to which they might float. There are tens of thousands of such crosslinkers; some fast-acting, some very slow, but in a life-time of over 70 years, every one of them will have some chance to connect and every possible combination will sometime be formed. In Figure 11, the crosslinking agents have attached to the macromolecules. The crosslinker now has one free unsatisfied bonding capacity which it will use to attach to another macromolecule as is shown in figure 12.

FIGURE 11 - CROSSLINKING AGENT ATTACHES ITSELF

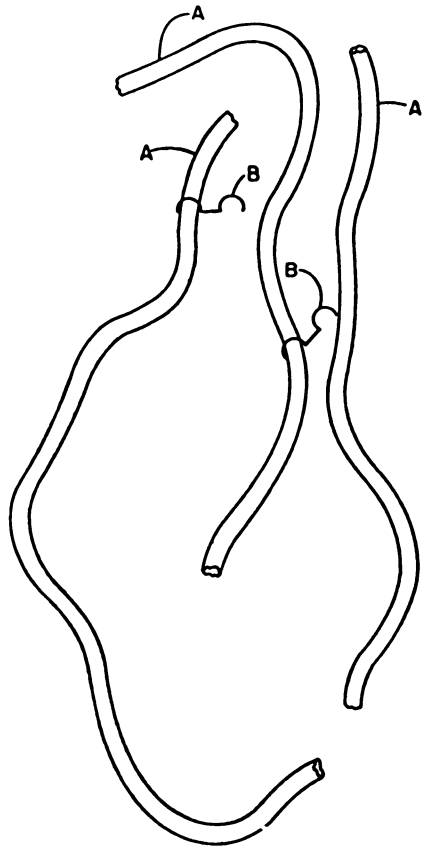
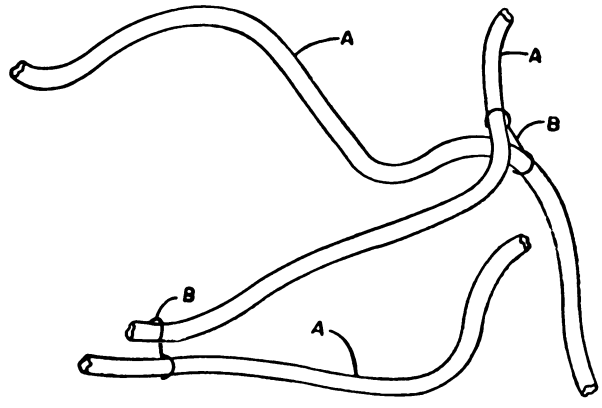


FIGURE 12 - CROSSLINKERS MAKE SECOND CONTACT, AGGREGATE IS FORMED



In Figure 12, the crosslinking agent has made a second contact with its free valence (bonding capacity). The two once separate, vital molecules are now one inert aggregate. Once the aggregate is formed, it will grow with subsequent crosslinks over time.

The larger the aggregate becomes, the larger a target it is for more crosslinking agents to attach themselves, as is shown in Figure 13. Eventually, as we see in figure 14, the crosslinking reaches the point where all transport within the cell is blocked, thereby choking off all cell functions.

FIGURE 13 - CROSSLINKING ACCELERATES BECAUSE OF GROWING TARGET

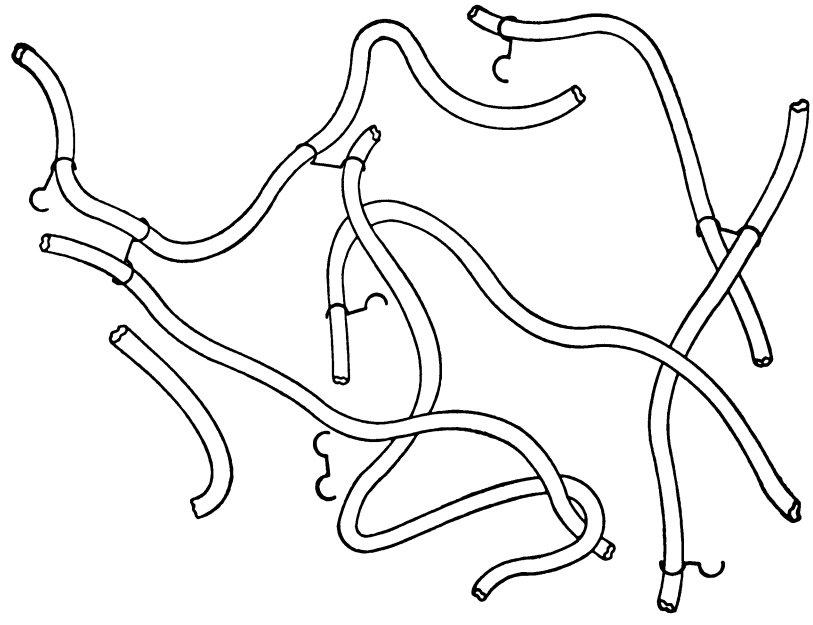
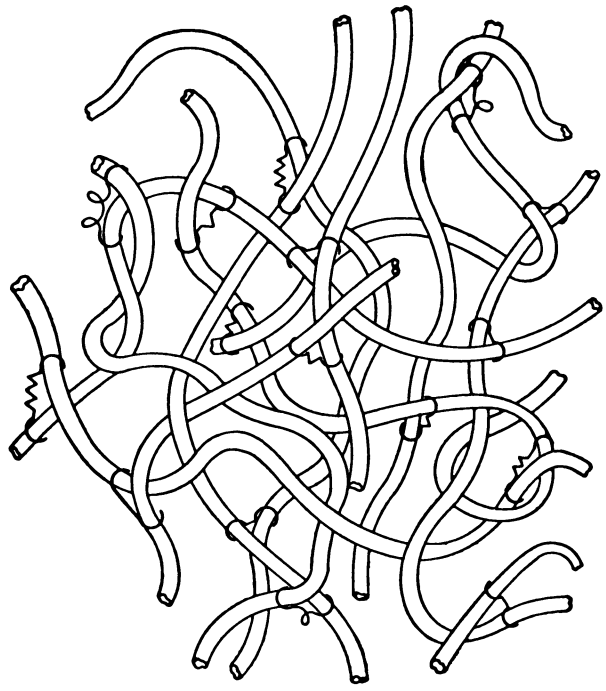


FIGURE 14 - THE RESULTANT AGGREGATE MASS



Crosslinks accumulate with age. It is possible that repair enzymes can reverse the crosslinking process in its early stages, but this process is not perfect. The repair enzymes generally do not cut crosslinkages - there are many hundred different crosslinkages and the enzymes are not adapted to deal with such a multitude. Rather, the typical repair enzyme will cut out the crosslinkages by breaking the bonds on both sides of these. If the crosslinking has gone far enough so that the web of linkages is too tight for repair enzymes to reach, the damage may be permanent, and will grow as additional molecules join the big mass.

There are many myriads (1 myriad = 10,000) of crosslinking agents, some of these very slow acting, others act almost instantly. To locate any particular one of them in a cell is much like looking for a needle in a haystack or in a bale of rice. The metallic crosslinkers are the easiest to find, because you can burn away your "haystack" and find your metal "needle" in the ashes. Of the metallic crosslinking agents, aluminum is by far the most common. In this chapter on the mental diseases it will play an important role. It's primary harmful action, so far as crosslinkage is concerned, is that it has the ability to displace calcium when this is present in a big molecule composed of links with only two binding forces each (bivalent). Calcium is a vital metal and has free access in all cells.

The occurrence of known crosslinking agents in human blood was listed (Bjorksten 1964) as follows:

Acetaldehyde	<0.1 mg./100 cc.
Methyl guanidine	0.2-0.3 mg./100 cc.
α-Ketoglutaric acid	0.2-09 mg./100 cc.
Pyruvic acid	0.4-2.04 mg./100 cc.
α-Keto acids, only generally identified	0-3.1 mg./100 cc.
Citric acid	1.3-6.0 mg./100 cc.
Malic acid	0.1-0.9 mg./100 cc.
Fumaric acid, in rat	<0.3 mg./100 cc.
Succinic acid	0.5 mg./100 cc.
Silicon	33-63 µg./100 cc.
Lead	18-49 µg./100 cc.
Aluminum	15-40 µg./100 cc.
Copper	73-115 µg./100 cc.
Iron	43-52 µg./100 cc.
Manganese	0-25 µg./100 cc.
Zinc	488-1262 µg./100 cc.

It is noted that Aluminum was listed first of all biometals, since it has the strongest bonds, and has always the same number of binding forces (valences) while the Copper, Iron and Manganese have variable bindings which makes their bonds escapable.

CALCIUM

The general importance of calcium in biology is its universal compatibility in biochemical contexts. Always bivalent, it can be introduced into any chain without ever causing branching or tangling. Ebashi, in numerous publications (1960-70) clarified the central role of calcium in muscle action. In 1985, S. Ebashi wrote: "Ca2+ is now accepted as the most fundamental regulatory factor for various kinds of intracellular processes."

ALUMINUM, CALMODULIN AND CALCIUM CONTROL

An excess of calcium ions in the cell is detrimental. Yet, calcium is a useful, indispensable component of the human body when present in the right concentrations and the right places.

The control of calcium concentration is therefore of great importance, particularly since its supply varies greatly.

To buffer the calcium content and keep the concentration near optimal levels in blood and brain fluids, evolution has endowed us with buffering systems. These systems include many proteins of which the most prominent are: Calmodulin, the calcium binding protein "cbp" and Troponins A and C. They act as

reservoirs and controllers to minimize the fluctuations of calcium so that it remains within safe limits.

Crapper-McLachlan has shown that the calmodulin content of the nervous system, which acts as a reserve supply of calcium, is very substantially reduced in Alzheimer's Disease.

ALUMINUM - CALCIUM RELATIONSHIP

Aluminum is plentifully available in almost any environment. Earth's crust contains about 8.4% of this metal. It is present in almost everything we eat or drink, except rain water. It is found in all clays, and in a great many stones and minerals. Of all the crosslinking agents, kAluminum is one of the most common and the easiest to identify.

At first glance, it seems strange that an element so plentifully available, yet very reactive, has not found any place anywhere in the metabolism of any known animal or microbe anywhere. Far less common and far less versatile elements have found some organism which uses them for at least something. It seems that all animal life has gone out of its way to avoid using aluminum anywhere in its metabolism, as if some hidden danger were lurking near it. Could this really be so? In that case, what might the danger be? Perhaps a closer look at the aluminum atom might give us a clue. First of all, let us look at the Aluminum (Al) atom in comparison with some other atoms of metals (notably calcium-Ca) which are widely used in animals or human life processes. The dots on the outer circles of the atoms represent free valence electrons, which are the binding forces.

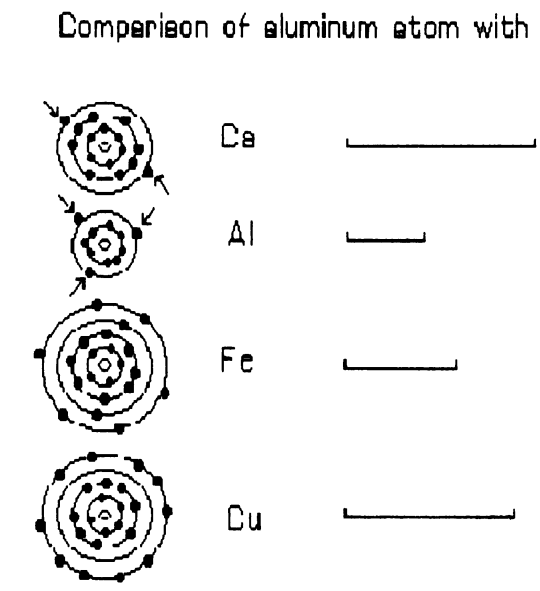
We can immediately see from this picture:

1. The aluminum atom is much smaller than any of the others.

2. It has on this small surface three binding forces, which means that it has a greater concentration of binding energy than any of these other metals.

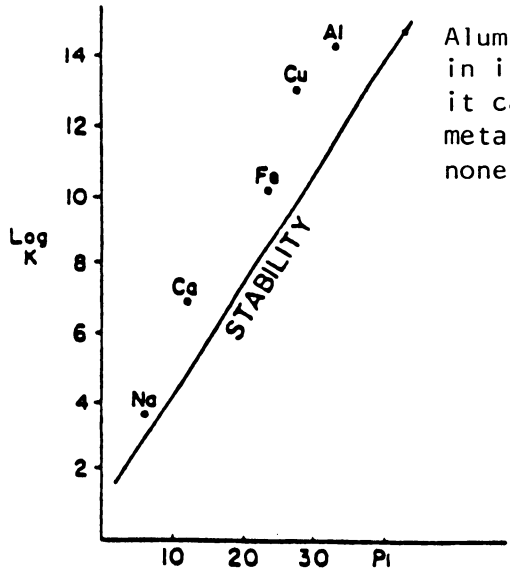
3. As we could expect from the above, the following picture shows that aluminum compounds are the most stable of those tested.

FIGURE 15 - COMPARISON OF ALUMINUM ATOM WITH OTHER METALS



(after Zinsser, Bjorksten et al, 1962)

FIGURE 16 - STABILITY OF ALUMINUM COMPOUNDS



Aluminium (Al) is the most stable in its compounds. In a soluble form it can displace all of these other metals, and can be displaced by none of them.

Figure Range of stabilities of various metal complexes is shown relating them to their electronegativity

(after Zinsser, Bjorksten et al, 1962)

These three observations tell us:

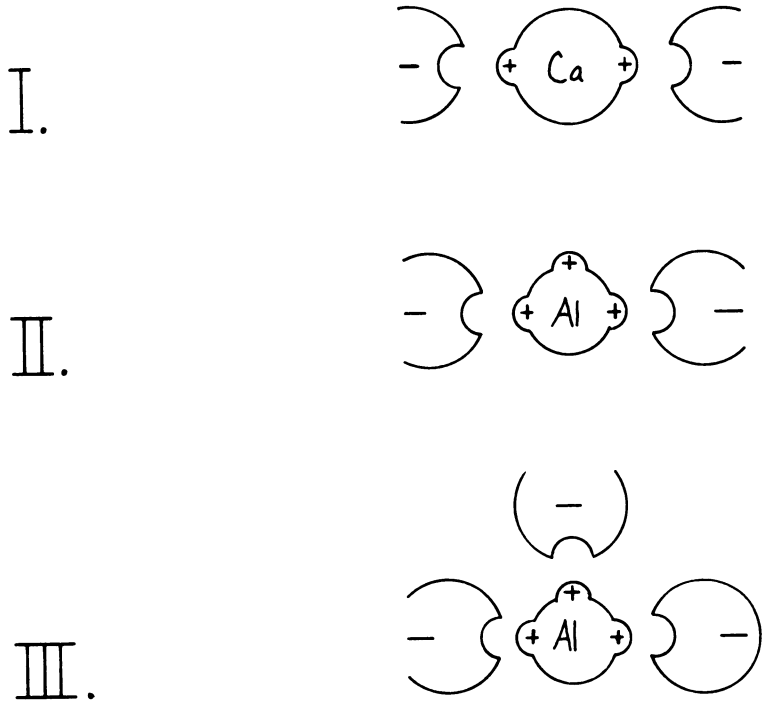
1. Because of its small size the aluminum atom can penetrate easily almost anywhere, including those places where some other metal should be for some specific purpose.

2. Because of its high binding energy, the aluminum atom can anchor itself in any such position. Once there, it cannot be dislodged by any force available to the organism.

3. The great stability of aluminum compounds causes them to increase at the expense of corresponding compounds of other metals.

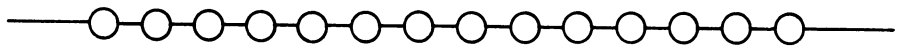
The mechanism of how aluminum can cause age-related change, and with it senility, becomes clearer when we consider that aluminum content increases steadily with age and is often quite elevated in cases of Alzheimer disease and senility. The critical property of aluminum, so far as its relation to calcium is concerned, is that calcium atoms can combine only in straight lines, while even the smallest amount of aluminum will cause branching, crosslinking, and tangling. How this occurs becomes clear when we view Figure 17. In these pictures only the essentials are shown, and those parts are emphasized which we should now watch.

FIGURE 17 - ALUMINUM AND CALCIUM ATOMS SHOWING VALENCES



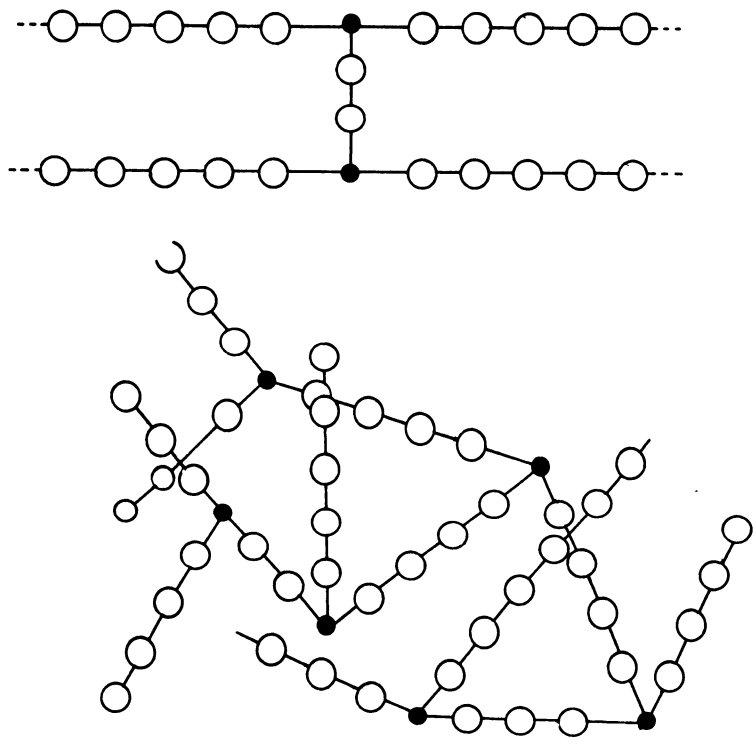
Calcium always has 2 binding forces (valences), and Aluminum has three. When calcium combines with anything else with two valences, there is no way in which branching can occur. A bi-valent macromolecular chain is shown in figure 18.

FIGURE 18 - CALCIUM COMBINING IN STRAIGHT LINE



However, when even the smallest trace of aluminum displaces anything with two valence electrons, there is no way in which branching can be avoided. This is because aluminum has an extra valence, or hook, which can combine with an unsatisfied valence in another bi-valent chain. Repeated branching, coupled together with growth, makes tangling unavoidable. This is illustrated below. The aluminum atoms are represented in the drawing as small black dots, the other atoms are bi-valent. The first drawing shows crosslinking in its earlier stages, the latter drawings show it in its more progressed stages.

FIGURE 19 - CROSSLINKING AT VARIOUS STAGES CAUSED BY ALUMINUM



Thus, as we can see from the example, it takes very few

aluminum atoms to totally interrupt and change the orderly simplistic chains of calcium atoms, and to introduce all sorts of surprising complications.

If one has trouble picturing this effect in his/her mind, put a thimble full of aluminum chloride into a glass of milk and see what happens.

Aluminum isn't the only substance which can have this effect. We know many organic substances which can do the same, but aluminum is the easiest to trace and therefore the most studied. Because of its wide distribution throughout the earth, it may well be the most common of this type of complication. Aluminum could account for most of the tangling observed in Alzheimer's Disease, and for the disease itself.

NATURAL DEFENSES AGAINST ALUMINUM

In Senile Dementia, (in conjunction with the normal loss of neurons with age), the continual increase of aluminum with age sooner or later starts the same events as occur in Alzheimer at an earlier age. It could be that AD patients have had an overdose of aluminum in their diet or that they lack the proper barriers to aluminum which are present in most persons.

In order to enable us to live on this aluminum infested planet long enough to have our children and bring them up, evolution has endowed us with six defenses against aluminum, namely:

1. The stomach and the intestine do not take up aluminum, but let it pass through. Nonetheless, nothing in this world is 100% effective. We unavoidably eat about 30 milligrams daily of aluminum. Most of it passes through us, but nonetheless about 0.015% passes through the kidneys, so some trace does get past the first defense.

2. The kidneys are more effective in removing aluminum, than in dealing with any other metal.

3. What little aluminum still gets past the kidneys, and stays in the blood stream is dumped into the bone structure, and stays there. The bones can thus without immediate harm take care of a good deal of aluminum, but finally the bone structure begins to approach a saturation point, and can take no more without damage.

4. The Blood/Brain Barrier resists the passage of anything questionable into the domain of brain and spine. Only very little aluminum can pass through it, but some aluminum atoms do. With advancing years this barrier weakens to some degree, particularly if there is not enough lecithin in the body. The body

can synthesize lecithin in three different ways, if it gets enough choline, which is a key part of the lecithin molecule.

5. The neuronal cell wall still bars aluminum from entry into the neuron cells. Some aluminum atoms nonetheless get in, probably by bonding to molecules in which they can hide, and gain entry without being recognized.

6. The nucleus of the neurons is the "Inner Sanctum", the Headquarters of the cell, and therefore, it is highly protected. It is where the DNA resides. The nucleus sends its commands via the messenger RNA which run shuttles between the nucleus and the outer parts of the cell, and also to the mitochondria, which is a chemical factory and power plant of the cell and where protein molecules are built.

Exactly how the aluminum atom might get past these last defenses will not be known for a long time, for the very small quantities make the research very tedious and place extreme demands on the instrumentation as well as on the skill and patience of the experimenter. However, in this case it is permissible to make guesses. Given enough time any reaction which is theoretically possible, will actually happen. A human lifespan of 70 - 80 years is enough time, so here goes: If I were an aluminum atom and wanted to get into the nucleus of a neuron, past defenses 5 and 6, I would watch for a calcium transport and board it. Calcium is needed in every cell so calcium has free access. I, as Aluminum, am only half as big as the calcium, but have 50% more strength, and as an "Ace in the hole", I have a third arm! So I would board the calcium transport, occupy a calcium compartment and use my totally unsuspected resource, the third arm either to hold camouflage or to defend my place against all comers. The calcium shuttle might be chosen from any of the four groups of calcium binding proteins previously mentioned.

I might slip out inconspicuously once inside the last defense, or I might even use my third free arm to kidnap the entire transport, converting it to a free radical by the force in my third arm, and then maneuver the entire unit to combine with literally anything I happened to hit.

NEURONAL DEFENSES AGAINST ALZHEIMER'S DISEASE

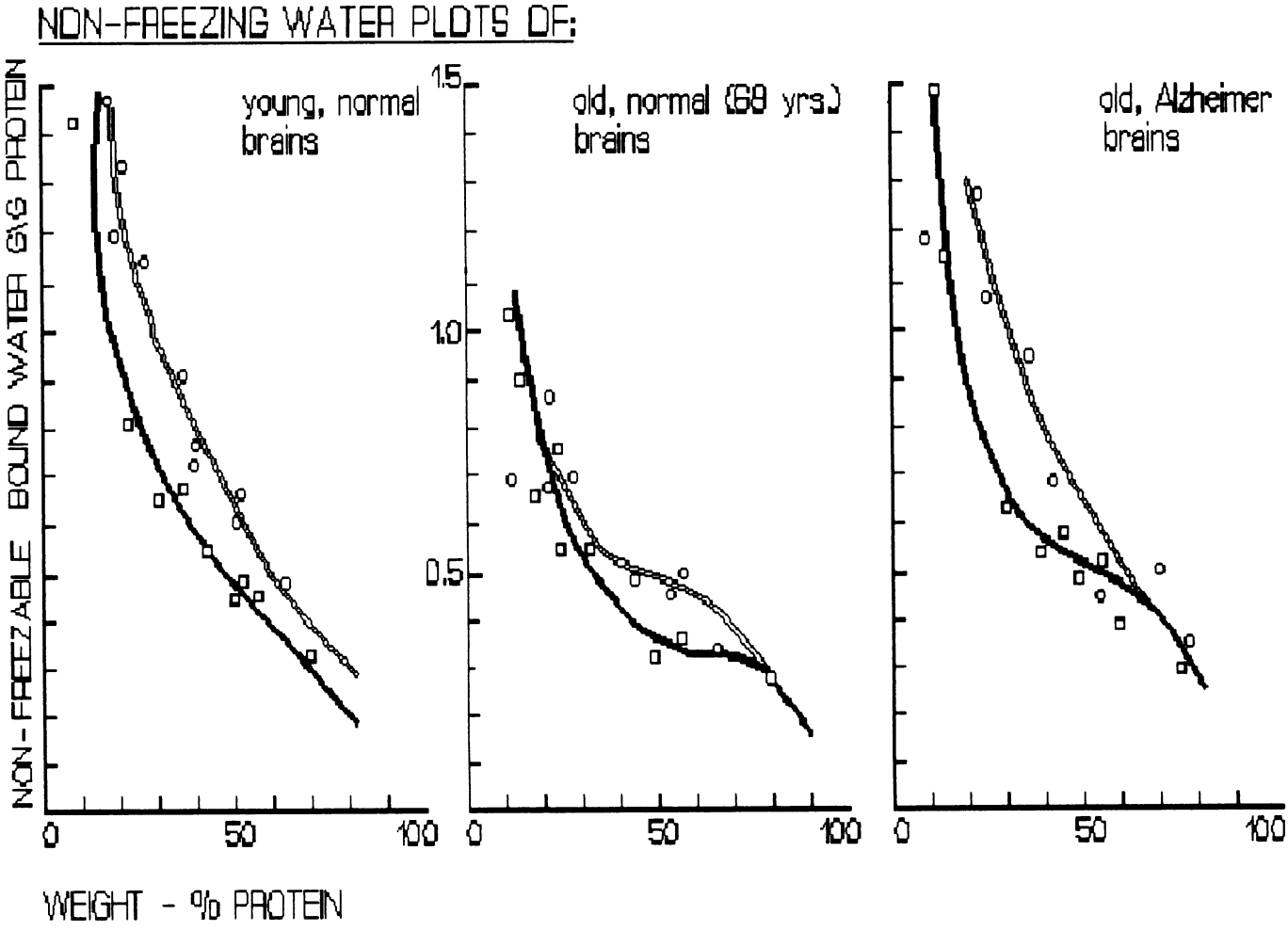
From the University of California, Dr. C. W. Cotman recently reported that in a study of Alzheimer's disease, there was evidence that the borderline zone between the diseased and still healthy cells showed neurons sending out additional neurites in evident compensation for territory lost to the disease. Thus there is a body defense and even though it may not be sufficient, it indicates a potentiality that might be supported and increased.

Manthorpe and Varon have amply demonstrated that neurons can be saved and their functional life prolonged by providing a supply of Nerve Growth Factors and/or Nerve Maintenance Factors derived from other species. Even though this could not stop the displacement of calcium by aluminum, it might permit replacement action which would gain time and perhaps with a reduction in aluminum intake, would have some possibility for controlling the disease.

CROSSLINKAGE STATUS OF ALZHEIMER BRAINS

Figure 20 (reading from left to right) covers two persons 25 and 30 years old; two persons between 66 and 70 who died from non-neural causes, and two persons in the same age bracket who died from AD. The left margin pertains to milligrams (mg) of non-freezing water per mg protein. The bottom margin indicates the percentage of protein present in the gray matter of the brains. Non-freezing water is water which is so protected inside a molecule that it will not freeze even at -90 degrees F. The more dense, rigid and the less "water-loving" a macromolecular aggregate is, the less non-freezing water it can protect in its structure. Therefore, the amount of non-freezing water in the molecules is inversely proportional to the amount of crosslinkage within the molecules.

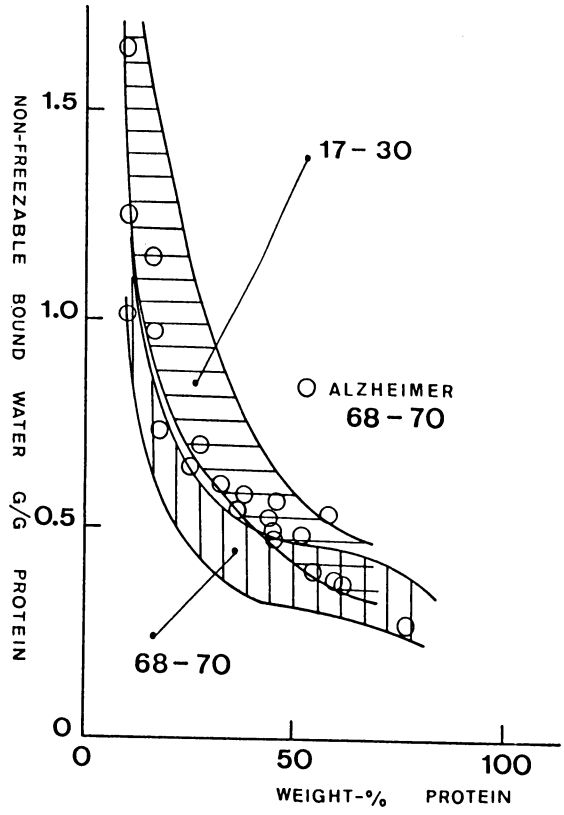
FIGURE 20



Notice that in the young brains, the curve extends high into the upper left corner of the graph. The highest amount plotted is about 1.5 grams of water per 1 gram of protein. In the old normal brains, the uppermost left coordinate shows that there is about 1 gram water per 1 gram of protein. However, the upper left Alzheimer curve in figure 22 is remarkably like the young normal brain. Therefore, the Alzheimer brain has protein which is significantly less crosslinked (younger) than in an old normal brain. This last mentioned protein evidently had accumulated with the onset of AD.

To help in visualizing this, figure 23 groups the three sets of brain on the same graph for comparison. Notice that the Alzheimer plot (designated by open circles) extends into both ranges of young and old normal brains.

FIGURE 21 - THREE SETS OF BRAINS ON SAME GRAPH



These charts indicate that the AD brains contain the same compact structure as the normal men of their same advanced age. So apparently, crosslinking occurred in some degree in both groups of older men. However, the AD patients in addition contained a large quantity of a protein which is clearly younger (less crosslinked) and seemed to belong more to the 25 and 30 year olds. The inference is strong that this last mentioned very recent protein started with the onset of AD.

THEORIES FOR THE CAUSATION OF ALZHEIMER'S DISEASE

There are several theories as to where, and how, AD begins. While these have ties to AD, the big question is: Which of these theories identifies the first cause? My answer is another question: Which of these symptoms could not be caused by any of the other theories' symptoms, but can explain all definitely known facts?

The definitely known facts are: Alzheimer brains contain on the average three times higher aluminum content than comparable non-alzheimer brains and have tangling of the protein fibers within the neurons. The previous charts showed that Alzheimer brains have a considerable amount of protein which is less crosslinked, and therefore more common in young normal brains than older normal brains.

1. AD is not a contagious disease. This is epidemiologically certain even though two slow virus diseases also affect neurons and have symptoms resembling AD.

2. AD is not primarily caused by damage in the cholinergic, adrenergic or any other transmission system, because none of these could cause the tangles, which are a general symptom of AD. The tangles are bound to interfere with any transmission system by restricting space and intracellular transport. In this way, **the tangles** could cause the transmission systems' failure.

3. AD is not an enzyme disease, because the loss of any one or even a few enzymes could not explain the tangles. Since the tangles reduce intracellular transport and limit functions, they indirectly interfere with enzyme production and function.

4. AD is not due to acute poisoning, because then it would become evident at a much earlier age. However, poisoning with a very slowly accumulating chronic poison (such as aluminum) cannot be excluded.

5. AD does not originate in the receptor system because the receptors are location specific. AD would then show a distribution pattern which would be more specific. Instead, AD affects the entire brain, and not just a few locations.

6. AD is not specifically connected with any of the several systems which transmit messages in, from, or to the brain; or serve in energy production or conversion. (such as adenosine tri phosphate, phospho kinase, and cytochrome systems, etc.) This is because none of these show any connection with the tangle formation. Once again, the space and transport difficulties caused by tangling are bound to greatly interfere with these complex and multi-step energetic processes.

What remains when all of the above is excluded?

None of the above theories could be the cause of the tangles, which is a general symptom of AD. Now we must ask, what could be causing these tangles within the cells? AD could be caused by a deficiency in conjunction with an excess of aluminum atoms in the brain. If the deficiency is caused by the aluminum, the aluminum could be the sole cause. The following scenario will give an example of how the deficiency, of what we do not yet know, will eventually cause AD. Among the many complex large molecules required for life is one protein we shall call "X".

This X, or a necessary precursor for it, is missing. The cell nuclei of the neurons (nerve cells) call for it. Since X is missing throughout the body, all of the neurons put in orders for it.

The call is answered and X is manufactured and sent to the nucleus, the management center of the cell. Unfortunately the X protein never makes it because it is distorted by more aluminum atoms than the cell can cope with. (As stated earlier, the presence of aluminum atoms could be caused by an overdose of aluminum in the diet or by a failure of one of the natural defenses against Aluminum, see pg. 63) When the nucleus finds that what it received is useless for its purpose, it repeats its call for X. The mitochondria or other protein synthesizing organelles did not realize that what they delivered was non-functional, so they continue to make the X. They make more and more of it in response to the increasing number of frantic calls from the nucleus. It is in this way that the cell gets filled with a proteinaceous material which forms the tangles by crosslinking. This explains the abnormally high amounts of new protein which are found in Alzheimer brains. Eventually, the nucleus also gets filled with these tangles until it is choked off and the cell dies. In the case of non-dividing cells, this effect is catastrophic.

This process is not in conflict with the failure of membranes or of the blood/brain barrier (natural defense against aluminum #4) caused by certain deficiencies, which Wisniewski has postulated as a cause of AD. This failure could explain the high amounts of aluminum found in Alzheimer brains. We know that more than one of the vitamins causes changes in membrane permeabilities, particularly Vitamins C, A, and B3, choline, as well as some antioxidant composites. Furthermore, there have been some observations that flagrant deficiencies of sodium or potassium or magnesium may increase permeability of membranes.

It might well be a question of multiple deficiencies. The Wisniewski theory could very well co-exist with the theory of crosslinkage. The membrane failure could be caused by crosslinkage of the molecules which make up this membrane. The amount

of crosslinkage of a substance is directly related to its elasticity. The more flexible or elastic the membrane, the less crosslinked it is. When crosslinking occurs, the effect is to make the membrane less elastic, and thereby more brittle. This loss of elasticity is apt to cause failure of the membrane, particularly if there's any motion in and around the membrane.

The effect of crosslinking (tangles) can also occur solely as a function of age (not in conjunction with deficiency) due to the known presence of several crosslinking agents in normal mammalian blood which will in the course of years cause a loss of elasticity in all tissues, which will result in micro-ruptures of membranes and endothelia. In these cases, this effect would be likely to be found in "ordinary" senile dementia than in AD.

It has been amply and conclusively shown that aluminum causes AD symptoms. Aluminum has been found in elevated amounts in most cases of AD, as well as in several other mental illnesses.

Aluminum is deliberately added to public water supplies for "purifying" the water. The reason for this is the very high de-flocculating power of aluminum. When a natural water supply is cloudy or "turbid" it is because it contains some very small particles which just don't settle and are too fine to be filtered. Such particles can be salted out by adding 3,000 ppm (parts per million) of ordinary salt, but that much salt would spoil the taste of the water. Five ppm of aluminum would have the same clarifying power as the 3,000 ppm of salt, and it could not be tasted at all. However, if it de-flocculates our brains, however slowly, it might be a high price to pay for absolute clarity of the drinking water. After age 18, when growth stops, aluminum continues to increase in the body. This accumulation, largely from "average" water supplies will reach dangerous levels by the time a person reaches age 70 - 100 years. Of course, we get aluminum in other ways too, but the water soluble forms are particularly dangerous. No other element accumulates with aging as steadily and at an accelerating rate, as does aluminum.

REDUCING THE PERSONAL RISK OF ALZHEIMER'S DISEASE

Once the neurons are filled with insoluble highly cross-linked and branched tangles, it is too late to do anything. The branched, highly crosslinked proteinaceous fibrils cannot be removed by anything the organism could tolerate. Might it not be possible to include a test for short term memory in every physical examination of a patient past forty? Any sharp decline in a year would then be the signal to institute treatment immediately. Might not this improve our chance to prevent the most serious consequences?

Would it not be advisable to minimize the ingestion of aluminum at the first sign of a sharp decline in short range memory or of fluency of speech, or even before symptoms appear as a protective step?

1. Reduce the unavoidable soluble aluminum intake by choosing other alternatives for any food or drug product which on its label declares an aluminum content. In particular, check the fine print on labels of Baking Powders, Antacids, and Cream substitutes.

2. Water supplies have been found to contain up to 40 times the amount of Al considered safe to drink and are the most obvious targets of concern. We need more information both on the aluminum content of water and on the areas where AD is most frequent.

3. Foods. All foods contain some aluminum. The most recent data are cited by Ganrot, 1986; P. Koivistoinen has data from Finland on Mineral Elements including Al in Finnish foods, 1980. An extensive overview was edited by Campbell in 1975. Cholak, J; Hubbard, D. M. and Story, R. V. (1943) determined Aluminum content of many foods with spectrographic methods.

The data now at hand are too different from each other in methods and the results are too scattered to serve as basis for a diet of acceptable quality and reliably low aluminum content.

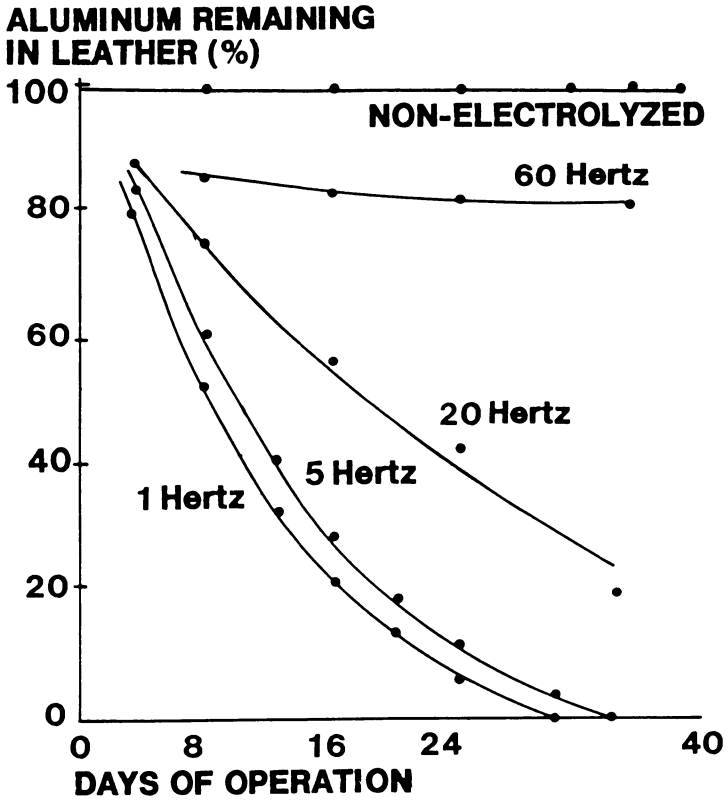
4. An important action of aluminum is to replace calcium atoms. This has been strongly implicated as a major cause of the tangling of fibrils which is basic in Alzheimer's Disease and common in other brain afflictions. Therefore, increasing calcium intake will increase the possibility of free aluminum atoms innocuously connecting with free calcium, and then leaving the body by normal routes. This might make it less likely that the aluminum would cause serious damage. A safe way of doing this would be to drink liberal amounts of skim milk, or of mineral water which contains calcium and magnesium. An excess of calcium can also be detrimental, but calcium deficiency is much more common than calcium excess in humans.

MODEL EXPERIMENT WITH ALUMINUM TANNED LEATHER

The following is still a long way from medical context, yet it might become important and therefore should be mentioned. The Crosslinking properties of Aluminum have lead to its use in making certain highly resistant leathers, for example baseball covers. Inasmuch as these contain Aluminum thoroughly bonded to protein, we used it in preliminary studies of ways to loosen that bond by means that could be tolerated by human tissues.

The following figure is self explanatory. Aluminum tanned leather was washed free from any loose aluminum and was then placed in a very dilute solution of a salt. The top line showed that there was no change in Aluminum content by just standing. However, on applying an extremely weak electrical current in the range from one and a half to nine volts and 1 to 2 millionths of an ampere per square centimeter (6.25 sq. cm. = 1 sq. in.), all of the aluminum could be removed. This removal was very slow in any ordinary alternating current (60 Hz) which switches poles 60 times per minute but removed all Aluminum completely in 30 days with one Hertz current. These currents are so weak that ordinary electrolysis can not be questioned. We believe this is a polarization effect, of the kind which has been used in bone surgery. This experiment is easily reproducible and has been repeated by us many times, with variations.

FIGURE 22 - METAL REMOVAL FROM DEEPLY ALUMINUM TANNED HORSEHIDE BY ELECTROTHERAPEUTIC EXTRACTOR (L.L. YAEGER)



CHAPTER 7

EPOCH FIVE - PROGRESSIVE CROSSLINKAGE

In a lifetime, every theoretically possible combination of matter present in the body will actually occur. Of all such products of random chance, those which are soluble, reactive, or in any way removable will vanish. With the years there will also be formed by random chance, a hard core of substances which cannot be removed by any means at all available in their immediate micro-environment. By far the majority of these products has resulted from repeated random crosslinkages.

In Epoch V, cancer, heart disease, and the brain/neural diseases will be plagues of the past. Persons will live longer than they do now. It is in this context that crosslinkage of large molecules will no longer be an **underlying** cause of death, but **the cause.** The average person will live long enough that even the random crosslinking will reach the point where higher life becomes impossible. As a person grows older, the cytoplasm of his/her cells will become more viscous, (resistant to flow) thereby blocking important substances in transit in the cell. Large masses (amyloid, lipofuscin) will grow faster as they grow in size because they become larger targets for chance additions to hit, and so continue increasing beyond the capacity of repair enzymes to restore. Thus they keep growing by continuing random crosslinkages until eventually some vital part is blocked and the cell dies.

One way to deal with crosslinkages is for the cells to keep dividing, so that new young cells will take the place of the old. However, there are cells, for example the neurons of the brain, which are not presently so renewed. Recent work by Manthorpe, Varon and others has shown that even old neurons can be brought to division by Neuron Maintenance Factors. This gives us some slight hope. For true regeneration it would still be necessary to transcribe the information, the memories, of the dying neuron into its successor.

As was stated earlier, the crosslinked aggregates of substances increase in size by repeated crosslinkings on chance contacts. The longer a person lives, the more his/her cells will be filled with insoluble crosslinked masses. Repair enzymes will clear away some of these, but never all. Slowly, with the years, the crosslinked masses will increase, and the cell dies before the entire cell cytoplasm gels into an inert, rigid mass. It is at that point that higher life will be impossible.

Since crosslinking will be the main cause of involuntary death in Epoch V, it is now appropriate that we delve into the crosslinkage theory in detail. If you do not quite remember the

basic process of crosslinking, it is a good idea to look thoughtfully at the figures on pages 54-57 of the chapter 6.

If you find it difficult to fathom how crosslinking could be the cause of aging, imagine a large office full of workers. Also imagine that every day an evil person manages to sneak in and handcuff two workers together by their wrists. They may still be able to work at this point, with one hand free, but it will be more difficult. Eventually, six months go by and almost everyone in the office has both of their hands cuffed to another person. It has become impossible for the workers to continue with their duties. The company eventually goes "out of business".

FIGURE 23

A very small weight of crosslinkers suffices to change order into chaos in a large hall where many worked together. It does not matter of what material the cuffs are made, nor exactly where they are placed, or which form they have so long as they are strong and attachable at both ends. A similar process is going on inside of our cells. The different "workers" within the cell are being tied together by undesirable bonds. Eventually, vital functions will not be performed and the cell will die.

Another way of illustrating this is to consider crosslinkage between boats. Crosslinks are useful and necessary when one boat tows a string of barges or in the construction of a catamaran which is essentially a product of crosslinking two hulls. But in these cases the crosslinks were not applied randomly but were the result of insight, to meet specific situations. It would not do to crosslink boat hulls randomly at any which point. Just as macromolecules form many intentional and desirable bonds with each other, there are still many random and potentially dangerous bonds which form insoluble aggregates. These aggregates could prevent passage of other important substances within the cell.

BACKGROUND OF CROSSLINKAGE THEORY OF AGING

I've found it difficult to summarize in a few pages that which has been my life's work for the past forty-nine years. Knowing where to start can often be the most difficult choice. However, for continuity's sake, I shall begin at the beginning. My entry into the mysteries of Aging was unconventional. The event which was to influence me throughout life took place when I was 7 years old. At a children's party we played a guessing game. One of us left the room; the others poured out hazelnuts on a large table, and agreed on which nut should be the "target". The child who had gone out could take nuts for himself, one by one, until he touched the "target" nut. Then he was out of the game, and another child was in turn.

When my turn came, most of the nuts were still on the table. I asked myself which nut I would have thought of, and then picked the other nuts one by one until only the target was left. This was of course pure chance, but it gave me the strong feeling that one could act on bold guesses and follow through successfully. Over the years I found that on such guesses I was right about three times out of ten. This was enough for many practical purposes. I had learned (much later) to take my losses and get out quickly when I was wrong, but to stay with it as long as the course of events continued favorable, even if this took a year - or a lifetime.

At that time I lived in Finland, and spent the summers at my parents' summer home in the archipelago. During World War I both Germans and Russians mined those waters. After the war, the chains which held the mines in place corroded, causing the mines to drift. The local fishermen found them easy to disarm. They would throw away the explosives (40 kilos of wet nitrocellulose) and use the mine shells as buoys or as floats for their nets. We boys found the nitrocellulose, and used it for fascinating and spectacular experiments on an uninhabited rock. We never had an accident. This was a substantial factor in awakening my lifelong interest in chemistry.

After working in biochemistry with Nobel Prize winners Hans von Euler and A. I. Virtanen, I came to the United States in 1931 on a post doctorate fellowship from the International Education Board of the Rockefeller Foundation. After a year of protein chemistry with one of the leaders in this field, R. A. Gortner at the U. of Minnesota, I entered industry. In 1936 I found myself as Chief Chemist of Ditto, Inc., now a part of Bell & Howell Co.

My task there was to increase the "life span" of hectograph rolls. These are rolls of a strong cloth or paper backing material approximately 15 feet in length. They are coated with a gelatin gel, which can absorb dye from writings or prints made with a special dye carrying ink, which produces copies when

contacting paper in an office machine.

Before the advent of Xerox, this was a large business operation. Our principal problem was to make the gelatin gels more resistant to heat, humidity, and rough handling. A principal way to go about this was to stiffen and strengthen the material by doing to the large molecule what a carpenter does to wooden beams in construction: making reinforcing cross bridges, beams or linkages to stiffen the structure. I worked 5 years on this problem with five full time assistants. After four years, I realized that the problem of aging in the protein gels in our hectograph rolls was very similar to the aging problems in human brains, glands, and muscles. This realization was forced upon me by fate.

In the Summer of 1939, during vacation time, we had some untrained people in the plant, and somehow a major mistake was made. The manager of the roll plant, Mr. Kennedy, came rushing into the lab, quite excited, and said: "Doc, what shall I do? One of the vacation workers put 100 times too much of the crosslinker into 2,000 gallons of hectograph mass!" I said: "Dump the batch and be quick about it for in a very short time the mass will be like rubber and your men will have to go into the kettle and cut it out with knives." -- "But we've already started making rolls!" -- "Cut the run" I said "Don't ship any of those rolls! But send ten of them up to the lab for observation." The rolls with hundred times too much crosslinking agent quickly became hard and useless, as was expected.

A month later the Vice President of Sales telephoned me: "Doc, one of our biggest customers THE big Insurance Company insists on getting more of the same kind of rolls we shipped them on July 13th. Kennedy says that you had that batch dumped and no more made. Why? The customer says they were the best rolls they ever had." I promised to call him back in 20 minutes. I then pulled out two rolls I had placed in the drawer. One of them was from the accident batch, the other from a normal batch for comparison. A quick examination confirmed that the roll from the accident batch was indeed useless now, the control normal.

I went to see the Vice President with both rolls under my arm. He agreed that I had done the necessary under the circumstances and asked what I proposed to do now. I said, "Make a lab batch duplicating the accident, and find out what happens if we "exercise" the roll with high crosslinker a few hours just as soon as the mass has gelled." We found that rhythmic stretching and relaxation while the crosslinking took place, indeed resulted in a roll with great strength and retained elasticity, but that the process was not practical in production. However, it started a train of thought which was to lead me to interesting experiences.

The experience with the effect of rhythmical stretch-relax cycling finally awakened me to something I should have thought of much earlier. The pulse wave from the heart does this very thing to everything in the body which is connected to this system. This might explain why the arterial system, including the heart and most organs, can function as long as they do. This realization in turn has a powerful bearing on the role of crosslinking agents in the aging process. I stated the crosslinking theory in 1942:

> "The aging of living organisms I believe is due to the occasional formation, by tanning, of bridges between protein molecules, which cannot be broken by the cell enzymes. Such irreparable tanning may be caused by tanning agents foreign to the organism, or formed by unusual biological side-reactions, or it may be due to the formation of a tanning bridge in some particular position in the protein molecule. In either event, the result is that cumulative tanning of body proteins, which we know as old age."

Crosslinking is the reaction in which the smallest input can cause maximal change

If two macromolecules with atomic weights of 500,000 Daltons each, are crosslinked by an agent however small, then the resultant product has a little more than doubled in size, and its properties are changed accordingly. Typically, it has become insoluble in all non-destructive solvents.

Any substance is a potential crosslinker if it has at least two "hooks" which can react with any site on each of two macromolecules. These are then tied together with the strongest type of bond known (co-valent).

The basic theory of crossslinking had been developed by the great German Chemist H. Staudinger in over a hundred publications. Staudinger and Heuer showed in 1934 that 0.01% of such a crosslinking agent suffices to effect such insolubilization regardless of solvent. It is not easy to define 0.01% of any particular unknown organic agent when many of these participate. This is like the proverbial needle lost in a haystack (or in a bale of rice).

In one particular instance we can recognize the agent with ease and in some detail. Aluminum is a powerful crosslinker, present almost everywhere in nature. In this case we can burn away the "Haystack" and look for our "needle", the aluminum, in the ashes.

CROSSLINKING STUDIES 1945 - 1962

During the war years I was Chemical Director of the Quaker Chemical Products Corp. and was mainly occupied by problems of metal machining compounds and other applications of surface chemistry. In 1944 I opened a consulting office in Chicago, and about 1946 had enough air under my wings to review crosslinking chemistry. I approached the Dept of Health and Welfare, and also several Insurance companies but found absolutely no sympathy, nor financial assistance, from either group. I found it more practical to go it alone.

During those years we found many strong indications of the significant place of crosslinking in the aging process: The life expectancy curve of humans could be matched by a crosslinkage chart in remarkable detail; the solubility characteristics of amyloid and of lipofuscin (examples of insoluble aggregates) could be simulated by crosslinking systems. Insolubility of proteins in aged animals matched exactly the corresponding data for animals receiving X-ray radiation simulating senility. These and several more observations taken as a whole were convincing to me, but they were not yet conclusive evidence. This had to wait for the development of more sophisticated and precise methods.

In 1951, "Advances in Protein Chemistry" published an article I had written at their request on Crosslinkages in Protein Chemistry. This was a useful task which gave me an update and added contacts. My 1951 protein survey had brought out at least two patents where aluminum was used to crosslink protein, and of course I knew Otins and Alexas paper on aluminum tanning of leather from 1938.

In 1953, I filed the charter for Bjorksten Research Foundation as a non-profit organization. This step enabled me to segregate this activity from the technical work which financed it. However, there was absolutely no encouragement from anywhere, except from the Office of Air Research, which gave us an award of $5,000/year for 3 years. I pointed out the savings they could make in pilot training if we prolonged the active life of pilots by even a few days. That was the only health oriented support we ever received from a government source.

I was scheduled to give a very brief talk on gelatin crosslinkages at the Gerontological Society meeting in Baltimore in 1955. I decided to bring up aluminum in the discussion and see if anything turned up.

At the meeting I found that I was scheduled for the first morning speech after a late evening occasion the day before. Not so bad, there would be a general discussion later in the day, and I might make my point then.

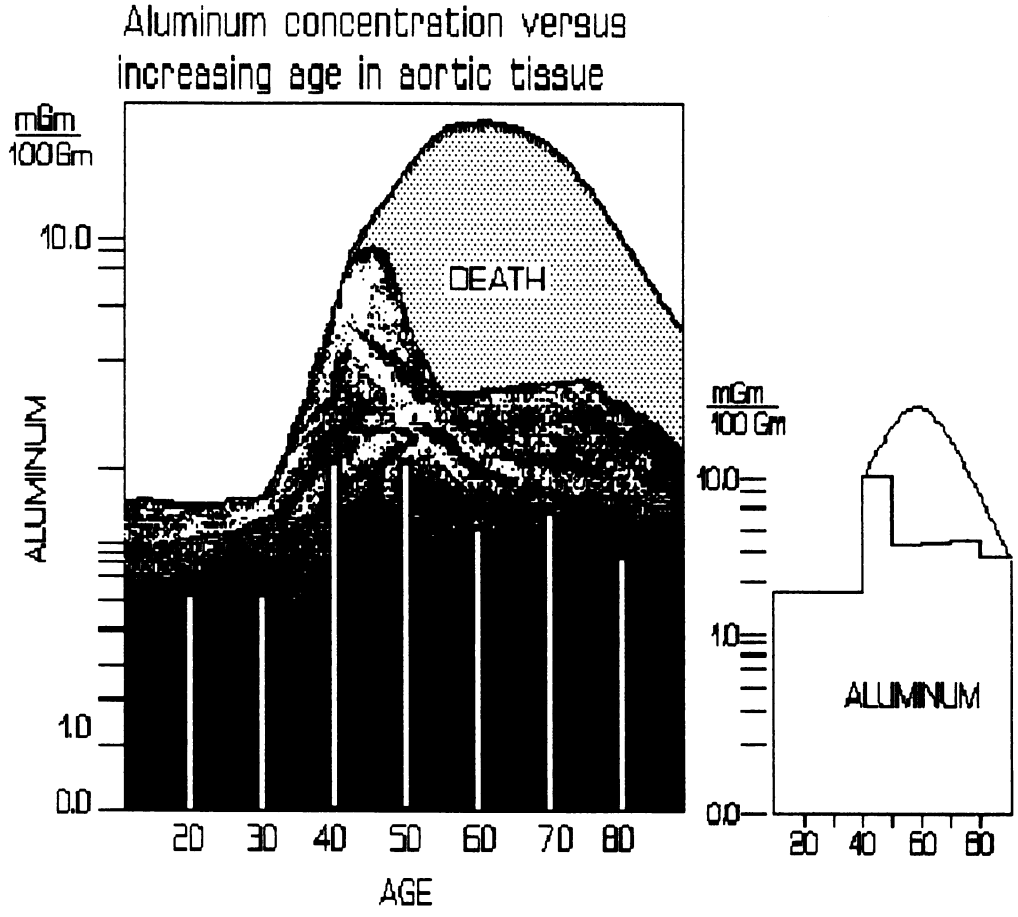
The meeting started punctually. There were 6 persons in the audience and none of them seemed particularly awake. At the coffee break I found the man who was to preside at the discussion session - he was the head of a large, industrially active non-profit Foundation. I told him I had only 6 persons in the early morning audience, could he give me 3 minutes to make a point at the discussion session? He looked away and made an evasive reply. I could sense that he did not intend to grant my request. Having nothing to loose, I told him: "If I do not get these 3 minutes I will make a scene and publicly accuse you of suppressing communications from your competitors." He was very angry but I knew that as an intelligent man he would see that 3 minutes to me would be less troublesome than the alternative. At the discussion session, after a few questions had been answered, the chairman took out his watch, looked at it ostentatiously and said, Dr. Bjorksten has requested 3 minutes to make a statement." I made it in 2 minutes, 52 seconds with no effect then apparent.

However, somewhat later Dr. H. H. Zinsser, Jr., professor of Urology at Columbia University, came to me. We had a long and stimulating discussion which marked the start of seven years of fruitful collaboration. In 1962 we published a joint paper: Dr. Zinsser as the Senior Medical Author, I as the Senior Chemical Author, seven of his associates and one of mine. This paper will be reviewed below in the context of Aluminum.

In our experiment, we measured the quantities of aluminum in the aortas of 84 persons (necropsy material). The results were grouped by age. The first age group was 10 - 40 years, then the successive groups followed at ten year intervals. The method was ashing the aortas in an aluminum free graphite furnace, and emission spectroscopy. Figure 24 shows the quantity of aluminum in the aortas of the different age groups.

This diagram is based on spectrographic determination which H. H. Zinsser, J. Bjorksten et al made on aortas from 84 persons, divided into groups, of which the first included 14 aortas in the age range 10-40 years, followed by 13 aortas in the age range 41-50; 22 aortas at 51-60; 15 at 61-70; and 7 at 81-90. A.C. Alfrey found that when aluminum exposure is exceptional, excess aluminum is dumped into the bone structure. When this approaches a saturation point, the heart and brain simultaneously show a rapid gain in aluminum content. For this reason we can be certain that the aluminum content of the aorta also reflects what is taking place in the heart and brian. The drop in the aluminum content after fifty thus indicates that those persons who at fifty reached a critical level of aluminum, did not survive the following ten year period.

FIGURE 24 - ALUMINUM CONCENTRATION IN AORTIC TISSUE FOR VARIOUS AGE GROUPS



Since the aorta does not function in isolation, but in fact in the same body system, the rising level of accumulation in the aorta has a close relationship with rising levels in the brain and heart. The graph shows a peak at 40 - 50 years of age at 2.7 times the level of the preceding group, then a drop and leveling off. This seems to indicate that those who already reached this aluminum peak at middle age did not survive the following ten year period. This interpretation best explains the known facts.

In this 1962 paper we also included results of studies of the chelation of aluminum as a possible means for removal (For more information on chelation, see section II). On the basis of this study, Dr. Zinsser, as well as I, approached the National Institutes of Health regarding a project for further study of aluminum in aging. In the total absence of any encouragement or possibility of financial support at the time, we directed efforts to other aspects. The studies of aluminum crosslinkages and aluminum in aging were not then considered worth supporting.

A change in this attitude was brought about by the excellent pioneering work of D. R. Crapper-McLachlan in Toronto. He showed that a single milligram of soluble aluminum salt injected into a cavity of the brain of a cat caused a whole sequence of a progressive disease of the brain, ending with death in about three months. Allen Alfrey's proof that aluminum in the water supply caused the group insanity and death of patients treated with the artificial kidney, helped direct attention to aluminum in the aging process as well.

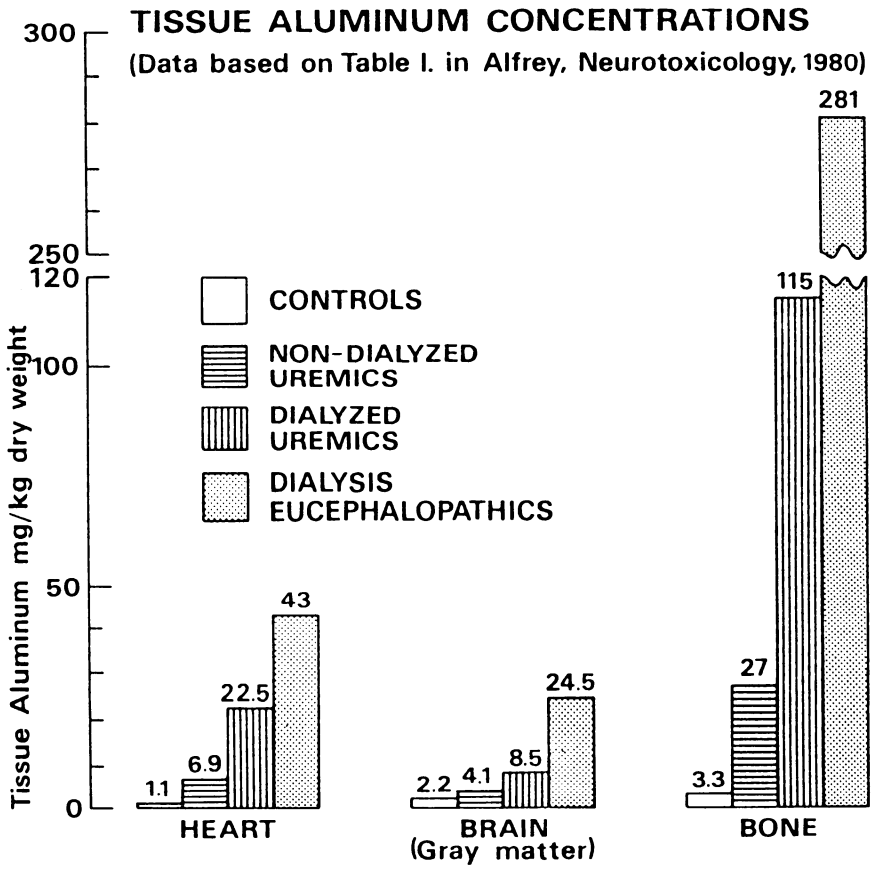
DIALYSIS SYNDROME

In the 1970's, kidney dialysis patients were plagued by the symptoms of Alzheimer's Disease. Within months, the patients went insane and eventually died. Originally, it was thought that the cause of this brain damage was a virus which was spread as a result of the dialysis process. However, A. C. Alfrey showed that these patients' condition was caused by the aluminum content of the water used in the artificial kidney. The blood of a dialysis patient is typically washed with 50 times the amount of water that a normal person would drink. Thus, since the corresponding quantity of aluminum causes insanity and death in one year, it might be feared that persons with normal kidneys will lose their minds and their lives somewhere between 90 and 110 years. This indeed appears to be happening.

The work of Alfrey (see Figure 25) shows that after the protective barriers of the intestinal wall and kidneys have been avoided, (as is the case with dialysis patients), the aluminum will first be absorbed into the bone structure. Once the bones become saturated with aluminum and are unable to safely contain any more, then aluminum content will rapidly increase in both the brain and heart at the same time.

Alfrey's comparison between rising aluminum levels in the brain and heart corroborated our results with the aortas. There could now be no doubt that the Zinsser, Bjorksten, et al. 1962 data on aluminum levels in the aorta were representative of aluminum levels in the heart and brain. As stated before, these organs operate in the same body system (aorta is almost a part of the heart). It would be strange if there were an excessive amount of aluminum in the aorta, and not also in the brain and heart.

FIGURE 25 - ALUMINUM ACCUMULATIONS IN BONES, HEART AND BRAIN (Alfrey)



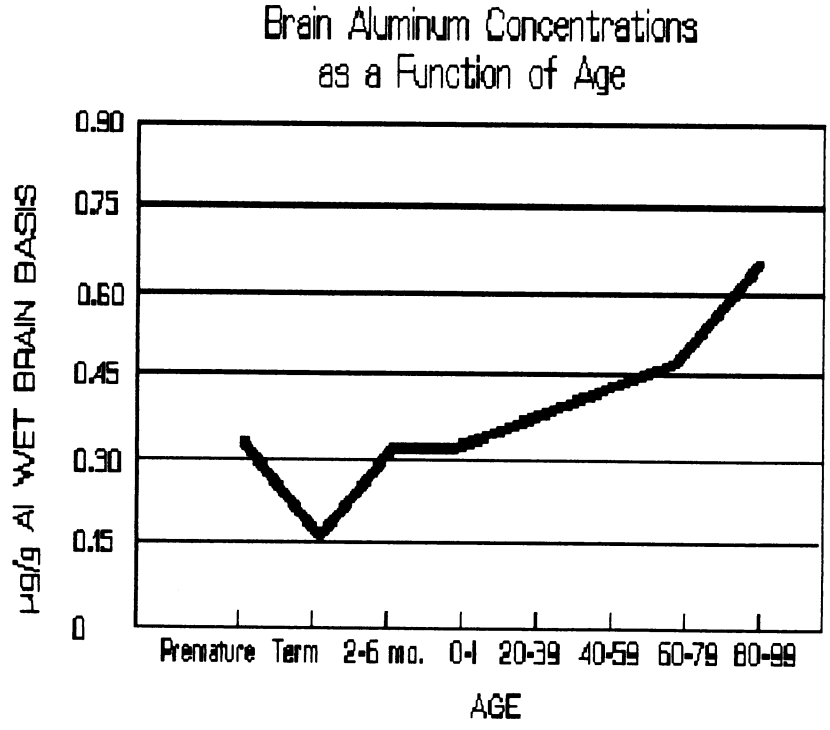
This "dialysis insanity" is no longer a threat, for dialysis water is specially treated to remove aluminum. However, the tap water from whatever source contains at least some aluminum, quite commonly about 100 parts per million (ppm) and sometimes up to 400 ppm. From this we can figure that many of us at the age of about 90 will have accumulated in our brains about the same quantity of aluminum as the unfortunate early dialysis patients got in about 6 to 10 months. Figure 25 confirms that this hazard is very real, and that a large part of the mental decline at high age is a likely result of the still continued use of aluminum in our water supplies. Would senility be abolished and health last longer if the aluminum limitations now applied to dialysis water were extended to all water used for human consumption?

This question is justified by known facts and should be answered.

The steady increase of aluminum in the brain with age, illustrated in figure 26, confirms that aluminum from drinking and cooking water is indeed an important cause of the loss of

mental sharpness which is now too readily accepted as "normal for the old".

FIGURE 26 - BRAIN ALUMINUM CONCENTRATIONS AS A FUNCTION OF AGE
(after Markesbery, Ehmann et al)



Later analyses of normal brains of various age groups confirmed this hypothesis of aluminum accumulation. Figure 26 shows Markesbery's and Ehmann's et al data concerning the amount of aluminum concentration as a function of age stemming from the fetus and extending into the late 90's. Notice that aluminum accumulation in the brain of a prenatal infant is almost the same amount of that found in the young adult. This aluminum was of course supplied by the mother. The amount of aluminum drops rapidly upon birth, only to have an almost equal rise of aluminum content by the time the infant reaches 6 months of age.

This information which has cost hundreds of patients' lives should not be forgotten. The addition of aluminum in any form to drinking water should be reconsidered. The difference is only one degree between the victims of dialysis (artificial kidney) brain sickness, and the senile dementia which cripples most people over 90 and which may prevent anyone from reaching say 130. The more aluminum in soluble form the public is made to drink or eat, the more persons will at an advanced age become

mental cripples.

CROSSLINKING AS A FUNCTION OF TIME

Even though some crosslinking reactions are very rapid, the majority are slow and therefore apt to be missed in a fast audit. They have been with us as long as life, often as an underlying base for other, more spectacular effects.

The same is true of the other causes of death which dominated earlier epochs. In the Stone Age, there's no doubt that the microorganisms of contagion were around and may have infected someone. However, if someone did fall ill with the plague, for instance, he wouldn't live long enough to die from it. In his weakened condition, he would be consumed by carnivorous animals first. By the same token, crosslinking is a major cause of the weakening of a person's defenses against disease as he/she gets older. However, in his/her weakened condition, he/she will probably die of something else, like heart disease, cancer, etc.

The progressive crosslinking is far more than a negligible underlying cause of the decline in resistance to all challenges, cancer and heart disease not excepted. This crosslinkage reduces the actual usable space within any non-dividing cell and hinders intracellular transport. In spite of various defense and repair mechanisms, the number of crosslinked big molecules keeps on increasing from year to year, slowing transport within each cell. This finally leads to the thickening of all liquids within the cell until nothing can move in it. This will be the fatal problem of those living in Epoch V and of some of those on the way to it.

Though crosslinkage is a frequent contributing cause of death, it is not usually so recognized. Not until the problems of Epoch IV have been solved, and the solutions applied, is crosslinkage apt to be generally recognized as the major cause of involuntary death.

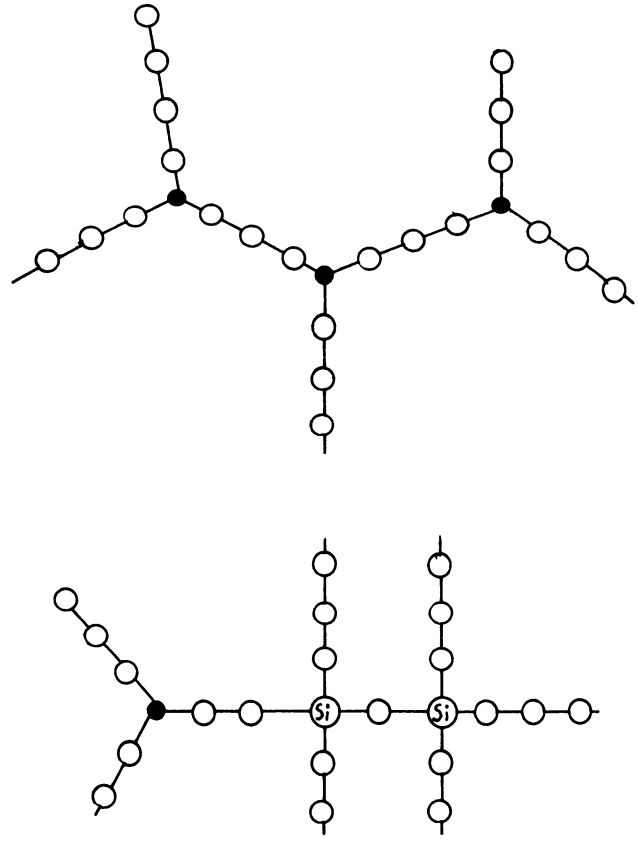
The gerogenic (caused by aging) aggregates known as "Amyloid", "Age Pigment", "Lipofuscin", etc. have no fixed composition, but are masses formed by repeated crosslinking of whatever large molecules happened to be close by.

CLINICAL EFFECTS OF CROSSLINKING

The clinical effects of crosslinking are far more hidden and subtle than those of any other factor. We have already discussed aluminum - a powerful crosslinking agent. It is difficult to prove exactly how much of its harmful properties are due to crosslinking, to its function as a de-flocculent (causing extremely small suspended particles to instantly loose the electric

charges that keep them from sinking, so that they quickly settle to the bottom), or to its blocking of active receptor sites, which excludes those elements which should normally react there. My guess is that much more than half of the harmful actions of aluminum are due to crosslinking. Those aluminum linkages which do occur have a peculiar malignant twist. This is due to the distorting action of aluminum's tri-valent linking (bonding forces) entering structures where the "backbones" are mainly composed of bi-valent (two binding forces) building blocks. The polyvalent atoms (those which have more than three bonding forces) are usually found in side chains. The first of the two figures in Figure 27 shows the tri-valent (3-fold binding) aluminum (represented as a closed black circle) distorting several bi-valent chains. The second figure shows an Aluminum/ Silicon (Si) system. Silicon is a polyvalent atom usually found in side chains. It is not as reactive as Aluminum.

FIGURE 27 - ALUMINUM DISTORTED CHAIN AND ALUMINUM - SILICON DISTORTED CHAIN



Calcium displaced by silicon

REMOVAL OF RANDOMLY CROSSLINKED INERT AGGREGATES

The Enzyme Approach

In 1966 I approached twelve pharmaceutical or nutrition-oriented companies with the following proposition: I proposed a joint effort to develop enzymes capable of penetrating aggregates formed in aging (amyloid, lipofuscin and particularly their precursors), with a view of developing or discovering products of geriatric merit.

At this point I wish to make it quite clear that we are not seeking to break crosslinkages individually. Since evidently there are a very large number of different crosslinkages it would not be practical even to try to attack them individually. Our approach therefore is to attack the already crosslinked aggregates and break them up into fragments that can be removed. Thus, our objective can be defined as an enzyme of the lowest possible molecular dimensions and the broadest possible action on the principal protein linkages.

The initial effort was to be directed to the field of using bacterial proteases, (bacteria capable of splitting protein molecules) but with the willingness to switch the path of inquiry whenever this seemed necessary.

For this purpose I proposed that a research corporation be formed on the following basis: Each participant commits a sum of $10,000.- yearly for each of the next five years. I would contribute a small laboratory building in Fitchburg - Madison, Wisconsin with equipment worth about $50,000. Ownership would be in proportion to the contributions stated. I would be available for this research at the outset, but asked for no employment contract. If the majority of the shareholders wanted to change anything in the arrangements, including my connection with it, nothing would stand in their way.

Several firms wrote of their active interest in this proposition. Two large pharmaceutical firms stated that they would not be interested in being one of many, but that they would only be interested in sole participation. They each agreed to pay a proportionately larger annual payment for the next five years.

An agreement resulted with one of the major pharmaceutical firms referred to hereafter, at their request, as "The Company". This contract was based on a five year program with a budget of $50,000 for the first year, with possible increases in the following years if progress warranted this.

The idea we would follow was to find microbes capable of breaking down very highly crosslinked protein by taking some very resistant, highly crosslinked substances, and offering it to

mixed bacteria (for example of rich garden soil) as their only source of nutrition. Most of the organisms would die or change into resistance "sleeping" stages, but a few of them might survive. These survivors must have the ability of breaking down highly resistant substances.

These surviving and thriving substances were then studied further, and those which not only had the enzymes, but also were convenient to culture and safe to handle, were used for further studies.

The work was envisaged as follows:

1. Preparation of insoluble material accumulated in old human brains by extraction with an array of non-destructive solvents.

2. A broad search for microbes which can use this insoluble brain fraction as their only nitrogen source.

3. The search for micro-organisms found capable of digesting insoluble brain substances, and defining their efficiency and their suitability for industrial production.

4. Exploring the properties of the most suitable enzymes and making test quantities.

At that point The Company would presumably take over the improvements of the production process and adapt it to commercial practice.

Steps 1-3 were carried out on a broad scale and with good success. From varied sources we isolated over two hundred cultures of organisms capable of subsisting on insoluble brain substance. Later we found that gelatin highly crosslinked with parabenzoquinone could be used instead of the brain preparation for screening the micro-organisms, and that these were lined in the same order of efficiency whether we tested them with brain or with the gelatin-quinone preparation. The active bacterial colonies were surrounded by a clear "halo", a circle within which the grey brain substance had been dissolved so that the area surrounding the colony was transparent. The width of these "halos" gave us a measure of how well the active enzyme could penetrate insoluble protein, and this in turn gave us an indication of the molecular size of the enzyme.

We spent three years on this phase of the study and screened hundreds of cultures. From the speed of the enzyme's penetration of the gel, we calculated a molecular weight of about 3,700. This is less than a third of the smallest enzyme heretofore known. The smaller the enzyme, the better it can penetrate dense, highly crosslinked structures.

The results of 4 years work were among others:

1. Isolation of numerous organisms capable of digesting brain insolubles. The selection of seven as the most promising in overall properties including ease of handling, freedom from hazards, enzymic efficiency in solubilizing some crosslinked masses and speed of penetration into such masses.

2. Preparation of these organisms in laboratory fermenters. Selecting optimal conditions of growth and culture media.

3. Preliminary toxicity tests.

4. Study of the effects of various metal ions and other factors in stabilizing or modifying the properties of the enzyme action. These can make very big differences in the behavior and stability of the enzyme.

Work that remained to be done when this work was tabled was essentially:

1. Isolation of the lowest molecular fraction (part) of our enzyme and its identification. This lowest fraction is seen only as a peak on a curve or a spot on a chromatogram. We should determine whether this particular fraction is a product made by our microbe directly, or whether it has been split off from a larger molecule.

2. If it is split off, will it re-combine with the molecule to form larger enzyme molecules, and if so where is the equilibrium point?

3. When this is clarified beyond the data published, the pharmaceutical base would be ready for an effort to prepare larger quantities of this enzyme for technical purification and clinical tests.

The Company was pleased with our headway. The appropriation for this research was increased in each successive year until 1970. In that year a spokesman of the Food and Drug Administration made the statement that 70% of the output of the pharmaceutical industry is worthless. This resulted in an understandable excitement in the pharmaceutical industry as a whole, particularly of the principal large pharmaceutical firms. The Company then concentrated its research money on short-term work, and as much as possible to clinical studies to refute the accusations of selling worthless drugs. The work we were doing was a long range project and as such had to step aside.

Relations with The Company remained cordial. All preparations and much valuable equipment were donated to the Bjorksten

Research Foundation. In order to tie up "loose ends" and complete work already in progress, I spent $100,000 of personal funds on additional publications defining properties and characteristics of some organisms, some enzymes, and some stabilizing characteristics.

Current Status of Low Molecular Enzyme

Having published our results, with the approval of the Company, I stopped further spending on this.

I had by no means given up hope for the "Micro enzyme approach", but felt that our limited resources should be reserved for research, and not for either clinical studies or pilot plant work and certainly not for promoting the pharmaceutical industry. In publishing the results I had done my share, and could now turn to the basic exploration of the ORD (Oxido-Reductive Depolymerization) process. I began to explore its different advantages and shortcomings, as will be further explained below, and it's effect on aluminum-induced crosslinked masses.

Still a few words about the current status of the low molecular enzyme. The Worthington Biochemicals expressed interest in making it available so we gave them our laboratory procedure. They listed the enzyme in their catalog at the time at a price too high for any feasible commercial production to stem from it. Later Micropore acquired Worthington Biochemicals. No sales had developed so the product was dropped. One sample we received, said to be of Micropore's production, contained a substantial amount of a much higher molecular weight than the enzyme we had isolated.

A large Swedish concern gave the enzyme serious consideration as a possible means for removing blood clots (thrombs). We were told that if it were to be offered at the same price as streptokinase and with the required research done, they would probably be interested.

A substantial pharmaceutical firm in Japan has done considerable work and has produced this enzyme with far better stability than we had achieved.

THE LEGACY OF TWO DEAD RATS

(A probe for means to dissolve amyloid, lipofuscin, and other "insolubles" of Aging.)

I soon directed efforts to another experiment designed with the same objective: finding a substance or substances capable of breaking up gerogenic (formed in aging) masses. My idea was this: Feed a pregnant rat a huge amount of radioactive nutrient a few days before and continuing until a few days after it gave birth to a litter. Using the radioactivity to track the paths of the nutrient in the body, we would then be able to tell where and how the radiation got stuck. Our friends at the radiation research center said this was futile for in time all of the radiation would be excreted. I wasn't so certain of that, for there was a paper by Joseph Still who showed that even after 180 days some radioactivity remained in the system.

But this was only the beginning of the plan. If we continued the test long enough, most of the radioactivity should get out somehow, but some might get stuck. Somewhat like how some balls in a pin ball machine can get stuck in the holes. So, in a couple of years, we might have full-grown animals which have had radioactivity trapped in their bodies from birth. Those radioactive molecules might then be molecules which were made immobile by the aging process. In other words, the radioactive molecules were "built-in" to the system by the aging process through crosslinking. In this way we might come to grips with aging itself.

But this is still only the first third of the plan. We would now have some test animals which held captive in their bodies some radioactivity locked in by the aging process itself. We followed this plan with two litters. The radioactivity was tritium which we gave in two different forms.

When this was finally achieved, we had in our hands an animal containing easily measurable radioactive tritium which had stayed in it, immobile, for a lifetime. If through our experimentation we administered a true anti-aging medicine, we should know if it was effective as soon as the next time the animal urinated; simply by looking for a sudden burst of radioactivity in the urine. If the medicine could unlock the captive radioactivity the animal had received at birth and had been unable to get rid of during the better part of its life, we could then say with confidence that we had now found a powerful anti-aging medication which could break up insoluble crosslinked aggregates, such as "amyloid", "lipofuscin", etc. This medication would be well worth further, more detailed tests to find out all about possible side effects and how best to use it.

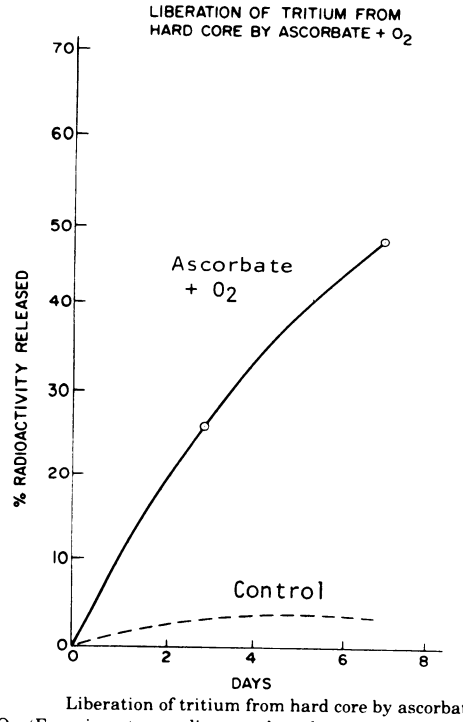
We never found this while the animals were still alive. One

of the rats died after 809 days from pneumonia, the second died after 609 days. Though that part of the experiment was negative, it was useful because it quickly told us that many of the possibilities before us were not worth pursuing. This saved us a great deal of time which would otherwise have been wasted in checking out these possibilities in much slower ways.

In both groups of these rats, most of the remaining radioactivity was concentrated in only five amino acids out of some 20 originally present. The amino acids where the radioactivity had been locked in all were characterized by a side chain, which would lend itself to easy crosslinking. This tendency toward crosslinking is why the radioactive molecules were "built-in" by the aging process. That is why a medicine which could break or excise (cut out) these crosslinkages would be an effective anti-aging medication.

When the two original mother rats, and their two radioactive litters had all died, we dried and pulverized their muscles, which contained bound radioactivity. We continued to use this muscle preparation to test for release of radioactivity by other possible agents. It was in this manner that we achieved our only positive result. The radioactivity was unlocked by the so called ORD reaction. Figure 28 shows this result.

FIGURE 28 - POSITIVE RESULT WITH ORD REACTION



Liberation of tritium from hard core by ascorbate + O_2. (Experiment on radio-tagged mother rat.)

In further exploring this lead, it will be necessary to proceed with great caution because the reaction uses free hydroxy-radicals which also have the power of breaking down all other molecules too. However, the presently popular emphasis on the negative aspects of free radicals has been overdone and it may be time to recall that hundreds of necessary reactions in our bodies depend on free radicals, and are essential to life as we know it. Free radicals are fragments of molecules which have free, unsatisfied bonding capacity. They have two predominant reactions: Fission - the breaking up of molecules into parts, and Crosslinking. Free radicals might prove useful because they can be diluted so that the destroyed normal tissues can be rebuilt, while such age-made things as the crosslinked giant molecules would not be formed again nearly as fast, if at all.

There are other clues which we have not been in a position to pursue as yet. We had found considerable radioactivity in the RNA of our rats. RNA is known to carry messages back and forth in the cell, and is thus most likely to contact crosslinking agents than is the well shielded DNA. A lecithin-like substance carrying a part of the original radioactivity present from birth also invites additional research. It could harbor surprises. I should have liked to explore it further, but decided against splitting efforts.

In 1977, I received the Modern Pioneer award of the American Institute of Chemists for our studies, particularly of crosslinkage effects in aging.

CROSSLINKAGES - THE SECOND EFFORT

An old Finnish saying is - in free translation: "Immediate victory is for the dogs!". Another word of wisdom of the same family: "The SECOND effort counts!" Long before the crosslinkage theory of aging was formulated in 1942, its foundation had been laid by two giants. John H. Northrop and J. Loeb showed in 1917 that the temperature coefficient of longevity is the same as that for chemical reactions. Hermann Staudinger, with patience and precision, gave us the quantitative foundation to build on. In 1933, he gave us the ways of measuring the insolubilizing effect of crosslinkages. This, among other accomplishments, earned him the Nobel Prize some 20 years later.

At this point it was shown, at least to my satisfaction, that crosslinking increases with age throughout life and could explain the process of aging. However, the positive identification and exact measurements had to await improved instrumentation, mathematical analysis and methods. We could then use these to determine, in exact terms, the number and positions of crosslinks, even when these were few and far between. That technology is now available and has made the second effort possible.

The ropes that tie a ship to a pier are a very small part of the ship's weight; but we can count the number of ropes and see how they are attached. The chemical composition of the rope makes no difference when we know its strength and its flexibility, and the points of attachment. When these are known, the crosslink is known well enough for practical purposes, even if we should have to wait a few generations for the detailed descriptions of the chemical compositions of each individual crosslink.

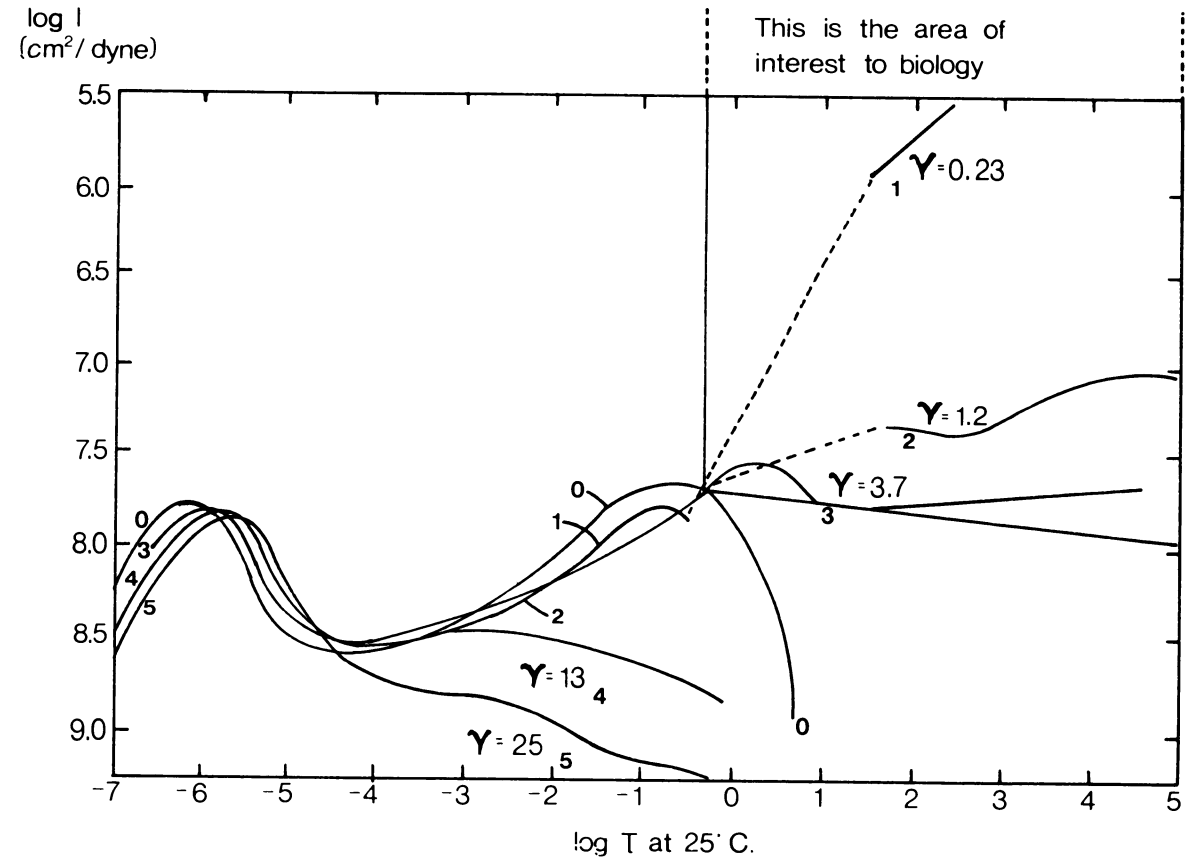
Determining the age of subject as a function of its degree of crosslinkage

Once a problem is defined and understood, it is often half solved. This could be true of the crosslinking problem in its relation to human aging. A major need during our research was a good method or test to determine the progress of aging, and to increase knowledge of its various pathways.

One of the best tests of modern science really stems from an ancient test said to have been used by slave traders to determine the true age of a slave. It is the so called "Skin fold test", a simple test (used also as a quick test among the many used by physicians) to judge a persons condition. It is simple. The person being tested places his hand flat on a table. The person testing pinches a fold of skin on the back of the hand with his thumb and forefinger, and lets go. In a young person, the skin snaps right back almost instantly. For an older person it comes back slowly, and the time it takes to come back is some measure of the age and condition of the person tested.

When the automobile tire industry had to improve the resistance of the tires to crosslinking by the ozone in some air, they used this skin fold test as the base for a very beautiful (in the engineers' eyes) machine called a Transducer. The Transducer measures elastic retardation much in the same manner as the skin fold test in humans, but in a mechanized way and much more accurately. Based on measurements with this machine, they created the rubber tires which resist crosslinking by ozone, and give us a tire mileage never even dreamt of thirty years ago. We can now use variants of this machine to probe crosslinkages in muscles and tendons, and even some small changes in thick liquids. Most of these measurements were made with rubbers and rubbery plastics. But in one paper two of the four authors were prominent academic scientists and it may be assumed that we owe to them that this study was extended beyond the range of solid elastomers of the rubber industry to include also crosslinkage measurements in liquid ranges of high interest to gerontology. Figure 29 is shown on the next page.

FIGURE 29 - TRANSDUCER (Valentine RH, Ferry JD, Homma T, Ninomiya K: J. Polymer Science, A-2, 6:479-492.)



The curves show, in effect, the property measured by the skin fold test, expressed as the crosslinkage coefficient "Theta" (looks somewhat like a cross between a Y and a T). Usually they stop their tests at the point where everything changes from a solid rubber into a liquid, but in this one case they continued their curve into the range of life, shown in the square to the right. The numerical values refer to the average number of crosslinkages per one giant molecule crosslinked to another. When this is 4, (at the lower edge of the square) everything gels - if it is blood, or the liquid inside a cell, nothing can move and no higher life is possible. We will not be far wrong in assuming that the top curve with Theta 0.23 resembles the fluids of a young person, the second curve, with Theta 1.2 a middle aged person, and the bottom curve with Theta 3.7 a person at the brink of death.

Other instruments can detect the presence of floating aggregates in a liquid medium, before these have reached a size permitting us to detect them optically and still in a biologic liquid.

The mathematics for analyzing these data are now available. The most striking feature of the curves above in the square of possible life is the wide spacing of the three curves. This means that the method is extremely sensitive. There is space between the curves to place accurately a great number of intermediate values.

Mathematical tools for determining crosslinkage status and geometry have been developed by Kan, Ferry and Fetters (1980). The work of Miller and Macosko (1976) is also important in this connection.

NON-FREEZING WATER

Another sophisticated method for determination of crosslinkage status of high polymers depends on the determination of non-freezing water. Water will not freeze even at -50 degrees C if it is very closely sheltered inside of giant molecules.

The more dense, rigid and the less "water-loving" a macromolecular aggregate is, the less non-freezing water it can hide and protect in its structure. Since crosslinking results in exactly these changes in a macromolecular aggregate, it follows that when we know the amount of non-freezing water in an aggregate, we can calculate the extent of crosslinkage. A measurement of the average crosslinkage density can be made using a recording microcalorimeter. This instrument draws a continuous record of the temperature changes in response to a constant input of heat. Since 80 times more heat is needed to melt ice than to heat the same weight of water 1 degree, the instrument will show very clearly and sensitively when freezing and thawing takes place. This is translated to indicate crosslinkage density.

Using this instrumentation, we determined the approximate age of the various proteins in the brains from the frontal lobe of (2 of each) a normal young person, a normal old person, and an Alzheimer brain. The amount of non-freezable water from the different brains is shown in Figure 30.

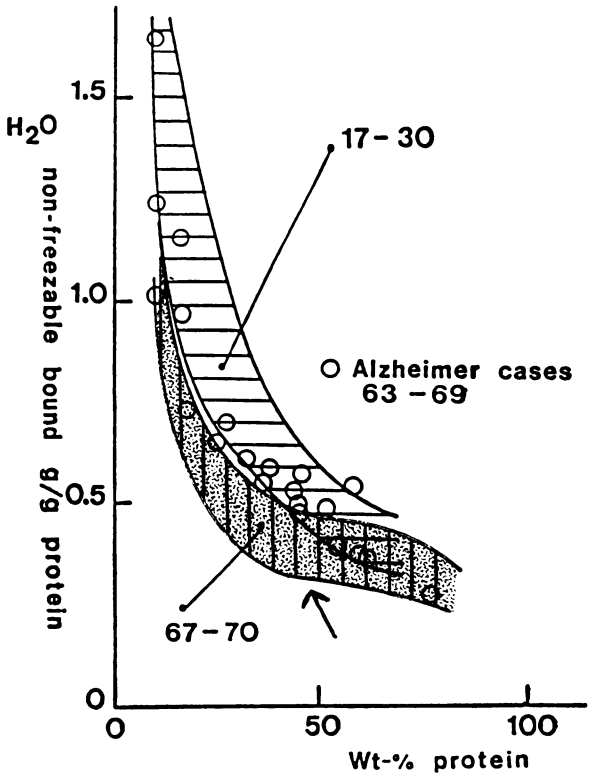
These curves appear to support the following conclusion. Old persons (67-70) in normal health have much more crosslinkages in the protein structures than do young (17-30) persons. <u>But</u> old persons with Alzheimer's Disease also have, in addition to the compact proteins observed in the normal old, proteins which are hardly at all crosslinked. This strongly indicates that in the Alzheimer disease a strong new synthesis of fresh protein is taking place.

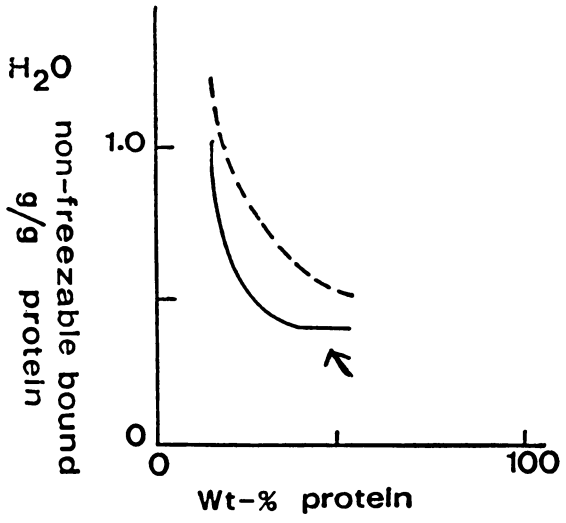
Additional tests have confirmed this general picture.

Figure 31 shows the results when we added two very different crosslinking agents, (sodium persulfate and glutar aldehyde) to

the 17-year-old brain. The change, **represented by the solid curve**, changed the amount of protein concentration, (and with it the amount of non-freezing water) so that it now resembled that of an old person. (Notice that the solid curve in figure 31 is the same as the curve of a 67-70 year old in figure 30). The only property which sodium persulfate and glutar aldehyde have in common is that they are both crosslinking agents. From this, we can conclude that since they produced the identical effect in the brain (giving it the appearance of a 70 year old brain), we can see that crosslinking is the dominant reaction in aging of the brain.

FIGURE 30 - NON-FREEZING WATER PLOTS OF YOUNG, OLD, AND ALZHEIMER BRAIN. FIGURE 31 - 17 YEAR OLD BRAIN AFTER ADMINISTERING CROSSLINKING AGENTS.





FREE RADICALS - A SUBSECTION OF THE CROSSLINKAGE THEORY

The Role of Free Radicals in Aging

The Crosslinkage Theory of Aging was formulated in 1942. In 1953 Charlesby stated that streams of free radicals cause crosslinking of linear polymers and it was so used to stiffen, and increase heat tolerance of plastic films. The idea that free radicals are a principal cause of aging is known as the Free Radical Theory of Aging.

Free radicals are fragments of molecules which have free, unsatisfied bonding capacity. The active free radicals, generally referred to by this name, react instantly with almost anything they happen to hit. They have a short "life" because if nothing else comes in their way, they will react with each other to form more stable compounds. The reactions of free radicals are manyfold, but two main groups are particularly important here: Fission and Crosslinking. Fission means here cutting a molecule into two parts by brute force in any which way. Crosslinking has already been explained. The typical active free radical can exist only for a fraction of a second.

The products formed by fission are obviously smaller molecules than the one from which they were formed. Therefore there should be little problem with their disposal. However, in crosslinking, the size of the molecule is greatly increased. The molecule becomes much less soluble if not totally insoluble, and more difficult to handle - that is the direction in which aging moves. Therefore, crosslinking is by far the more important reaction from the viewpoint of aging.

Free radicals are therefore considered as one group of crosslinking influences. As such it may account for about 10 to 20% of the crosslinking in aging. Their efficiency as such is limited by the very short life (fraction of a second) of the active free radicals. This life span makes it very unlikely for a crosslink to be completed by less than two strikes by a radical at the same point. Since free radicals are only one group of the many myriads of crosslinking agents, the Free Radical Theory can be considered a sub-section of the Crosslinkage Theory.

CROSSLINKING - A TWO-STAGE REACTION

Free radicals are widely present in nature. They are formed by solar radiation, from oxygen, water, carbon oxides, and from high tension electricity, including lightning. They are also formed from Vitamin C and other enol dienes in the presence of peroxide and a metal catalyst (copper or ferrous), and from many enzyme reactions.

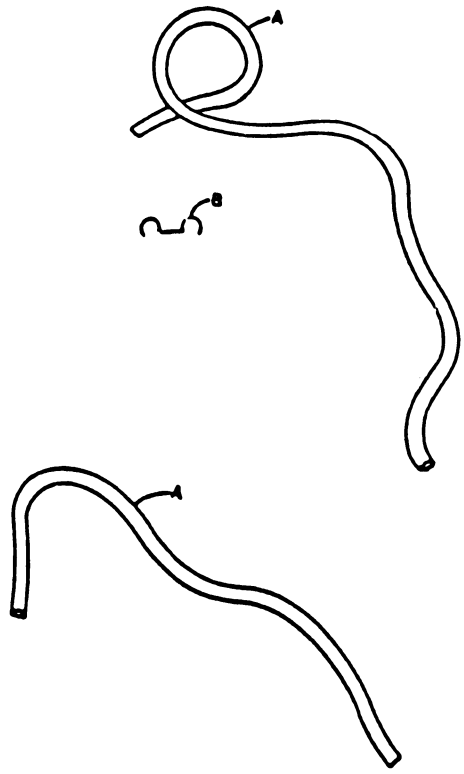
Violently reactive, the free radicals combine with each other, or with any other organic substances they may strike. This may yield a wide spectrum of substances. Virtually everything theoretically possible will be formed to some extent. In two-stage reactions, however, there are limitations, which the following will exemplify.

Crosslinking: a two-stage reaction.

The Set-up: The reactants have not yet made contact.

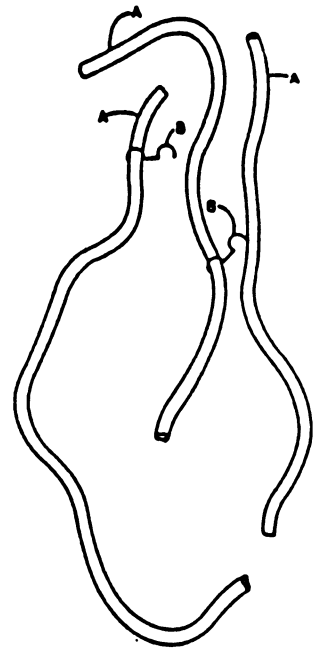
They are: Macromolecule A
Crosslinker B

FIGURE 32 - TWO MACROMOLECULES WHICH HAVE NOT MADE CONTACT



Stage 1: The reactants connect at appropriate sites. Every crosslinker has by definition at least two such polar sites (shown in the drawing as hooks) The macromolecule is much larger than the crosslinker. Typically the crosslinker has mol. weight 16-30; the macro-molecule 100,000 -1,000,000+.

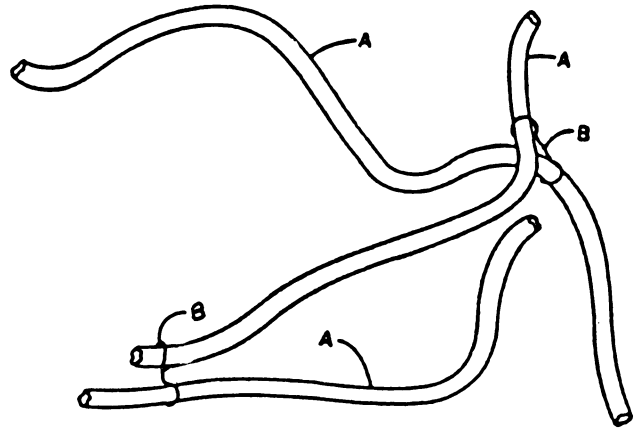
FIGURE 33 - CROSSLINKER MAKES CONNECTION



A pause - The crosslinker B attached to macromolecule A follows Brownian molecular motions, which enables it to react with anything it can reach when its other end is fixed by the initial linkage. At this point, repair enzymes may appear and excise the attachment of the crosslinker. This may result in fission of A or in an overlapping repair such as is often apparent in electron micrographs of old DNA. B may also react with some wandering small molecule - damage if any is then local. This pause often last days, weeks, even years.

Stage 2: if nothing of the above intervenes, another huge macro-molecule may drift so that one of its reactive sites comes within the radius of the motions of B and connects. The crosslinkage is then completed. This is shown in figure 34.

FIGURE 34 - COMPLETION OF CROSSLINKAGE - STAGE TWO



The target area for other macromolecules to connect to is now increased as the process is repeated. Steric hindrances (hindrances caused by structure) will begin to prevent repair. The situation soon gets out of hand.

The pause between Stage 1 and Stage 2 is much longer than the life of any free radical. It is a billion to one chance that two macromolecules should drift close enough together so that at least one reactive site is within a free radical's radius from the other. It's in those instances that a free radical can join them together.

Free radicals cannot ordinarily cause crosslinkage because their life-span is fractions of a second, and the Pause lasts days to months, even years. They can, however, create new reactive sites where they hit. They can also come close enough to macromolecules so as to greatly increase the probability of crosslinkage. In some cases this is possible. For example, a direct hit by a free radical where double bonds of two large molecules are very close to each other, could cause a crosslinkage.

Experiment

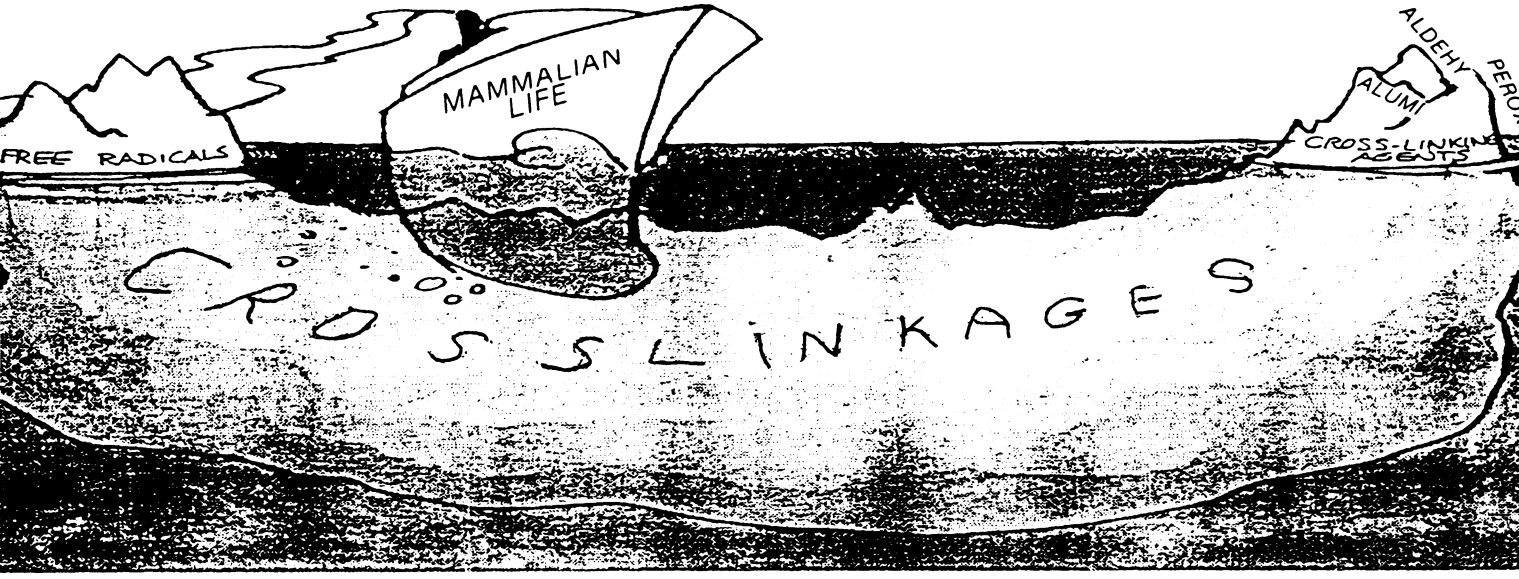
We decided to conduct an experiment to test the validity of our hypothesis that free radicals are not the major factor in crosslinking. To check whether crosslinking would be caused by a flux of short-lived free radicals, we irradiated (flooded with free radicals) a combination of gelatin and unsaturated fat, and found that very little reaction occurred in the next few hours. The crosslinking did not become noticeable until about three days after the irradiation, and not until the 12th day was the crosslinking strongly evident in the irradiated samples. We concluded that no **direct** crosslinking was caused by these radicals, but instead that the radical reactions formed crosslinking **agents**, which then, much more slowly, caused crosslinking of the gelatin.

Numerous crosslinking agents circulate in the blood: lower aldehydes, including formaldehyde, acetaldehyde, acrolein, methyl glyoxal and glutaraldehyde. Some of these react so rapidly with blood proteins that their concentrations at any given moment are close to detection limits, (quinone derivatives including the quinonimines, a host of partial oxidation products from interaction of oxygen or free radicals with unsaturated fats, and multi-reactive metals such as aluminum, mercury, cadmium, and iron). These are mostly very fast reacting. However, even the slower reacting agents can give rise to many insoluble substances such as "amyloids" or "lipofuscins", in less than 60 years. The list of active crosslinkers encompasses more than 10,000 different substances.

When we further consider that the majority of these crosslinkers act much slower than free radicals and that crosslinking typically is a two-step reaction requiring much more time than a single step reaction, it becomes apparent that crosslinking is by far the more important factor than free radicals are. Free radicals aid crosslinking by planting reactive groups at otherwise inert parts of large molecules, but except in a few special cases involving double bonds, crosslinking cannot be completed within the life span of free radicals.

In 1956 Denham Harman stated that free radicals cause aging. Accordingly, the free radical theory is a special case of the crosslinking theory, or, as it has been suggested, the free radical theory is a sub-category of the crosslinkage theory.

FIGURE 35 - FREE RADICALS ARE THE "TIP OF THE ICEBERG"



FREE RADICALS - THE OTHER SIDE OF THE COIN

As we have seen in "The Enzyme Approach", there is a limit to an enzymes's capacity of breaking up and solubilizing age-created gerogenic masses. The smallest enzyme molecules we had been able to find have molecular weights no smaller than 3,500 Dalton. An enzyme of this size is much too large to penetrate a tightly structured mass. Even if we were able to split these enzymes into two separate molecules of 1750 each, they would still be too large to enter into one of these aggregates, in most cases.

On the other hand, the free hydroxy-radical OH+ has a molecular weight of only 17, which is a hundred times smaller than the tiniest enzyme that could possibly be in question. Such a minute particle could readily penetrate anywhere and cause a variety of structural changes. The ORD reaction (oxido-reductive depolymerization) uses free hydroxy-radicals.

The ORD reaction is used by our immune system in fighting infection. Ascorbic acid (Vitamin C) is the driving force behind the free hydroxy-radicals which the immune system directs at intruders. C. W. M. Wilson in Dublin has shown that Vitamin C goes directly into the white blood corpuscles, and then is consumed

very rapidly when a target is seen. H. Tauber and B. M. Babior proved that free hydroxy-radicals are produced in bursts by human neutrophile cells. If our immune system can do this, and direct the bursts at enemy targets, we should be able to use this force better once we understand exactly how this is done.

The ORD reaction was named by the famous carbohydrate chemist Ward Pigman who, with his co-workers, showed that the free hydroxy radicals formed by hydrogen peroxide, iron, and Vitamin C are available everywhere in the organism and are highly maneuverable. They could break down any carbohydrate, including the most resistant starches and cellulose. Other researchers have shown that the ORD reaction can be used to break down many other substances. C.W.M. Orr has used the reaction on catalase, the important blood enzyme which causes blood to foam when you put hydrogen peroxide on a wound. Richheimer and Robinson, in the Linus Pauling Institute, found that the ORD reaction can break down transferrin, a giant molecule which carries iron around in the body. Skanse and Sundblad had already used the ORD reaction in 1943 to break down hyaluronic acid. Herp, Richards and Matsumura showed that this reaction even breaks down synthetic polymers such as pulverized Acrylate plastic.

The beauty of this reaction is that it can be diluted to slow speeds, and that none of the ingredients in themselves are particularly toxic. So - I tried it on insoluble substances formed in aging **AND IT WORKED (See "Legacy of Two Dead Rats" pg. 89)**. After 40 years of searching, I've found that this is the only tolerable reaction that dissolves these compounds. True, it will also dissolve everything else in the cell but this needs not disturb us so long as we can vary the dilutions, and thus control the speed of the destructive reaction to give the body time to re-build what is healthy. The DNA holds the blueprints for everything which is necessary in the cell. Unnecessary substances, such as gerogenic masses will be gone for good.

But you may well ask, haven't we learned from the cross-linkage theory that free radicals are harmful? Free radicals are everywhere. They can be good or bad depending on where, when, and how they are acting. When controlled by the immune system, the free radicals are powerful weapons against invading organisms and abnormal cells. The ORD Reaction and the closely related and overlapping Fenton and Haber-Weiss reactions have been used by phagocytes to cause bursts of free radicals (composed mainly of free hydroxy- radicals) to kill bacteria or destroy targets of the immune system. It would seem extremely important to determine exactly how the phagocytes or killer cells can direct these bursts of free radicals and how they themselves can escape from being destroyed. One possible explanation might be the relatively fast turnover of such cells. It could be possible that the cells accept damage to themselves and sacrifice their individual lives for the good of the more lasting unit, a higher

organism. Unsung heros of biology?

However, we can not take for granted that this is a self sacrificing operation. It just could be that these phagocytes possess some way of protecting themselves from free radical damage. If so, it would be wholly justifiable to spend time and money on further study of this process.

The essential fact is that a combination of these well tolerated substances (mentioned above) will release particles that can destroy the damaging crosslinked substances accumulated during a lifetime. The secret of eliminating these crosslinked substances without removing any of the necessary cell substances lies in the control of the ORD reaction. The means are there. It behooves us to master them.

CONCLUSIONS ABOUT FREE RADICALS:

1. Free radicals substantially predispose macromolecules to crosslinkage by creating additional receptive sites.

2. The short life of active free radicals makes it in most cases impossible for these to complete a crosslinkage since crosslinking is a two-step reaction usually requiring days, or weeks for the second step. A direct hit by a free radical at a particularly receptive spot of the protein can lead to an immediate crosslinkage. The overall probability for this is much less than for the slow 2-step process.

3. Free radicals can cause direct damage to organs by breaking up irreplaceable molecules through their fission mechanism.

4. When controlled by the immune system, free radicals are powerful weapons of defense against invading organisms and abnormal cells.

RE-DISCOVERIES OF THE CROSSLINKAGE THEORY OF AGING.

A most impressive form of corroboration of a theory is when that theory is being proposed by other competent scientists, in good faith, without being aware of the original publication. The crosslinking theory of aging has been thus re-discovered at least five times:

1. A. L. King, in 1946, on the basis of pressure-volume relationship in human aorta clearly spelled out that his observations could be best interpreted on the basis of an age dependent crosslinking in this, the strongest artery in human anatomy. (Applied Physics, 17:501 - 505.)

2. F. Verzár, in 1955 proposed the theory of crosslinkages in aging, on the basis of his work with collagen in tendons and skin. A year later, after his first publication my prior work was brought to his attention by Dr. K. H. Gustavson in Stockholm. Dr. Verzár wrote me a very polite letter of apology. We had occasions to collaborate later and became good friends. (Helv. Physiol. Acta.13:64.1955.)

3. D. Harman, in 1956 proposed free radicals as causative of aging. Free radicals have many effects: crosslinkage, fission, effects of direct hit. To the extent that crosslinkages are in question, the free radical theory is a subsection of the crosslinkage theory of Bjorksten, who proposed the broad theory in 1942. Charlesby showed in 1953 that ionizing radiation rich in free radicals causes crosslinking.

In view of these two prior findings, any effect of free radicals which causes or predisposes molecules to crosslink is a re-discovery of the crosslinkage theory.

4. Donald Carpenter, in 1968 presented the Diffusion Theory which in addition to several new thoughts contains a rediscovery of the crosslinking theory. (J. Geront 20:192-195)

5. M. L. Tanzer, in 1973 pointed to crosslinking as "The Rosetta Stone of Aging." I could not agree with anyone more heartily. (Science, 180:561-568)

Now, soon at the very crest of the Great Barrier we can look back even to the Stone Age, and forward to the distant peaks of the ultimate future and ask, which of the basic causes of deterioration with age will remain when all medical practices and procedures have been optimized?

The answer now seems to be: Uncontrolled, non-enzymic random crosslinking.

In view of the enormous variety of crosslinking agents and infinity of sites on which they can react, our ability to control the process of crosslinkage is very slight. The rate can be reduced, but cannot be reversed. Gradually removing crosslinked aggregates faster than they are formed could be our last remaining challenge before we reach the ultimate future, where death is not caused by aging, but only by accident, suicide, or violence.

CHAPTER 8

THE GREAT BARRIER

Evolution has provided a design life for all living beings which care for their offspring. The design life of humans ensures that people will normally have the time to bring their children into the world, protect them in infancy, teach them, and give them a good start in their adult life. The human is designed to last about 60-70 years. After that, any one of a still unknown number of independent causes of death will eventually take over.

Let's not confuse two seemingly similar terms which are in fact quite different in meaning. Life expectancy refers to the amount of time the average person can expect to live given the circumstances of his environment. In the Stone Age, a person could not expect to live long, because of the high risk of being eaten by a carnivorous beast. Few children reached maturity. Design life, on the other hand, is the amount of time a person is equipped to live, by the powers that be, be it Evolution, God, Fate, or whatever you name it. As we have progressed through the epochs, our collective life expectancies have increased considerably since the Stone Age. As previous causes of death have diminished, other causes have taken their place, thereby pushing the average life expectancy higher and higher.

Not only the general public, but also a large part of the scientific community, mistakenly believe that human life is genetically limited to an immutable maximum of about 70 years for the healthy part of life, followed by death within the next 30 years. This erroneous belief sustains the idea that our life expectancies can not extend far beyond our design lives.

The principal scientific reason for this belief is that whenever any medical or environmental improvement raises the average life expectancy, the maximal age attainable by the species remains essentially unchanged, as if it had hit an immovable wall. For humans, that maximal age appears to be about 25% above the design life. This holds true not only for mankind, but also for every experimental animal studied under varying conditions.

The following schematic curves will show that infant mortality has improved very greatly. Adolescent and middle-age mortalities have improved considerably. But mortality for men over 60 has increased only slightly in the past 80 years. Woman's mortality has improved much more since the development of modern diagnostic methods, the Pill and hormone therapy.

FIGURE 36 - LIFE EXPECTANCIES FOR WHITE MALES SINCE 1900

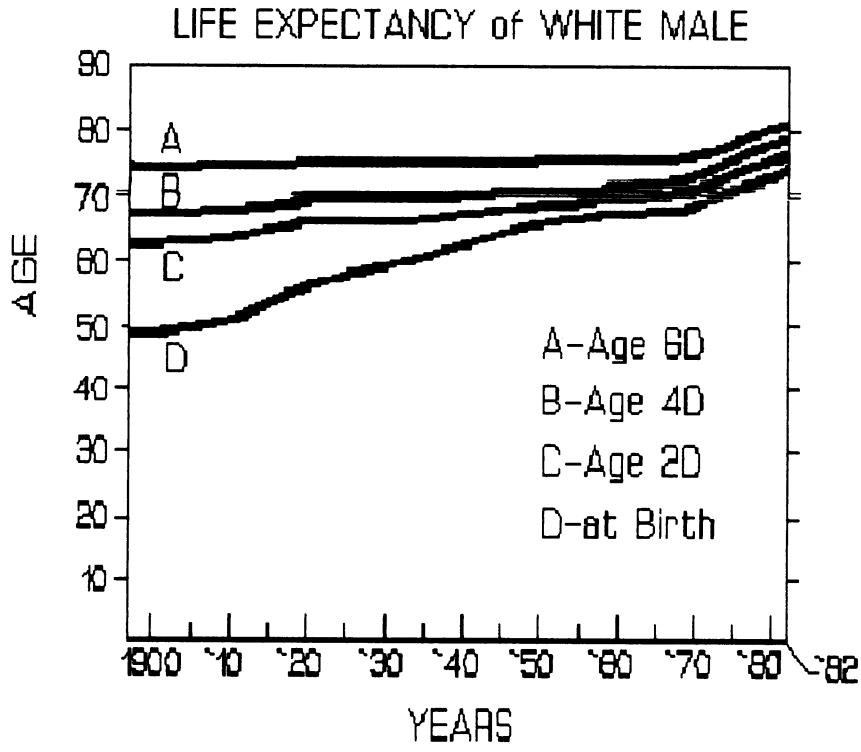
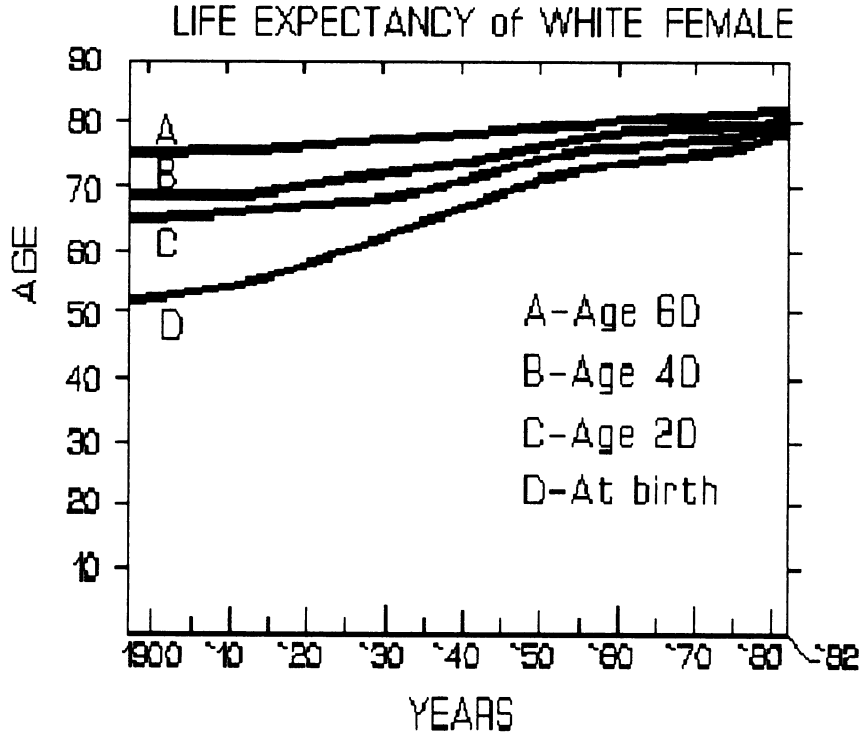


FIGURE 37- LIFE EXPECTANCIES FOR WHITE FEMALES SINCE 1900



(The data for the time period 1900-1970 was obtained from Historical Abstracts of the U.S. The data for 1982 was the most recent data taken from the 1986 edition of the Statistical Abstract of the U.S.). The left axis titled "Age" refers to the average age that a person could expect to live to. The bottom axis refers to the particular point in time that a person is living in. Here are a few examples of how to read the graph. For the white male, notice that in 1900, a newborn (line D) would have an average life expectancy of 50 years. An infant born in 1982 (still following line D) would have an average life expectancy of about 72. A sixty year old white male (line A) in 1900 could expect to live to be 75. However, in 1982 a sixty year old male could expect to live to 79, an increase of only 4 years of life in the past 80 years. The expectancy curves for all ages are converging, especially the curves for females.

The maximum length of life attainable by both men and women has hardly increased at all. Studies of experimental animals show similar results. So far, most of the improvements in average life expectancies are due to a higher survival rate in the early stages of life, not in living longer. For example, Antonie van Leeuwenhoek lived to be 91 in the seventeenth century, when the average life expectancy was less than thirty years. And Luigi Cornaro, a couple hundred years earlier lived to 98. This is still considered to be a long, full life, even by today's standards. The alleged much higher life spans reported in Vilcabamba, Equador were proven a fraud (see chapter 17) and similar claims from Grusia and Kashmir cannot be credited.

The facts conveyed by these curves have led many to believe that our systems are equipped with a genetic "Time Bomb" or "Death Hormone", something inside designed to destroy us when we have outlived our design lives. Several considerations lead us to reject the generalization of these beliefs:

1. There is no evolutionary reason why the survival of individuals should be detrimental to the biological success of the human species.

This reason does exist for some species. For example, the Pacific Salmon return from the ocean to the rivers where they were hatched, to spawn. Immediately following that, they die from atrophy of their digestive system. This serves a clear purpose, for these big fish, hungry after a strenuous swim against the current, would eat their eggs and offspring if they did not die soon after spawning. It is clear that in the example of the Pacific Salmon, the survival of the parents would prove to be a hazard to the next generation; therefore, to the species in general. Further, no human culture exists in which parents threaten the lives of their children.

2. Another example sometimes advanced to support the idea

of a preordained life span are the Lycaste spiders. The larger and stronger female spider eats her mate after he has completed his purpose in life. Some human females have been known to express such desires on sufficient provocation, but if such an ambition has ever been realized, it is at least statistically unimportant.

3. Furthermore, if a genetically predetermined limit for human life existed, most people would die from an identical cause, without the great changes which have taken place in the transitions from one epoch to another.

4. Finally, Death now comes to us very much earlier than would be the case if we came even near our possible maximal age. The theoretical maximum life span would be approximately 2400 years for women and only 900 years for men. These figures are based on the assumption that a complete control of age dependent deterioration could be achieved after growth ceases. Clearly, we are a long way off from this maximum. However, it points the way to a great deal of possible gain if the present causes of age-dependent decline were all mastered.

Then what is the nature of this barrier which seems to extend between the ages 75 to 100?

Nature of the Great Barrier

As previously mentioned and shown in Figures 36-37, the projected survival curves from epoch to epoch, or from successful animal experiments, show about the same maximum life span. Actual increases have been slight and not always reproducible. This seemingly unchangeable maximum life span can be explained as being due to the many different causes of death for which we have nót yet developed "cures". (Please note that many of these can be prevented.) These causes of death were all pushed back by the same evolutionary pressure until they met the common blockage: The Design Life of the species.

Evolution has developed man to function well up to this age. After that he is on his own. Evolution has no reason either to remove him from the scene, nor to preserve his existence beyond this boundary.

This scenario has been disputed, and such devices as "Genetic Time Bomb", "Death Enzymes", and "Death Gene" have been supposed to exist. These ideas are not realistic. Recent work with aluminum shows that the amount of aluminum increases throughout life and at the age range of The Barrier (about 75 - 100) reaches values high enough to kill anyone who gets appreciably beyond that point.

This finding is of great theoretical importance, because it proves that humans in their natural states will die within that range by the aluminum mechanism alone, even if no other cause of death intervenes. Thus, there couldn't have been evolutionary pressure to develop any additional death-causes like a genetic time bomb for removing old humans.

The apparent Barrier to life beyond 75 - 100 years is fully explained by the many different causes of death which all have been pushed by the same evolutionary pressure up to the defined common limit of the Design Life (see figures 36, 37). Therefore, it isn't just cancer that is holding us back, or heart disease, or Alzheimer's disease, but the sum of all these causes of death together which is keeping us from living longer and healthier lives. Once we have conquered the major death causes of all epochs, there will still be attacks from epochs past (persons will still die of death causes of previous epochs). The overall percentages of persons dying of these causes will be of minor proportions, but taken together will still be formidable.

As these successive causes of death are mastered one by one, the Barrier changes its character. When the epochs are passed, their Principal Causes of Death are no longer very large, but there will still be some attacks from each epoch past, until these remaining causes taken all together, will become important.

Even the wild beasts of the Stone Age are still responsible for a considerable number of deaths. These beasts which lurk around and suddenly bring death to some of us are now known as automobiles.

Epoch II, the contagious diseases, are still taking many lives of persons whose resistance is low, or when a strain of a dangerous microbe becomes resistant to current antibiotics.

Cancers and heart disease are still principal causes of death, though they will decline in importance in the course of the present transition. We already have the knowledge to prevent 90% of these deficiency diseases, but we may have to wait a century for a full application of that knowledge. As this happens, there will be a higher percentage of the population approaching Epochs IV and V, still on the outer reach of the Great Barrier.

Even when the remaining deaths for each of the epochs of the past is only in the 5-10% range, they could together account for a substantial part of the barrier.

That will be the signal to begin centering efforts on strengthening the immune system and reinforcing it by developing markers which attach to the pathogens and attract concentrated attacks by the immune system, and by improving the nutritional support. The successful solution of even the few remaining major

"epochal" death causes will free so much research time, facilities, and funds, that the remaining lesser causes of disease can be attacked with confidence, and solved in their turn. The greatest leap in life expectancy ever experienced should await us on the other side of the Barrier.

As research is accelerating and the several components of the barrier are bridged, the day will come when the last of these is brought under control. Once beyond the Great Barrier, we may look forward to an extended period of much faster progress.

CHAPTER 9

THE ULTIMATE -- HOW FAR AND HOW?

Let us look again at the overview of longevity, beginning at the bottom with the Stone Age. We know Epoch I - III from the experience of our forebears. The Big Beasts, now represented by automobiles, still take their toll on young and old alike. Common colds remind us of the more serious contagions of the past. Deficiency diseases, mainly represented by heart disease and cancers, are still causing deaths of which 90% could have been avoided.

Epoch IV, where brain and nerve-system diseases will have lost their edge, is a recently opened territory. Hardy pioneers have already arrived and surveys are being made preparatory to broad settlement.

A few pioneers are valiantly thinking of Epoch V, and the consequences of continuing crosslinkage: loss of elasticity of all tissues, loss of water retention of all tissues, and embrittlement of bones and cartilage.

There might be some more epochs to come, still unsuspected.

Far, far beyond all this we can sometimes glimpse a snow crowned mountain top, radiant in distant sunshine - the Ultimate, when aging itself has been conquered and death comes only when invited (barring accidents and violence).

Here we stand now in 1987. Our average life span is 72 years for men, 78 for women in the USA. In much of the rest of the world it's a little lower, but in Japan somewhat higher. We know what we can do to prevent 80-90% of the current principal causes of death. As a group, we shall not make use of this knowledge anytime soon. We'll have to wait for lengthy and often, in our opinion, needless testing, arguing, and convincing in countless committee meetings. Historically, we cannot expect general application of major medical improvements until a majority of existing medical facilities are occupied by cases of the following epoch. The last time a step into a new epoch was completed was during World War II, when mass production of antibiotics became a fact. The rapid cure of infection cases shifted the load of death causes to cancer and sclerotic - heart disease. This shift created the necessary public demand and political pressure to find cures for these newly predominant killers.

The medical and nutritional base is now ready to move on to Epoch IV, but public acceptance can be expected to take another 50-100 years for completion. The above applies to humanity at large. For the individual, however, it is possible, with the

guidance of her/his physician to benefit from advanced knowledge of contemporary medicine and biochemistry. As individuals, we could use for our own benefit what is now known about the recent past and the next two future epochs. This should enable us to gain the average life expectancies predicted for the year 2000: eighty years for men and a century for women. The trend is for the longevity gap between the sexes to keep on widening as we continue humanity's slow but steady advance toward the Ultimate.

Why the delays in transitions between epochs?

Viewing past transitions from the vantage point of the present, one wonders to what extent it may be possible to use past experience to shorten present delays from epoch to epoch.

The transition from the Stone Age to the epoch of contagion seems not a good model to follow since it lasted thousands of years. The principal reason for this is that in the Stone Age low population density, as well as slow methods of communication and limited travel, made it difficult for epidemics to spread. Also, individuals infected by the microbes of contagion were easy prey for bears, wolves, cave lions and many other carnivores. The development of weapons effective against large animals came slowly. Finally the idea of striking at a distance of more than arm's length took hold. This idea yielded spears, swords, arrows, slings and long shafted clubs. The struggle against the beasts lasted uncounted centuries, but was finally won by the early efforts of human brain power.

Having progressed this far, humanity fell prey to the microbes of contagion. Medical practitioners at that time had no idea about these new adversaries since they were invisible to the naked eye. Not even Antonie van Leeuwenhoek, who in the 17th Century discovered the microworld, had any suspicions that this might harbour humanity's most implacable enemies. The transition began with van Leeuwenhoek. When he made his lenses with 300 times magnification, it was a foregone conclusion that humanity would be the victor in the long struggle which until then had been one sided.

One hundred seventeen years passed before Anatomy Professor Henle of the University of Göttingen (Germany) pronounced the fateful words: "The contagion has a life of its own, which in relation to humanity, is parasitic." Robert Koch was then a young student at the University of Göttingen. Thirty years later, Koch was to publish the book which showed the techniques for isolating, culturing and identifying bacteria. I do not know whether Koch attended Henle's lecture or whether he learned about it from discussions with fellow students. Koch studied medicine at the University where Henle was professor of anatomy. If he missed the particular lecture when Henle had made his statement

about infection, Koch certainly made up for it later.

In France, the industrially oriented chemist Louis Pasteur had proven that life only comes from life. This ended the theory of spontaneous generation, the medieval notion that bugs are somehow formed from the materials in which they live. Development accelerated, but not until 1950 was the epoch of contagion finally terminated with the mass-production of effective antibiotics and their predecessors, the sulfa drugs. The second transition was now finally behind us, and the deficiency and environmental diseases became the prime concern.

We are now in the center of the transition between Epochs III (Atherosclerotic disease and Cancer) and IV (mental disease). How long will it take us to complete this transition so that the average person will get, and use the knowledge we now have? This includes the knowledge, not to cure, but to prevent 90% of the diseases of Epoch III.

Many forces now work in our favor:

1. The techniques and the tools of research are more developed than even at the beginning of this century.

2. Information and its retrieval are better organized.

3. The breakthrough of computer use in research and its applications have introduced a new dimension in the use of data.

However, the widespread use of the computer brings new problems. The most serious of these is the loss of time due to the failure to check literature more than 8 - 10 years old. The younger generation of researchers is frequently content with a computer search which only goes back a few years, and often is not programmed for the 10 - 50 year old literature which holds a great wealth of useful data and experience. This often leads to waste of time on duplication of research already done.

As the computers and their programming age, this will slowly improve. At the present time, however, the belt of neglected knowledge is wide and holds a wealth of useful information.

Very long time lags of the transition periods between epochs are largely due to a great difficulty in changing deep rooted habits, customs or life styles. Very much could be gained by comparing diet deficiencies and exposures of the many cultures on earth, analyzing available data, and taking appropriate action.

I am not optimistic nor naive enough to believe that this will have an immediate effect, but conceivably it might shorten the probable length of the next transition period from say 150 years to only 50. More importantly, it would introduce a

positive factor of evolution in giving the more intelligent persons the benefit of knowing how they can improve the probability of a long and healthy life.

It might even shorten the time needed to break through the Grand Barrier and emerge strong to face such further challenges as destiny may still hold for us.

Epochs have followed epochs. It has been my fate to recognize and express some small parts of their continuity throughout history and to define some essentials of the present: The random, accidental crosslinking as an underlying cause of aging, including the role of aluminum as a major negative factor in longevity; the multiplicity of death causes and their interdependence which have set needlessly early limits to human life span.

Yet, there is hope! No "time bomb" is set against us. The number of active causes of death is limited - possibly only ten, or less. When all of these have been mastered, there should be a major gain of healthful, pleasant life. Be that as it may. A major extension of life awaits us when the last of the present post-design life cluster of death causes have been vanquished. May humanity prove worthy of it!

Season follows season:
Spring with hope and confidence;
Summer with growth and warmth;
Fall, with harvest, colorful;
Winter, with withering,
retrenchment, hoping for a new spring.

SECTION II

FACTORS AFFECTING IMPROVED LONGEVITY

CHAPTER 10

THE TIME FACTOR IN RESEARCH ON AGING

Summary

A common objective in gerontological research is to gain time for:

1) Enjoying a pleasant life already attained.

2) Adding new disciplines of knowledge and creativity to those already mastered.

3) Gaining the time necessary to complete a specific task to which one is wholly committed.

4) Such other purposes as may appear.

To achieve these objectives in time for those now active to enjoy, the following research strategy is suggested:

I. Cut down support of gerontological work with any animal which has a much shorter life span than humans. Those chemical reactions which underlie human loss of both mental and physical health and strength with aging are largely different from those acting on shorter lived animals. The slow rate processes which affect a person's longevity do not become evident before 40 years. These are the processes which humans do not have adequate defenses against. Therefore more studies should be done with animals of equally long life spans as humans, of which there are not many. These animals, whales, elephants and crocodiles for example, are expensive to feed and handle. Even at that they might be less expensive than working with humans under present regulations which require informed consent and double blind test organization. A "double blind" test is one in which neither the researchers nor the people participating in the experiment as subjects know whether they are in the experimental group or the control group; nor do they know the results desired.

II. Center work on humans in an age range far enough advanced to give meaningful results, but not so advanced that secondary damage overshadows basic aging effects.

Organisms are by evolution endowed with protective mechanisms which give them enough time to have their offspring, to give it proper education and a start in life. For a mouse this is perhaps a year or two, for a human 60 - 70 years. The molecular happenings which set the stage for needlessly early death in humans are, therefore, largely those which require 60 years to become critical. The answers which we seek are to be gained by

study of humans old enough to show the critical events, but before these become hidden by secondary complications, preferably about 45 - 55 years.

While an 80% probability would be totally unacceptable in most of the short range studies to which we are accustomed, the picture changes when the time required for these studies extends beyond our present life expectancies.

A projection shows a probable duration of 400 years if the study on longevity is carried out with present test procedures and insistence on multiple animal tests prior to any work with humans. On that route, the probability of a breakthrough in our lifetime is diminishingly small.

Unfortunately, until such an exhaustive study is completed, there will always be scientists who allow themselves to be hampered, and who delay others by insisting on having all details cleared beyond even the most remote doubt before moving on to the next logical step. Even when there's a reasonable chance of saving the lives and sanity of millions of people now, there are overly meticulous persons who insist that every last possible objection, however far fetched, must be cleared before proceeding with the work.

However, if we could content ourselves with less precision in those steps which would greatly increase time requirements, it would be possible to complete this work in a much shorter time, quite possibly within ten years. We would need to start sequential tests as soon as the previous tests have given a fair indication of which way to go. The price we would pay for speed is perhaps a 20% risk that a serious flaw may have been overlooked, and that we must backtrack some, at worst all the way to the beginning. The time that could be gained may justify the risk.

This estimate presupposes capable overall direction and responsibility centralized in one competent and inspiring leader.

If the necessary clinical work cannot be done in the USA, let it be done elsewhere! The world is wide and the instinct of self-preservation is universal to all life.

The Keshan Disease Group of China gave the world an impressive demonstration of what can be accomplished with good planning and large numbers of persons being tested. (The Keshan Disease Group was able to wipe out a form of heart disease which was inflicting 1/2 of one percent of all children between 1 and 9 years of age in just three years of testing). One way to further medical knowledge dramatically would be international cooperation in large-scale testing. A most important part of international cooperation might be to centralize major clinical studies in countries which can apply the necessary organization and

controls. In nations such as China, researchers are not required to explain and obtain informed consent from the parents of each child. They aren't faced with interference from poorly informed outsiders, or the personal hazards of malpractice suits. They can also avoid well-intentioned but very time-consuming multiple distractions imposed by bureaucracies like the Food & Drug Administration. The expenses of such research could be shared worldwide in exchange for these extensive tests.

When we compare the work of the Keshan Disease Group with the great multitude of not yet accepted results of scattered, uncoordinated tests such as those with ascorbic acid in the Western literature, we cannot avoid thinking that a large enough well-supervised test over three years with about 12,000 persons each year, would have settled all uncertainty once and for all.

However, with or without this advantage, to gain the desired breakthrough in our lifetime we cannot afford to work with higher precision than is necessary, when it could lead to a major loss of time. We have to adopt a strategy of concentrating support on work which will be clearly relevant to the artificial extension of the human lifespan. We must move on with a belief that the target can be achieved and with a firm resolve to succeed in time to reap the rewards of a greatly extended lifespan in good health.

CHAPTER 11

NUTRITION AND OXIDATION

Oxidation means combination with oxygen. An antioxidant is anything that slows the combination with oxygen - from a mild slowing to a total stop. We all get our energy from the oxidation of principally sugars and starches ("carbohydrates") or fats. If there were no restraints on oxidation, we might all burn up in a flash. The antioxidants are a very necessary moderating influence. Not only are they a protection against overheating, but they also make possible the fine tuning of life processes, without which no higher life would be possible.

Lack of antioxidants such as Vitamin E, C and Selenium can open the door for heart and circulatory disease. Antioxidants are necessary for the smooth and constant burning of fatty substances. These come in two forms: saturated and unsaturated. Examples of unsaturated fats are cod liver oil, and most cooking oils. Examples of saturated fats are animal tallows. Cocoa butter has some of each.

In the body's fat reserves, both unsaturated and saturated fatty acids are usable interchangeably. Under normal conditions, the body contains substantial quantities of unsaturated fatty acids. The unsaturated fatty acids or fats have the advantages that they are easier for the body to burn or to process, and that they are liquid at body temperature. It seems obvious that it is easier for the organism to handle and process a liquid substance than a hard wax. The disadvantage of the unsaturated fats is that a sufficient amount of antioxidants need to be present. Otherwise, the unsaturated fats could easily undergo a spontaneous slow combustion which produces some of the identical stinky and poisonous things that you would get by burning the fat with insufficient air, or overheating it in a frying pan. When burning saturated fats you can get by with much less antioxidants in the diet.

But for a full understanding of life, its origin and what it consists of, we should remember that energy production by oxidation is a late comer in evolution. When Earth was young, it had just cooled from the original melt, so much that a thin crust had formed around it. The temperature then had come down to less than the boiling point of water. What a rain it must have been when all the ocean water was steam in the air and then came raining down! At that time there was no free oxygen in the air. We know that for a fact, because all iron compounds found in the rock layers in which life from that period was found were in the oxygen poor "Ferrous" form. Whenever free oxygen is present, this is converted to the oxygen rich "Ferric" form. Thus when life first developed on earth it could not have been based on any oxygen breathing, but was probably akin to something that can

only be found in Yellowstone or Rotaroa in New Zealand, or in the hot springs of Japan or Iceland. In these areas there are bacteria which gain their life energy from oxidizing sulfur compounds into sulfuric acid (very diluted to be sure), or other reactions which don't involve oxygen at all.

When oxygen finally became available and manageable, oxygen breathing was a much more efficient way of producing energy for life processes. The results of this metabolic change are in evidence all around us. The success of the oxygen breathers was in no small measure due to their mastery of antioxidant systems.

We have seen that man generates his energy by oxidation. Oxidation of what? Those substances preferred by the body as energy sources are the carbohydrates, starches, dextrines, and those sugars which the particular individual can process. Glucose is by far, the optimal of the simple sugars. Also, fats are a particularly high form of concentrated energy. Among the fats, the body finds it easier to process unsaturated fats when they are backed up with effective antioxidants in optimal quantities. Finally, only if neither carbohydrates, nor unsaturated or saturated fats are available in sufficient quantity, proteins will then be utilized for energy.

In the utilization of energy let us picture a waterfall. The water falls a long distance and in doing so it can be channelled through a turbine where the falling energy of the water is converted into convenient form such as electricity. It is much easier for the engineers and much cheaper for the builders to have as much energy as possible generated in one place.

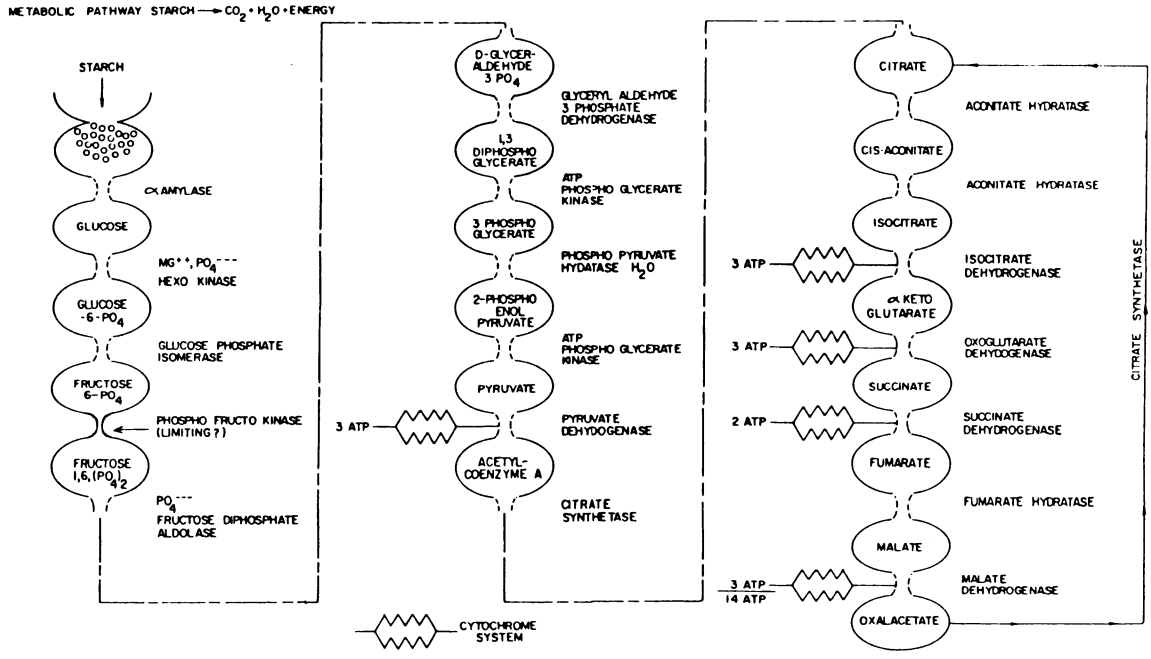
If the same amount of water falls along a distance of several miles, the energy would be much more gradual. It could be running water wheels which were far apart. The total energy would be the same but the means for producing it would be different.

It helps us to keep this picture in mind when we try to understand the path that evolution has taken in providing energy within the human body. If all the energy chemically bound in our food were to be released all at once, like a waterfall, there would be a big flash and we would be burned to death. Therefore, the release of this energy must be channelled like a long, gently sloping river so that the energy is taken out at many stages, a little each time and no more at any one point than we can easily handle.

The smoothness of the oxidation (which is the base of energy) corresponds to the slope of the water in the river. The quantity of antioxidants determines this slope. There is one most desirable point, where oxidation of the fuel in our food releases energy at a rate which meets our needs, and still does

not burn us up or hurt us. To give you an idea of the degree of complication of this, I shall show here one of the many energy releasing paths in the body, namely one route beginning with starch and ending in water, carbon dioxide, and energy, with all the steps in between.

FIGURE 38 - ENERGY PATHWAYS FROM STARCH TO ENERGY



This picture was included mainly to give the reader an idea of the complication of one of the most basic chain reactions, the one which starts with starch and sugar and seventeen other steps not counting the cytochrome energy gathering and storing steps shown here as the 6 "accordions". The actual names of the different stages are not important in this context. This figure also helps to show that these oxidation processes are similar to the flowing of a meandering river (follow it from the upper left to the bottom right).

The energy which is released at the several "bottlenecks" of the process comes out partly as heat (not shown) or as "ATP" meaning Adenosine Tri Phosphate. This ATP is chemically stored energy which can be transported and discharged anywhere and whenever the organism chooses. It is the staple of energy in all higher animals, and in very many other life forms. For example, many reactions that release energy (like water running down hill), can be reversed in direction and made to go backward (or uphill, like a pump could send water uphill). ATP is essential for such reactions.

The mechanisms for making the ATP are indicated by the accordion symbols of which there are six in the diagram. These are the places where energy is taken out. Each of them is identical or very similar to the others. They are not shown in more detail because that would take a lot of space and is not needed to make the present point.

For this type of reaction, **glucose is the ideal fuel.** Fats contain more energy and can give it out in a shorter chain, meaning faster energy release, yet still controllable. With all these long chains of chemical reactions it is important not to exceed a certain rate of feed. Between the different steps are "Bottlenecks". These are points where only a certain amount can be handled or allowed to pass through at any one time. If the food comes in too rapidly, it may back up in front of one of these bottlenecks and then only a partial combustion takes place. A half-way product then backs up at the bottleneck and can leak out, causing harm. Many half-way products are poisonous. For this reason it is better to eat several smaller meals rather than eat everything at once. Many of the half-way products are known crosslinking agents which would be apt to cause slow but real damage.

ENERGY SOURCES

Somewhat unconventionally we oxygen-breathing organisms have approached the nutrition problems from the standpoint of the mastery of oxidation. We shall now take a closer look on what we oxygen breathers are oxidizing and what we have to use to build up the organs to do this. These substances include three main categories. They are discussed and dissected in all books on nutrition: The carbohydrates, fats, and proteins. The two first mentioned are the energy producers. Protein is the building material for the machinery of life.

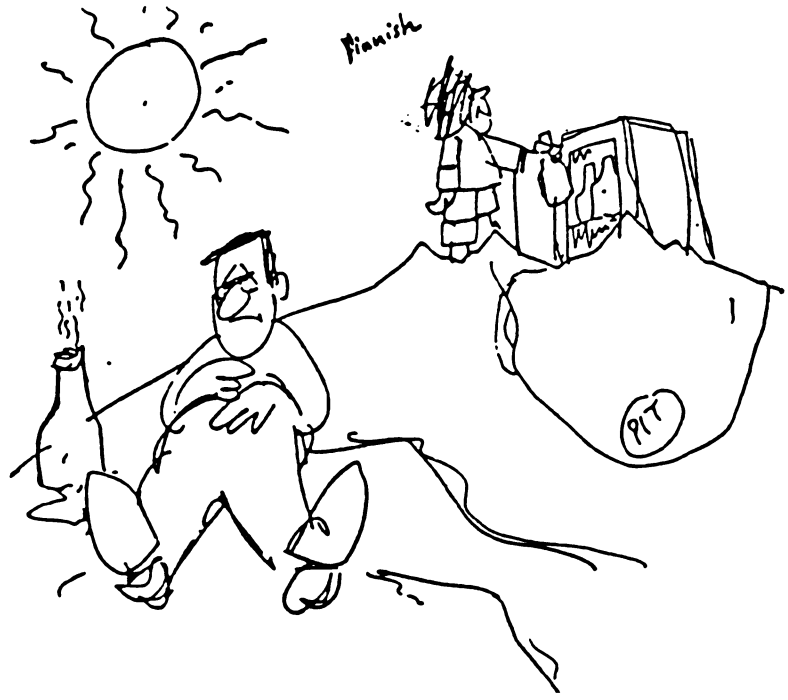
The Carbohydrates

The carbohydrates are composed of carbon, hydrogen, and oxygen but with a much higher percentage of oxygen than any fat. Accordingly, they are as a group still easier for the body to process than even the unsaturated fats. There are, however, great differences between the various carbohydrates. These differences depend on the details of just where and how the oxygens are placed on the carbon backbone. Milk sugar (Galactose) is an interesting example of these differences. Ninety percent of the people in the mediterranean area and nearly 100% of all black persons lose at an early age the ability to use galactose. Because of this, they cannot find pleasure in milk drinking after the first months of life. In the northern areas just the reverse is true. Ninety percent have a complete set of enzymes to

benefit from milk sugar and proteins.

The reason for this difference seems quite clear. In Southern countries, there was no way to keep milk for several days. Milk at mediterranean temperatures is a breeding ground for bacteria. Those who tried to use it got stomach upsets even to the point of being fatal for infants. On the other hand, in the Scandinavian countries there was no alternative to milk for vitamins and trace minerals, and milk could easily be stored for the necessary number of days. In early spring, while the lakes were still frozen, the farmer would dig a pit for the storage of milk and other perishable foods. He would fill it with the ice from the nearest frozen lake or river and cover it with a good heat insulator. In this way, it was possible to have cheap refrigeration in all seasons.

FIGURE 39 - ILLUSTRATING THE DIFFERENCES OF MILK DRINKING ABILITY OF PERSONS IN BOTH WARM AND COLD CLIMATES.



When mankind set out to make the brain its principal weapon and protection, it was soon faced with the problem of limited space in the skull. Making the skull much larger would upset the weight on the neck and become inconvenient for fighting. Evolution arrived at the present size of the skull as something rather fixed. As the brain developed and became more and more important, extraordinary steps had to be taken to utilize completely the limited space inside the skull. One place where space could

be saved was in standardizing on one single fuel. This would enable the brain to do without any processes for converting one fuel into another or any inefficiencies that could result from using anything other than the very best fuel.

For this reason our brains today are standardized on the exclusive use of one single carbohydrate, namely glucose (same as dextrose, same as grape sugar). Glucose, is the only carbohydrate the brain can use directly, and was shown by NASA research on astronaut diet to be less cholesterol generating than either sucrose ("ordinary sugar") or fructose (fruit sugar). Most of the complex carbohydrates are converted in the digestion to form glucose, so the preference for glucose is entirely consistent with it's use.

If you make a sculpture of the molecule of glucose, you will find that this particular formula has its most favorable oxygen groups uniquely arranged in a plane easily accessible to the largest number of combinations with other molecules. Even the plants have made a similar selection. In most plants, energy is stored in the form of glucose molecules tied together to form starch, cellulose and dextrines. Starch and dextrin are essential in nutrition and are most common in edible plant substances and most plant foods.

Some of the special diets stress the use of "complex carbohydrates" as preferable energy sources. This is quite correct in most cases because these complex carbohydrates are composed of glucose which they gradually release. However, these same dieticians condemn all simple sugars. In many cases this is acceptable, but an exception should be made for glucose.

Dr. Mildred Adams was in charge of certain research for the U. S. Department of Agriculture. She made a study in which a group of rats were given a diet composed entirely of eggs throughout their lives. Much publicity had been given to the undesirability of high cholesterol content and Dr. Adams was interested to see if there was any real hazard in eggs, which have very high cholesterol content. To her considerable surprise, she found the life expectancy and health of the rats which ate only eggs was almost equal to the life expectancy of those control rats which had the most healthful laboratory feed she knew. However, there was another control group of rats which had twenty-five percent eggs in their feed. These rats showed a much shorter lifespan than the other rats. Obviously the twenty-five percent of egg diet could not be blamed for this since 100% eggs were near perfect. Tracing this further, Dr. Adams found that the feed of this second control group contained substantial amounts of cane sugar, and that the cane sugar was the cause of this decrease in life spans.

Further tests with various sugars showed that glucose was

decisively the best for nutrition. The ordinary sugar (cane sugar) came in as second, and fructose as the poorest. Cane sugar is a combination of equal parts of glucose and fructose. To the taste, fructose is twice as sweet as cane sugar and cane sugar is considerably sweeter than glucose. As you recall, starch is composed of glucose so that when a syrup is made, it will be a glucose syrup. But the manufacturers will go through a second operation to change this glucose syrup into a sweeter fructose syrup, much to the detriment of the nutritional quality.

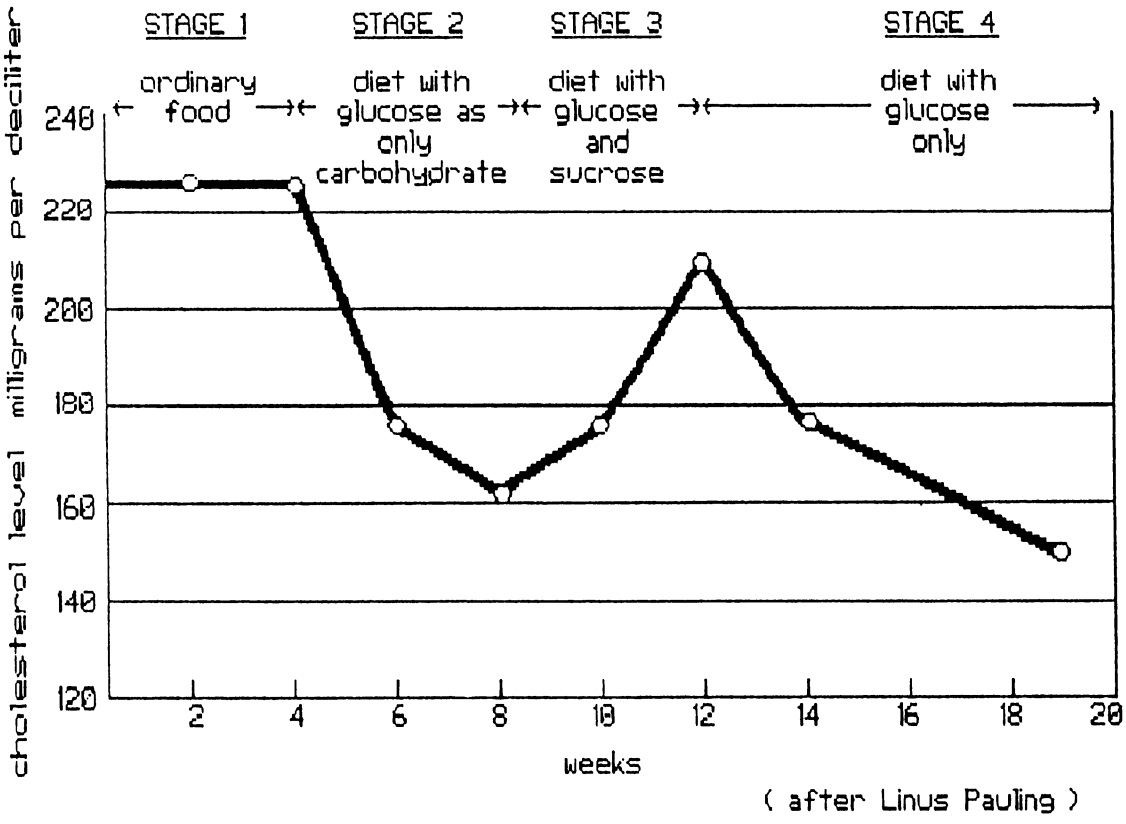
A few years later at a meeting I happened to sit next to the Vice President of Research of a food corporation in the billion dollar class. I asked him if he had verified Mildred Adams work. He said yes; he had made the same rat test somewhat extended. He told me that they had compared the longevities of rats in the following five carbohydrates categories, **proteins being equal:** group 1 was fed boiled starch, group 2 glucose, group 3 cane sugar, group 4 fructose, and group 5 unboiled starch. He found the longevities ranged in the order above. In other words, those rats in group 1 had the longest longevities, those in group 5, the shortest.

This is easy to understand because boiled starch is easily converted to glucose by the enzymes at the beginning of the digestive tract, and thus was a slow release of glucose. This slow release is evidently used more effectively than getting glucose all at once. The cane sugar was a compromise (equal parts of glucose and fructose) and as such came in the middle. The fructose is poorly utilized by mankind. On the average, a person can digest only about 8 grams per day of fructose so that the rest of the fructose may be effectively lost. The unboiled starch (group 5) could not be split by the digestive enzymes but would get all the way to the colon where a lot of bacteria will feast on it and may convert it into a variety of questionable products.

A similar test with the same result was reported from NASA studies with groups of young men, in which the glucose and sucrose were alternated in periods of 1 month each, with cholesterol content and blood pressure data recorded. Both of these parameters were substantially lower when glucose was the carbohydrate.

The superiority of glucose in human nutrition is shown in Figure 40. The data for this figure was obtained with Linus Pauling's permission from his recent book, <u>How to Live Longer and Feel Better</u>.

Figure 40 - A HIGH GLUCOSE DIET DEPRESSES CHOLESTEROL LEVELS
(After Linus Pauling)



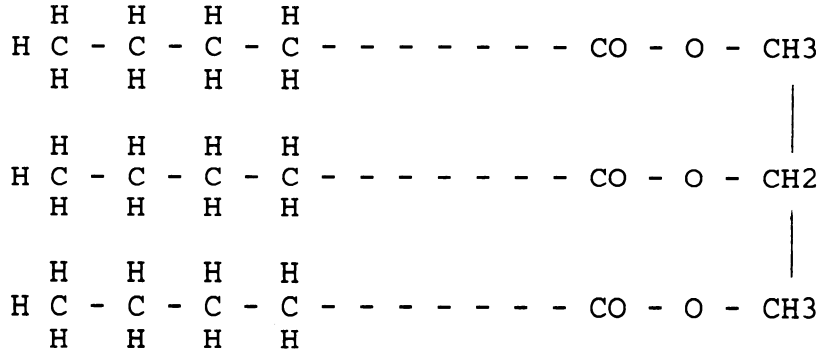
The Fats

The fats are the most concentrated energy source. They consist of carbon, hydrogen, and very little oxygen. For primitive man, who depended on hunting, fat was a preferred food because of its high energy content. In modern times, when longevity has brought us to an age where sclerosis (hardening of the arteries) is connected with the principal causes of death, the reduction of fat in the diet is recommendable.

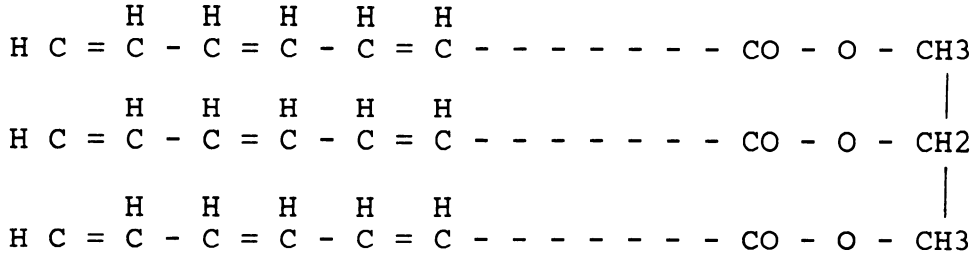
The saturated fats are fats in which the carbon atoms are connected with just as much hydrogen as is possible, typically a saturated and unsaturated fat chains would look like this:

FIGURE 41 - SATURATED AND UNSATURATED FAT MOLECULES

SATURATED FAT



UNSATURATED FAT



The result of this is that the double bonds in the unsaturated fats are ready to snap open and receive any new connection that comes along and fits into the pattern. Thus the unsaturated fats are much easier to use as building materials or as fuels in the chemical processes of life. On the other hand, they are also much more sensitive to undesirable connections. They are more likely to become rancid by taking up too much oxygen and in the wrong places. The consequences of this is that unsaturated fats are preferable to the saturated fats provided that they are backed up with a strong supply of antioxidants to protect them from the undesirable oxidation processes.

Another important difference is that the unsaturated fats are oils at room temperature while the saturated fats are solid at body temperature like soaps or candles. This makes a difference when it comes to controlling undesirable deposits in the arteries. It should be clear to anyone that small particles of solid fat are more likely to be trapped in narrow passages than

are drops of liquid oil. It would seem common sense to have whatever quantity of fat you wish to consume to be a mixture of saturated and unsaturated which is liquid at body temperature.

Some years ago the U.S. Government undertook an extremely expensive, large scale study with human subjects to find out "once and for all" whether unsaturated or saturated fats were better in human nutrition. There couldn't have been any fat chemists on the learned committee, for when they compared the unsaturated fats, they used it without antioxidants. The result was that both were equal. If they had added adequate antioxidants for the unsaturated fats - (or why not to both, it would have been nearly unchanged for the saturated fat), the unsaturated would have proven substantially superior for nutrition. The test would have been valid and significant and should have resulted in nutritional improvements.

Proteins

If the energy supplies of fats and carbohydrates together are insufficient to meet the body's need of energy, it can burn protein. However, this is undesirable from many standpoints:

1. When protein is burned for energy, the nitrogen contained in protein is released, usually in the form of ammonia which can upset the degree of acidity (pH). This can have many largely unpredictable effects.

2. Protein foods, such as meats, are usually the most expensive, so the burning of protein for energy is a wasteful practice.

3. Anything taken away from the needed proteins weakens some important link of the organism. If continued, it leads to often fatal deficiency diseases (for example: infantile kwashiorkor which is a protein deficiency common in African children).

The proteins are composed of about eight to twenty-five amino acids tied together in various configurations. Of these amino acids, the body can make some but there are fifteen to twenty which the body can not make. These are contained in various amounts and proportions in the proteins we eat. The quality of a protein varies a great deal and is determined particularly by the content of some of these amino acids. Generally speaking, the amino acids which best match those the human body needs are found in meat, eggs, and fish. A varied diet of these should provide what is needed. Fish diet has less disturbing factors than meat but is perhaps not quite as closely adapted to human needs as mammalian meat. On the balance however, much is to be said for fish. We should note that the Japanese diet largely consists of fish. This may be one of the factors accounting for the superior longevity record of Japan.

Eggs are excellent from the protein composition standpoint. The high cholesterol content of egg yolks is largely compensated for by the equally high content of lecithins. In nature, lecithins often accompany the cholesterol. I have not seen any quite binding investigation regarding this interchange, but from individual cases, I infer that eating steak daily will increase the blood cholesterol very much more than eating the number of eggs that contain the same amount of cholesterol. At least for many persons a couple eggs daily is entirely consistent with blood cholesterol below 200, and the effect on cholesterol of one egg daily was barely noticeable.

Proteins more than any other group of nutrients are apt to influence allergic reactions.

ANTIOXIDANTS

As stated earlier, antioxidants are necessary for the smooth management of unsaturated fats, which are easier for the body to process than saturated fats. They help prevent the back up of harmful half-way products in the energy pathways. Keeping this knowledge in mind, we will now look into the different properties of the antioxidants more deeply.

VITAMIN E

Vitamin E was first developed millions of years ago by an unknown early life form. This life form is either an ancestor of a monocellular green alga, or of chlorophyll-producing protozoans.

Vitamin E was produced in a microscopic quantity as a result of an accidental mutation in the then new process of photosynthesis. Vitamin E gave this organism an advantage over others since it then had sole control of a highly useful oxygen saving device. Vitamin E was the antioxidant which made it possible for its possessors to out perform others in using the scarce and dangerous oxygen and so it prospered.

The advantages Vitamin E gave were:

1. Ability to survive on lower oxygen concentrations than others.

2. Ability to get along with less protein than others.

3. Ability to control the flow of these functions so as to avoid over production and build-up of harmful products in the

bottlenecks of the narrow passages of the energy conversion process.

4. Ability to use biochemical pathways less accessible to others because of the oxidative instability of some of the intermediate products (Hickman, Harris, 1946).

The first of these points explains why Vitamin E ensured survival of the organism during competition for oxygen in the warm shallow seas eons ago. It also explains why these organisms were the first to be able to live on land in those days when the earth's atmosphere contained but a minimum of oxygen. Today, all green plants can make their own Vitamin E.

Vitamin E can be a useful tool in the quest for longevity. The likelihood of multiple functions of reactive molecules, like Vitamin E, present in an organism is aptly illustrated by Hickman's screwdriver analogy (Hickman, 1949-a, p. 102):

"You buy a screwdriver for your house to drive a particular screw, but you extend its use to all kinds of screws. Eventually you cannot lay your hand upon it because it has strayed to your wife's sewing machine and later to the kitchen for opening a soup can, and finally it is bent by opening a jammed window. In short, wherever it can be employed, or even misused, there it will be put to service. And so it is with biochemically potent substances. The functions of each will be as many as its utility and versatility warrant. We tend to forget this essential fact, and when we have found one obvious function of a new metabolic agent such as a vitamin or enzyme we are apt to say: 'Well that's that and look no further.'"

This has been eminently true of Vitamin E. The complexity of its variants and functions has delayed understanding greatly. Presently, 38 years after Hickman wrote the above, an enormous amount of argumentation has taken place and millions of dollars have been spent uneconomically to cover points which Hickman and his co-workers had already made clear. Their documentation was quite sufficient to have made it possible to push on to more important tasks than seemingly interminable quibbling about points already clarified and sufficiently proven. The intelligent overall direction so much needed is now slowly developing.

What has just been said about Vitamin E is more or less applicable to each of the vitamins. Each of these has been developed long, long ago, and has been tried millions of times for myriads of uses. So it is no wonder that every vitamin has found several seemingly unrelated uses in life processes.

Uniqueness of Vitamin E

Vitamin E has two characteristics which set it apart from other vitamins, with possible partial exception of Vitamin A:

1. It is a requisite for all tissues and therefore is contained in these in so large a total quantity, that day-to-day, or even month-to-month fluctuations in intake are slow to become apparent and slow to disappear.

2. Vitamin E, though fat soluble, can also function as a water soluble vitamin in the form of a lipoprotein, when in combination with lecithin and other phospholipids (Hickman, Harris, 1946, p. 477).

Vitamin E exists in many physiologically similar, but not identical forms. Perhaps this manifold choice is a reason why evolution has selected Vitamin E as its antioxidant ("free radical scavenger") of choice.

A daily dosage of 100 mg/day seems perfectly safe, and a wise precaution. When a deficiency exists, and a rapid build-up is desired, dosages of 400 - 600 International Units (I.U.) are sufficient. (I.U. and mg are not interchangeable terms. The amount of International Units varies from vitamin to vitamin and even within different categories of the same vitamin, as in Vitamin E. Some forms of vitamins are best measured in I.U. and will be so labeled on the vitamin package.) One thousand (1,000) mg/day dosage seems rather high, but no harm has been reported. However, some of the reaction products of Vitamin E are pro-oxidants, and account for the reversals in action which have been observed with dosages above 1000 IU. Tests conducted by physicians seem to indicate that even a dosage of 600 mg/day would be quite safe. Do not take iron at the same time with Vitamin E since they neutralize each other.

In 1943 McCay, Sperling and Barnes tested Vitamin E on rats for longevity. The Vitamin E was administered in the form of wheat germ oil. The result was a 21% gain in longevity for the females. The males only gained 4% which is not significant, but the sperm's motility was increased from 150 days for the controls to more than 750 days for the rats receiving the Vitamin E. This was the first positive test on longevity with Vitamin E. It has been repeated in many variants with essentially the same result.

McCay's observation on increased spermatogenesis is supported by Adamstone's finding (1941) that castrated cockerels require less testosterone when Vitamin E supply is high.

Hickman concluded (1949-a): "As I view the longevity problem, it contains as a central question, 'How much can we have of the preservative factors without depressing active metabolism,

making the organism as a whole lethargic?'" Vitamin E is foremost of the preservative factors to which Hickman refers.

Dr. Hickman stressed the importance of oxidation protection, which Vitamin E provides for vital molecules in transit in the body. A molecule may need a few seconds for the task it has to perform at its destination; yet, it may spend many hours in getting there. In transit, it will encounter saliva, gastric juices, stomach acid, the bile acids, alkaline conditions in the intestines, numerous enzymes, cells of the immune system, and bacteria. It will further pass through the intestinal wall, then through lymph ducts to the blood, and a ride in the bloodstream on some lipoprotein molecule if it is water insoluble, otherwise it is dissolved in water and exposed to whatever else is dissolved there. The water soluble antioxidants, Vitamin C and Selenium are directly soluble in the blood, but have greater difficulty in passing through cellular membranes.

During the long journey wherein an energy source is converted to energy, one of the biggest hazards is oxidation, and Vitamin E gives protection there. The degree, or how much, of antioxidant protection is an essential part of the longevity problem. There is a whole family of Vitamin E; each member being a little different from the other. It is illustrative of the problem that the most effective antioxidant in the test tube (gamma tocopherol) is a very poor protector in the body. This may hinge on a lack of resistance to some hazards in transit.

In 1949 Dr. Kaunitz is reported to have remarked at the second international meeting on Vitamin E that since so many deteriorative processes are oxidations, it does not take much intelligence to realize that antioxidants favor longevity.

Since Vitamin E protects molecules on their trip through the body, it would seem that the larger the dose, the greater the protection. But, doses above the 400-600 mg range become counterproductive. As the Vitamin E works, some of its byproducts <u>increase</u> oxidation, making larger doses counterproductive. To increase the activity desired, it is necessary to combine Vitamin E with other antioxidants. Since Vitamin E is oil soluble, and most of the life processes are in a water medium, we should supplement Vitamin E with a water soluble antioxidant. Particularly, two of these are obviously suitable; but both have some drawbacks.

VITAMIN C

The first is Vitamin C which, in addition to many other uses, is a good antioxidant. Its use as such in bacon was even patented by Swift & Co. long ago. While it is a useful supplement, it fluctuates in intake as well as in amount needed. Its dietary sources in most countries are seasonal. However, this is no drawback since an excess is easily metabolized and does not remain in the body, so excess intake is safe and recommendable. This is the reason why Linus Pauling advocates taking as much as ten grams daily. Vitamin C is a nutrient, so an excess does not harm. When taking such a large dose, the danger of deficiency vanishes. With a reasonable level of Vitamin B6, the possible danger of oxalic acid increase is avoided.

Consumption of Vitamin C should be increased several times over if the body is fighting a cold, or any other infection. Free radicals are released by Vitamin C through participation in the ORD (oxido-reductive depolymerization) reactions. Free radicals may, in some circumstances, be harmful. However, their overall effect in aging, though appreciable, has often been exaggerated. The "screwdriver analogy" is particularly fitting of this vitamin also; so much so that an entire chapter is devoted to the life enhancing properties of this versatile nutrient.

SELENIUM

Selenium is also a very good antioxidant. On a weight basis, it is about ten times more active an antioxidant than Vitamin E. It is not only effective in preventing muscle weakness, but it has also been found that cancer incidence is reduced in locations where the Selenium level is high. Two very good examples of how Selenium is effective in prevention of heart disease are the Keshan Disease of China and the problem with livestock in Finland.

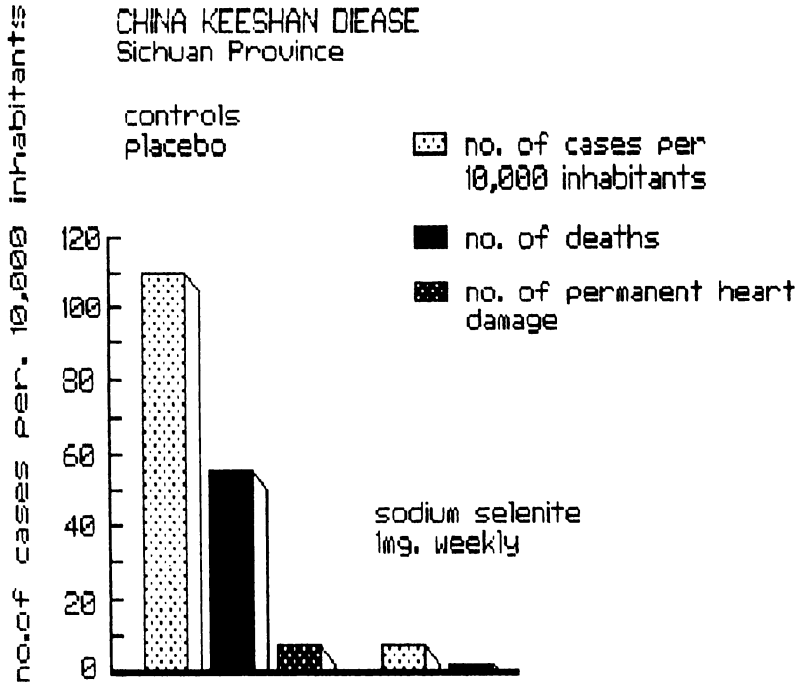
A. The Chinese Children - The Keshan Disease

The Keshan Disease was prevalent in a certain area of China. About 1/2% of all children between 1 and 9 years would fall ill with this disease. Fifty percent of those ill would die of heart failure.

The Keshan Disease Group of the Chinese Academy of Science, in Beijing attacked this problem. One working hypothesis was that the low Selenium content in food and soils of this district was a factor in causing the disease. Experiments with 8,495 children aged 1 through 9 were performed in 1974; 12,212 children were tested in 1975; and 12,579 children were the subjects of experiments in 1976. These experiments proved conclusively that this myocardial disease with 50% lethality was due to a Selenium

deficiency. The Keshan Disease was abolished in just 3 years with these experiments. The disease was eliminated by giving each child in the risk zone 1 tablet of selenium weekly; 1/2 mg to children aged 1-4 and 1 mg to children 5-9. The Keshan Disease Group gave the world an impressive demonstration of what can be accomplished with good planning and large numbers of persons being tested. The following graph may help in visualizing these astounding results. The first 3 bars on the left represent the incidence of this myocardial disease and the number of deaths and permanent damage stemming from it. The last two bars on the right represents the results, i.e. a dramatically reduced number of cases of the disease, few deaths and no permanent damage.

FIGURE 42 - CHINA KESHAN DISEASE - BEFORE AND AFTER SELENIUM



B. The Finnish Cattle

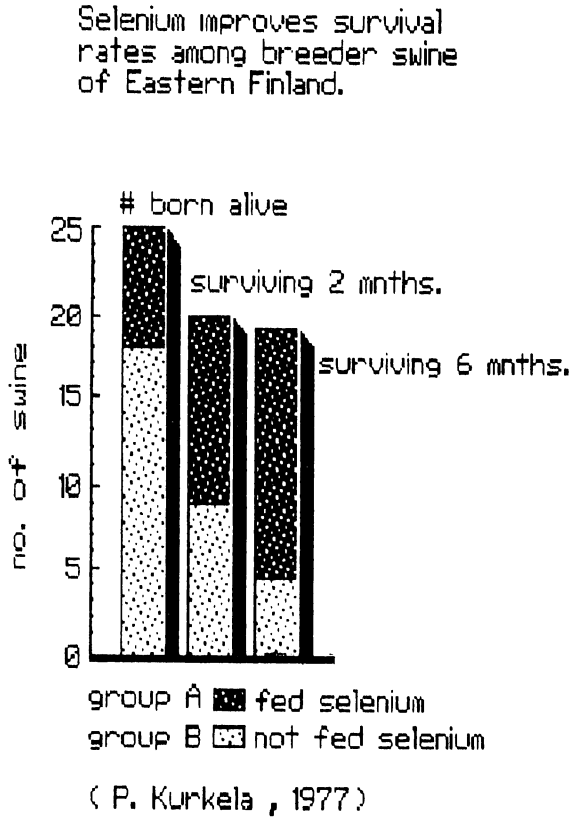
Worldwide, the lowest selenium content in water, soil and crops is found in Finland and in New Zealand. Finland also until recently had the highest death rate from cardiac arrest followed by New Zealand. Apparently, this is much more than a coincidence. New Zealand's lower death rate from cardiac disease could

be due to the fact that the year-round availability of green vegetables assures a reasonable supply of tocopherols, (Vitamin E). This abundance of Vitamin E could supply, at least in part, the need for antioxidants, and therefore could offset the environmental lack of selenium.

In Finland, this selenium deficiency problem was also adversely affecting the death rate of livestock such as cattle, goats, pigs, horses, and poultry. The animals' lifespans, like humans', were being shortened prematurely by myocardiac disease. Since experimentation with humans and their diets on a large scale is impractical, the responsibility of solving this problem fell on the shoulders of the veterinary profession.

The problem of nutrition for the Finnish livestock was worked out by adding dietary selenium to the feed of the animals in question. Figure 43 shows the improved survival rates among breeder swine of Eastern Finland. Group A was given dietary selenium in their feed; Group B wasn't. The results speak for themselves.

FIGURE 43 - FINNISH BREEDER SWINE AFTER GIVEN SELENIUM SUPPLEMENTS



In Finland (as also in the USA), Selenium is now routinely given to cattle, poultry, goats, and swine. Only the humans have been left without it. Impressed by the obvious great advantage to cattle from the Selenium supplement, many farmers in Finland began to take Selenium personally in the form they had it for their cattle, and also gave it to their families.

This was discouraged by the Finnish Drug Administration who sent out a circular stating that people should not eat animal medicines. Now finally a study by Luoma has confirmed, in a double blind study with humans, that the incidence of heart failure was reduced by adding Selenium supplement. This fact, which had been stressed by veterinarians much earlier, was analyzed in my article "The Primary cause of the high myocardiac death rate in Eastern Finland defined as Selenium deficiency" in Rejuvenation VII, No. 3, 1979. The delay in acting on this knowledge (which should have been obvious in view of data then at hand) took seven years. The hesitation might be somewhat excused, however because an overdose of Selenium is toxic. However the warning sign of overdose, a garlic odor of the breath, is clear enough.

In most of the USA and in volcanic countries such as Japan, Selenium is plentiful. Also, If you eat much fish or reindeer meat you do not need to worry about Selenium - both are good sources. Only in areas where rainfall is much higher than the average, as it is at the North Pacific corner of the USA, or where glaciers have scraped away the surface layer during ice ages of the past, as in eastern and central Finland, parts of China (the Keshan-Disease belt), New Zealand and South Africa, is the Selenium required for domestic animals. The need for Selenium supplement in human diet is now also being generally recognized in these areas.

Due to the near impossibility of testing humans in large scale studies, the optimal percentage of Selenium in human diets is still unknown. It will however, exceed natural levels in the environment almost everywhere. However, an overdose of Selenium is toxic. Selenium could slow oxidation down to the point that the heart can not get the oxygen it needs to function. For this reason, any Selenium dietary supplement which exceeds .5 mg (1/2 milligram) of 100% Selenium should not be taken unless under a physician's care and supervision.

In summary, Selenium has its proper place in the antioxidant formulations, but has to be handled with care.

A balanced supplementary nutrition formula with combined antioxidants is shown in Appendix 1. This formula was arrived at so that every addition was tested for antioxidant efficiency together with the rest of the formula. The control formula was the best previous formulation of the antioxidants. In this way

we included in each test the effect of synergism, (those effects which could not be achieved by any one antioxidant alone but only with various combinations). In the case of antioxidants, the effect of synergism cannot be over-estimated. If we had tried testing each antioxidant separately and then combined them from these data, it would be like trying to walk up a ladder while keeping one foot on the ground the entire time.

Antioxidant formulations are greatly increased in their effectiveness by further compounding with Vitamin C, Lecithin, and the common food antioxidant TBA and TBT. Vitamin E and Iron should not be taken at the same time of the day, because they neutralize each other.

TRACE ELEMENTS

When earth was young, life first began to make an appearance in the shallow warm seas of the newly formed earth. It is certain that life began in water because it must have started as a single cell and in order to grow, a cell must have a liquid medium for easy interchange of materials. This first liquid was the water which had rained down when earth had cooled down to below the boiling point. At that point the crust of the earth had just formed so it was pretty smooth and had not yet been wrinkled up in cooling. Thus the water covered the earth's surface fairly evenly. Millions of years must have passed while the rocks cooled to below the boiling point of water. There was plenty of time for everything soluble on the earth's surface to dissolve in the water. Thus, that water contained some of everything that was at all soluble in it. This was the liquid in which life first appeared.

Eons of time passed. The first living cells developed and ultimately some life forms moved from water to land. When they made this move, they could succeed only if the organisms contained in them the necessary water and those ingredients from the oceans which had become necessary for life. That water was the beginning of the blood in our veins. The chemical composition of our blood is still remarkably similar in proportion to what the composition was of the sea water which the very first land life left behind uncounted millions of years ago.

Among those organisms, the balance between pro-oxidants and antioxidants became more important as oxygen became more plentiful. This occurred as a result of the green plants beginning to convert the carbon dioxide content of the atmosphere to sugars and oxygen. Copper and Iron, examples of trace elements, are both pro-oxidants. Both are needed for several different life processes. These metals have the ability to switch from one number of binding force to other forms. In this way, they serve as catalysts for other reactions. Many chemical processes in the

living organism depend on the ability of those two metals as well as of manganese and vanadium to switch valence.

All of those metals from the original mother ocean which could serve any possible useful function in life must have found that function in the course of millions upon millions of years. Some of the elements are required extensively and in large quantities, (examples: carbon, oxygen, hydrogen, nitrogen, iron, magnesium), while other elements found only a few or one use which required only small quantities. However, these trace metals such copper, iron and vanadium, are still required for certain vital functions. Today, there remain only a few metals which despite the trials by all life forms never found a single use by a single organism for any purpose. These are the outcast elements: aluminum, mercury, cadmium, and beryllium.

The trace elements (not the outcasts) play an important part as do the important life elements iron, sodium, potassium, magnesium, zinc, and calcium. The best protection against a deficiency of these is a varied diet. This diet should favor foods that are connected with active life such as fresh vegetables, sprouts and fat-free milk (not the so-called "light milk", which contains 20% fat if we count it on the solids present, not on the water as present labeling does).

I usually take a hair analysis for metals a month or so after a move to another diet area, to make sure that everything is in line. However, none of the present methods is ideal. Analysis from blood could reflect what you ate at recent meals, particularly the last. Hair analysis, or analysis of skin scrapings reflect averages over a longer period of time, but they are too slow.

CAUTION

Every person has his individual characteristics and sensitivities. Before settling on anything related to your health, talk it over with your physician, who knows your personal characteristics and possible sensitivities. The following biochemical facts may be taken as guidelines, subject to your physicians review.

Suggestions:

Heart disease is to a very great extent preventable, by the following:

1. A lecithin intake of at least several grams daily. The author takes 7 grams of 100% lecithin in the form of the dietary supplement of vitamins and antioxidants shown in Appendix 1. Twenty two grams of this contains 7g of lecithin. The best natural sources of lecithin are egg yolks and brain. Because of

the protective effect of lecithin, no objection is seen to eating one or two eggs daily, despite the cholesterol content of egg yolk.

2. Take an antioxidant composition comprising both Vitamin E and Selenium. These two antioxidants work on different mechanisms, so their effects do not greatly overlap. Do not take more than about 500 mg daily of Vitamin E as a steady diet. After correction of any deficiency, 100 to 200 mg/day should suffice a suitable dose. Do not take Selenium without your doctor's knowledge and approval.

3. Take a liberal daily amount of Vitamin C. Under normal conditions 500 mg/day suffices for women, 1000 mg/day for men. In case of infection of any kind, the dose can be safely multiplied and should be maintained by frequent portion. A person fighting infection may take a couple of grams on awakening and still be short of the vitamin by noon, so additional Vitamin C may be taken hourly. The leucocytes use Vitamin C in generating the free hydroxy radicals which they use in fighting bacteria or destroying foreign molecules. Vitamin C is also important as an antioxidant, so that in an infection, the Vitamin C supply must be large enough to satisfy both of these needs, and a few more. A total of 10 grams daily is not too much, but it should then be spread over the day.

4. Keep body and brain active. Use at least 1 hour daily for motion of an endurance type such as walking, rowing, skiing, dancing, anything that keeps the muscles, including the heart muscle, working for an hour a day at a comfortably increased capacity. Additional reasons for a daily regime of exercise will be discussed in Chapters 15 & 16.

5. Take a physical examination twice yearly whether you think you need it or not. Tell your physician what you are doing and why and take his advice. I can only discuss averages, your physician knows you.

If everybody could be brought to do all of the things recommended here, it is a reasonable expectation that heart and circulatory troubles would decline to no more than 10% of what they are at present. If you applied all of the above, the probability of your having trouble with heart or circulation would be less than 10% of the average.

CHAPTER 12

THREE PARABLES

The Parable of The Highway Commissioner

In the rich and motor-minded republic of Xenobia, lived a clever and politically appointed Highway Commissioner. The capital of the country was Herotown. The next largest city, Tradetown, was 220 miles to the North. The network of roads between Herotown and Tradetown were well developed, but most travelers preferred the 8-Lane Superhighway No. 11.

One day the Highway Commissioner came to the office of the City Director of Herotown and said, "The cost of maintaining Superhighway No. 11 is too high. Our budget is running dangerously low and we can't be sure we'll get the money we need appropriated for this problem. Let's save the government some money and close down Superhighway No. 11. As far as I'm concerned, that highway was a mistake made by the former administration and will be nothing but a liability if we spend all the money in our budget on keeping it up. Since there are plenty of other available roads between Herotown and Tradetown, I don't think closing Superhighway No. 11 will affect travel."

The City Director objected, but the Highway Commissioner said, "To prove the point, we'll shut down Superhighway No. 11 "for repair" for a month. I don't believe you'll see a difference in the number of travelers between the cities, but just to make sure, we'll take a count and see." The City Director agreed to this temporary situation.

After a month the situation was reviewed. The Commissioner said, "The complaints regarding the closure of Superhighway No. 11 have been minimal and we have saved a lot of money for other things. Let's save even more money by shutting down two more roads. We'll still have more than enough roads to handle the traffic." Soon four roads were closed. The traffic still ran, not without some grumbling, but the situation was still tolerable. At the end of the year the Commissioner received official commendation for his zeal and the great savings he had made. Everything seemed well in hand.

Then Disaster struck. A large dam failed without warning. An enormous flood swept away villages and towns. Two large valleys became rivers under the great swell of water. The remaining highways could not begin to take care of those who wanted to escape, nor those who would come to their aid. The old highways, including Superhighway No. 11, had already been practically destroyed by cannibalizing equipment in order to repair other

highways. The bridges weren't maintained either. Fifty thousand people died, including the Highway Commissioner.

A news conference was held at Herotown's hospital, which had become the crisis center. The new Highway Commissioner, as well as some of the prominent health professionals, were asked to comment.

When asked about what was going to be done to avoid future catastrophes, the new Highway Commissioner said, "This was a horrible lesson. In the future we must ensure that we have plenty of roads and see that every one of these roads is always in a condition to handle any emergency."

The Chief Surgeon agreed, relating the Highway Commissioner's statement to other aspects of life, "We know that there must always be an excess of facilities to handle any possible emergency. This axiom can also be applied to our own bodies".

The Chief Pathologist at the University Hospital said, "Xenobia's plight can be compared to the management of our own body systems. There must always be an excess of critical nutrients, and of capacities to handle emergencies".

"The blood circulation is just like a highway system where the blood corpuscles are the cars. The more a person has developed his collateral circulation, by sensible exercise, the better his chances are of surviving an emergency which might close any one of the blood vessels, our internal highways".

The Gerontologist completed the comparison, saying, "This axiom follows from "Le Compte's Law". The chance of surviving any emergency is better when there are fewer deficiencies in anything the body needs, be it food, vitamins, trace minerals, hormones, etc. When the number of deficiencies rises and they continue to get worse, the aging process is speeded up, leading to a premature death. In the case of Herotown, if only one highway had been closed and the bridges on that one had still been maintained, most of the people could have been saved. In the case of our own bodies, if only one blood vessel is blocked, our bodies will, in most cases, have access to several other blood vessels to take care of any bodily emergency on its' own".

Finally Doctor Wise, the old family physician whom all loved and respected said quietly: "Now I finally understand why vitamins are so different from all the new synthetic pharmaceuticals we use. Each vitamin has been in existence millions of years and in all that time evolution has found numerous, often totally different uses for each of them. Therefore, it is wrong to determine the needed dose of a vitamin from any one test. We should make liberal allowance for the large number of tasks each vitamin must cover. Dosage for the synthetic medicines can usually be

judged from one definite property. For the vitamins we must allow ample reserves for the many things each does, some uses perhaps not yet discovered.

The Sea Captain and His Chain

Once upon a time there was a sea captain who owned a trading ship which he loved dearly. This ship had been his livelihood and had served him well. However, he loved the anchor chain of his ship even more. This anchor chain had more than once saved his ship and his life by holding it safe in tempests, off leeward rocky coasts.

Now after all these years of good service, the anchor chain was getting old. One of the links had broken from wear and corrosion and had to be fixed. He contacted a chain manufacturer who said that the chain wouldn't be worth the price of fixing it and that the captain would be better off buying a new one. To this the Captain responded with a thundering "NO. This chain has saved my life and my ship. I'd be an ungrateful Son-of-a-Bitch if I let it go to the scrap heap in its old days. Repair that link for me so that it will be unbreakable and never mind the cost!"

The chain manufacturer said: "Sorry, that would be a custom job out of our line. Why don't you see John, The Smith? He does special repairs and will do exactly as you tell him to."

John, The Smith, promised the Captain that the link would be repaired and would be able to hold virtually anything. The chain was due to be ready in a few months, when the Captain would be back from his next long trip.

Time passed, the Captain returned and John, The Smith, brought out the chain. Proudly he pointed to the former broken link. It was really something to behold. It was reinforced with boron and graphite fibers, had an outer shell of titanium and no doubt would stand up under any conditions. The Captain was pleased with how the chain turned out and paid the smith his exorbitant fee.

The Captain soon got the chance to test his newly repaired chain. He was due back out on a voyage that night. However, he wasn't even out of port when the chain broke again. The Captain was furious and stormed back to John, The Smith, to get back his $5,000 fee.

The Captain was surprised to find that John, The Smith, was really unconcerned about the whole affair. "You'll not get a penny from me", he said. "I did exactly as you asked; I fixed the break in the chain. It's not my fault that the other links,

which were obviously corroded and worn, finally gave way."

"Well, why didn't you tell me that fixing only one link was a waste of time!!!", bellowed the Captain. "Well, you were so dead set against replacing any links from your "precious" chain that I knew my advice would be wasted. Besides," John said with a smirk on his face, "at $5,000 a link, you're my best customer."

The Captain's reply can be imagined, but not printed.

This story will bring out that when maintaining a chain, it does not help to make any one link infinitely strong. If one link fails, the chain fails. If we look at the chains of chemical reactions upon which our lives depend, there is no point in letting any of the vitamins, trace elements, exercise programs, or fad diets become the most important element in our lives. The break will come only at the weakest link - the one where a critical substance is missing or faulty. Yet, we see at every step how merchandisers push one diet or exercise plan or vitamin as the thing.

There is no merit at all in taking anything in larger quantity than is required for optimal function. There is also no merit in emphasizing one form of food over all others. Variety of diet is more important. The same can be said of exercise; many people erroneously believe that if they engage in strenuous exercise daily, then it doesn't matter that they eat nothing but fast food or other junk food products. Again, the break will come at the weakest link, so don't concentrate all of your efforts on one aspect of health, instead use a holistic approach to living better and longer.

The Parable of Two Prisoners

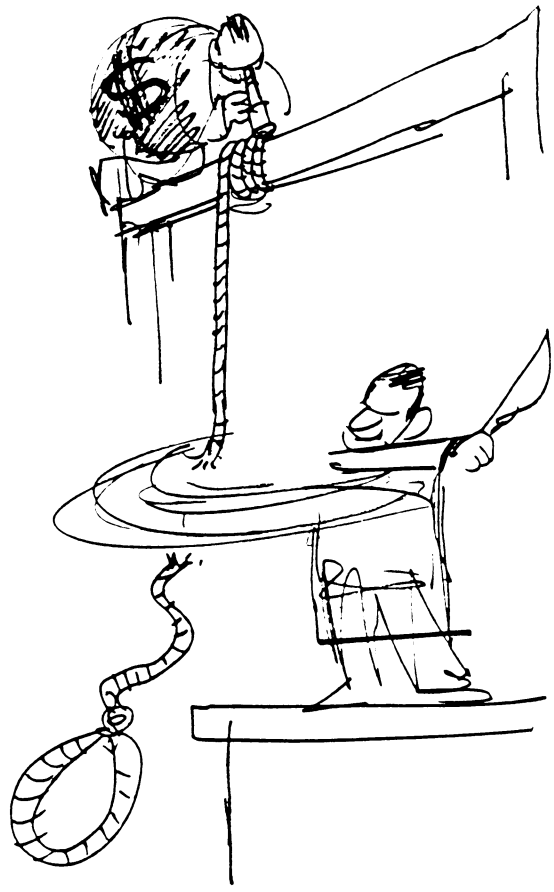
Once upon a time two men were held in a prison, awaiting their execution by hanging. They had dared to teach theories which did not agree with the old books.

Three days before their execution each of them had a visit from a supernatural being who appeared to each of the condemned men in their cells, and said: "A higher Power who commands me will give you one more chance. I am to give you one and only one of the two things I hold. In my right hand is a knife, which is invisible to all except you. In the last moment you might be able to cut your rope and escape in the commotion. In my other hand I hold a microscope and a piece of the rope which will be used to hang you. If you chose the microscope you will have the

satisfaction of examining to the utmost detail the structure of the rope which will end your days. Choose, and may your choice be wise."

We are all under a sentence of death, only the date is uncertain. Many of us have received the strange visitor and have heard his offer. I chose the knife. Many of my colleagues chose the microscope, and are spending their remaining time in pursuits which could not in any event give them longer life.

FIGURE 44



THE EXTENSION OF HEALTHFUL LIFE

First of all, beware of two pitfalls:

1. There is no one best way or most important supplement, no matter what anyone may tell you or what you believe you have experienced.

2. If you want to repair an old chain, you would not make any link enormously strong and stop there! You would, no doubt, continue to look for the next weakest link to strengthen. So continue in this vein, keeping in mind Le Compte's Law: The rate of Aging is proportional to the number of deficiencies ("weak links") and to their severity.

Sometimes a person tries one certain thing, and it works! She/he then joyously exclaims: "I have found IT." She/he tells the physician. He smiles tolerantly since he has heard that many times before. Her/his friends are impressed. They also try it, mostly without spectacular results, unless they happened to have had the same deficiency.

Merchandisers know that it is inefficient to stress more than one thing at one time in an advertising or publicity campaign. Knowing this, they will stress one product exclusively until sales decline. They'll then start a new campaign to sell another product. This has gone on in cycles since the time when the Snake sold Eve and Adam an apple with such disastrous or at least questionable results. Whatever the product is, the Merchandiser will find several cases where it actually took care of someone's deficiency so that striking results were obtained. These results can then be truthfully cited. Think of all the "testimonial" commercials for The Weight Reduction Plan. Only those people who were successful with the diet are on the commercial. You don't see the multitudes who didn't lose an ounce, or even got sick from following the diet. Again, keep in mind that there is no one right way for each and every person.

The reader, who has before her/him The Parable of the Sea Captain and his Anchor Chain will be happy to have eliminated one weak link, and will continue to see that she/he does not again run into a deficiency on that particular point. Knowing that the job is only partially complete, she/he will give serious thought to other possibilities, and after each success will again ask: "What is now most apt to be the weakest nutritional link in my system, and how can I best strengthen it?

For more detailed comments on this subject, Dr. Linus Pauling's book "How to Live Longer and Feel Better" is warmly recommended. It is a "must" for all persons who wish to go deeper than the surface. Roger Williams' books are acknowledged for their conscientious information.

In this context we must not forget the book by Luigi Cornaro, written in 1550 entitled "The Art of Living Longer". He was born in 1467 and after a stormy youth, his physicians told him he had to cut down on his calorie intake and change his lifestyle - which he did. He died in his 99th year. Cornaro recommended the following foods: bread, panado, some broth, an

egg in the broth, or a spoon of meat, preferably veal, kid, and mutton, poultry of every kind, likewise fish of which he mentions several, sea fish as well as fresh water fish such as Pike. This is a remarkably well planned diet for that time with its emphasis on egg which gives choline and lecithin (which counterbalances cholesterol) and lean meats and plenty of fish. In Italy, fruits and fresh vegetables can be taken for granted for most of the year. Cornaro wrote: "All my faculties, at 95, as good as ever, judgement, memory, spirits." And wisely he says: "Illness does not happen without cause, remove causes, and this illness disappears." Mr. Cornaro's book has never been spectacular but has enjoyed a new edition every hundred years. The last edition was printed in the U.S. in 1979. It has certainly stood the test of time, and will probably have many editions in the future, as may well the other books just mentioned.

Dr. Durk Pearson and Sandy Shaw achieve in their book a high degree of coverage of the recent literature by capable utilization of computer technology. The factual material, logically arranged saves considerable time and many computer searches for the person who has some knowledge of the field and who has an independent judgment.

All of these books have one thing in common: They bear witness of a true dedication of the authors to their subject. Linus Pauling's book is not only the work of a great scientist, but also of a great humanitarian with true dedication to the ideals which he champions.

Roger Williams' many nutritional books are likewise not the work of an ordinary man, but of a clear mind, concentrating on assembling and passing on to others his great experience in the field of nutrition. Sandy Shaw and Durk Pearson are dedicated persons who have the courage and persistance to assemble an impressive and useful collection of computer processed knowledge representing an important range of information of all degrees of applicability. They leave it largely to the readers as a challenge to further scan an extremely rich and varied collection of fact of all degrees of relevance and credibility.

Dr. R. L. Walford's book on immunology is in a class by itself in that subject, and Dr. Alex Comfort's books are of general interest and value.

CHAPTER 13

OTHER HEALTH CONDITIONS ASSOCIATED WITH ADVANCED AGE

Diabetes

Diabetes occurs in many forms, of different character. It can occur in children even as a birth defect. However, in its principal forms, diabetes is an age-dependent disease. While it has not been a dominating cause of death in any of the epochs, it has a longer background in history than the other deficiency diseases because it has a clear diagnosis: Mainly that sugar is filtering through the kidneys.

In the United States, diabetes is extremely common in advanced years. If the medical standards used for young people were used in testing glucose tolerance of old persons, a majority of these might be found diabetic. This percentage is very much lower in Japan where the diet is richer in carbohydrates and less fat oriented.

The human brain depends almost entirely on glucose for its energy supply. All other carbohydrates must be transformed into glucose before the brain can use them, and it cannot use any fat whatsoever. In this regard the brain is to be likened to a very high combustion motor, which requires 100 octane fuel. It cannot work with lower octane, let alone alcohol or turpentine.

This is understandable because of the space limitation: the skull confines the brain and prevents further expansion once the skull bones have hardened. As it is, the brain uses 25% of the energy supply of the average human. A much heavier head would become unwieldy, and could probably only develop in sea mammals. Other factors have limited the development and use of its potentialities in sea mammals.

Thus, early in the history of life on this planet, evolution chose glucose as the specialized fuel of the brain. The reason for this selection seems clear enough -- glucose is manageable, generally available, and chemically attractive (having all of its reactive groups in the equatorial plane of its structure), thus being optimally accessible. This dependence on glucose makes us susceptible to a deficiency disease: the deficiency of glucose.

The brain has the master control of very many processes in the body. It does not hesitate to use this control to protect its own interest, whenever it finds a critical supply threatened. No supply could be more critical than the supply of the unique fuel of the brain processes, namely glucose.

When the supply of glucose runs low or becomes irregular,

the first action of the brain is to forbid the muscles to use any glucose. The brain accomplishes this by controlling the insulin production. This can be done without too much general damage, because the muscles are quite capable of burning fats as their only energy source.

The second step will be a more radical modification of the pathways which will lead to production of acetone and gamma butyric acid. The brain cells can use these substances well enough to function tolerably although not nearly as well as when glucose is available.

Once the brain, in self defense, enforces a monopoly of whatever glucose there is and switches the chemical setup of the body to a production of its' substitute fuels, diabetes results. If at this point all sugar is prohibited, the diabetic condition may become permanent. In some types of diabetes, the "disease" may be cured by carefully controlled and medically supervised administration of glucose.

Glucose in the diet every day and at every meal is an effective precaution against one principal type of diabetes. This form of prevention should not be difficult. Starch is a polymer of glucose which converts into glucose when boiled starch contacts the appropriate body enzymes. Glycogen is the corresponding glucose storage of animals. Sucrose is composed of one molecule of glucose bound to one molecule of fructose. In longevity tests, glucose is substantially more favorable than sucrose or fructose. The reason why this is so was discussed in Chapter 11, under "Energy Sources" pg. 121.

In a diet rich in complex starches or dextrines, both found in most vegetables, the glucose supply should be no problem. Almost all starches are composed of glucose as their main building block. Glucose, in its isolated form, can be found in health food stores at fairly high prices. It can also be purchased in 60, to 100 pound bags from most of the large corn processors substantially at the world market price for sugar. The technical grades as sold to food manufacturers are satisfactory. Glucose is the same as "Dextrose".

While the above is basic to diabetes generally, we must not forget that there are types of diabetes which have quite different causes, and where accordingly differing therapies are called for. Among these are the juvenile diabetes, in which there is an inborn defect in the "Langerhans islands" of the Pancreas gland. These are small cell groups in the pancreas gland.

It should be bourn in mind, however, that a common cause of diabetes is irregularity of its glucose supply.

Loss of Height with Aging

Recently, while at a college reunion of a class which entered a university in 1924, one observation struck me forcefully. In 1924, many of those in this group were taller than I, and now I was surprised to find myself the tallest by a considerable margin. What could have caused this substantial shrinkage about the age of 80? Which of the many things I have worked with might have been the cause of my avoidance of this particular loss? First of all, was this loss of height with age a general phenomenon, or something specific for the particular group where I made this observation?

I found an answer in reading Ward Dean's recent book, "Biological Aging Measurements": edited by Hans U. Weber. The loss of height is generally accepted as a "normal" effect of aging, which begins with the cessation of growth, and accelerates from age 60 on. J. Faredlander et al. published a curve based on records of Veterans. The effect was general.

FIGURE 45 - LOSS OF HEIGHT WITH AGE (FAREDLANDER ET AL)

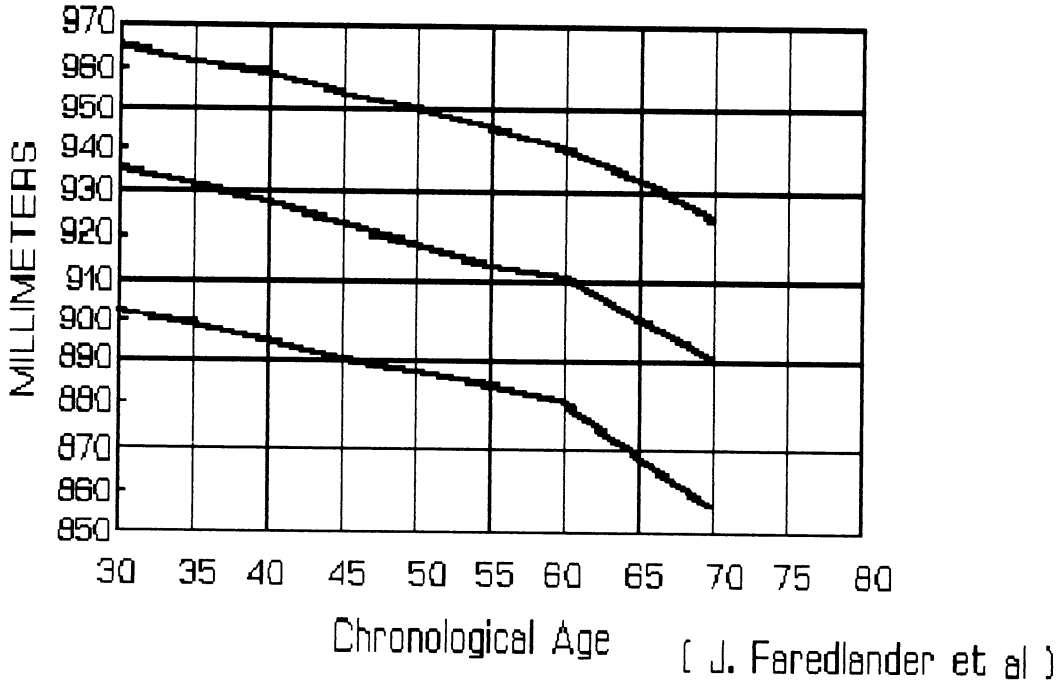
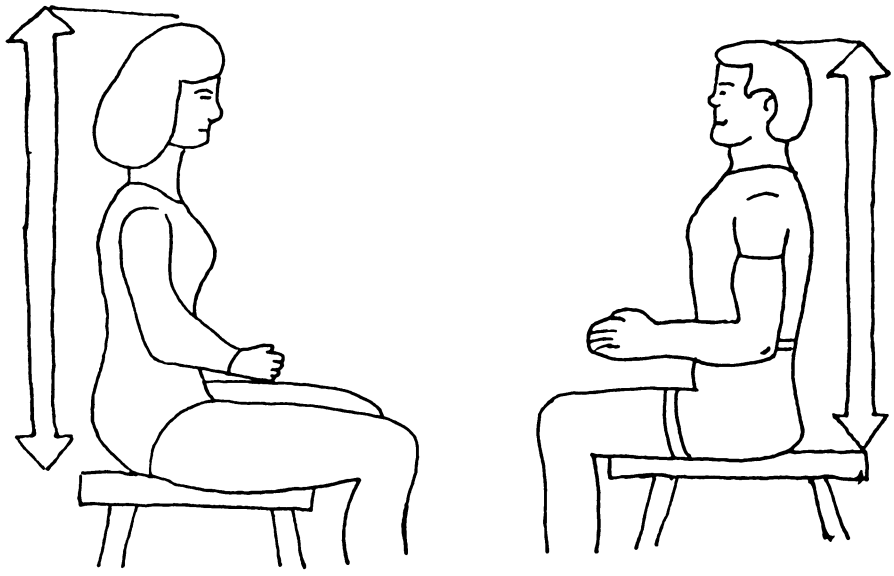


FIGURE 46 - TECHNIQUE FOR MEASURING SITTING HEIGHT



The technique used for measuring sitting height is as follows: The subject sits erect on a flat bench with his/her buttocks, shoulders and back of the head against the wall. Then a tape measure and draftsman's triangle were used to measure the distance from the sitting surface to the top of the head. The heights were expressed in millimeters.

The changes in sitting heights are particularly revealing because these are measurements of the loss of elasticity and compressive strength of the discs. The discs separate the hard, bony segments (vertebrae). The vertebra, together with the discs, make up the spine, which encloses the nervous elements. It is the discs which fail with age. The reason for this failure appears to be two-fold:

1. The discs are softer than the bone. When young, they are very elastic. They have a collagenous base, which is gradually hardening due to progressive reaction with some of the large number of crosslinking agents which continually circulate in the body. Thus, with age and embrittlement, the discs become more prone to deformation on impact by mechanical forces such as hammer blows. Every step on a hard surface with an unyielding hard heel is in effect a hammer blow. This, repeated hundreds of thousand times during a lifetime, will finally cause some, and then some more of the discs to fail. With fewer discs to share the shocks, the failure of the discs becomes more frequent - the rate of failures after the age of 60 is apparent from Figure 45.

2. Calcium is a key substance not only in bone, but in every cell in the body, including every muscle both striated and

non-striated autonomous muscles. Aluminum will displace calcium wherever they compete. The most disastrous results occur in the brain and heart, but several recent papers in The Lancet have connected aluminum with osteoporosis. The next few years will tell whether these last mentioned cases are exceptional, or clinically important.

Aluminum, important though it is, is only one of a huge number of crosslinking agents, many of which have the same effect: crosslinking the proteinaceous substances in the bone structure and in the discs, which then gradually lose elasticity so that their normal binding and buffering capacities begin to fail.

I have always had a preference for soft shoes and rubber heels, and have thus avoided much of the "hammer blows" of hard heels.

In clinical research, one case has very little weight, as exceptional factors quite unrelated to all theories might have been at work. I should therefore not like to comment on the question why it happened that out of a group in 1924, I seemed to be the only person who had kept my height practically unchanged. A factor could have been that I have had a low fat, high carbohydrate, normal protein diet. It could be because I have been drinking at least 3 quarts a day of fat free milk, thus having a high calcium diet. It could be because in 1935 I started on an antioxidant diet which I have improved on from time to time but never omitted, and it could be for some different reason which I do not believe, but cannot exclude.

The best way to settle this question would be by large-scale double blind tests with proper controls and sufficient duration.

LIGHT EFFECTS, SKIN COLOR AND LONGEVITY

Natural and Artificial Protection from Solar Radiation Effects

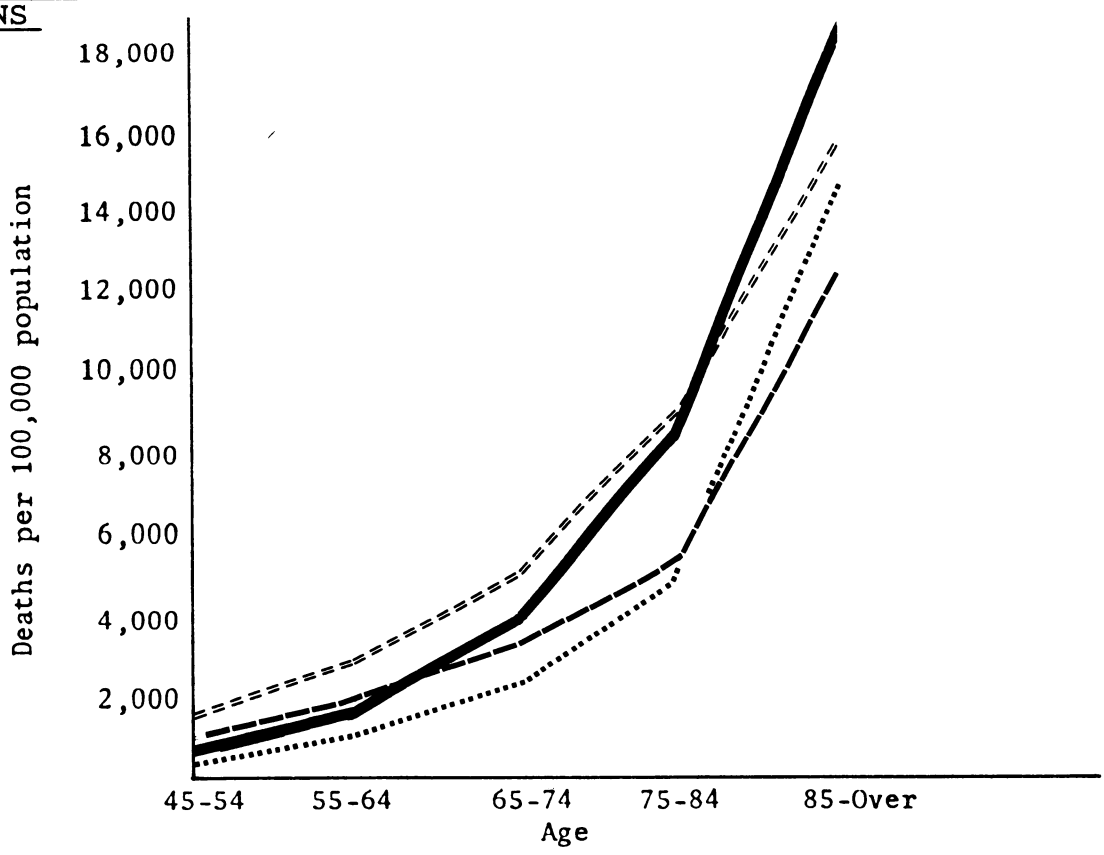
The long term effects of light on human surfaces has been thoroughly studied by dermatologists. In this case, there is no lack of comparison material. Every person has some skin regularly bare and thus exposed to light as well as adjoining skin that is regularly covered.

In studying the longevity curve for various population groups, it became clear that life expectancy has a relationship to skin color. The longevity curves for white and non-white persons cross about age 75. Below that age, the non-white person has a shorter life expectancy. Beyond that age, the non-white

person has a higher life expectancy. Figure 47 shows the death rates per 100,000 population for these groups. Notice, for example, that the death rate for black males is higher than for white males until the two lines intersect at about age 75. Then after age 75, the death rate for black males is lower. At about age 85, the death rate for black males is about 25% lower than for white males. This can hardly be explained by economic differences because this phenomenon does not correlate with any of these factors.

The explanation for this "turn-around" could be that beyond the age of 75, a person with a dark skin color which absorbs or blocks high energy radiations, such as ultraviolet, has a longer life span than persons whose skin does not give them such protection. The gap between the curves increases with the years so that at age 84, a black woman has almost twice the life expectancy (can expect to live twice as many more years) of a white woman according to the U.S. official population census. The difference between the males is not so pronounced but it is in the same direction.

FIGURE 47 -COMPARING DEATH RATES OF WHITE PERSONS TO BLACK PERSONS



Death rates by age, sex and race: 1983
Source: U.S. National Center for Health Statistics
White Male:▬▬▬ White Female:·····
Black Male:======== Black Female:▬ ▬ ▬

While many speculations as to why solar radiation has this effect could be possible, the most likely one is that when the ultraviolet radiation can penetrate the outer skin layers, it will cause some systemic changes which affect the organism as a whole. Every person past 40 can observe that the skin of exposed parts of the body shows much more marked aging than parts not so exposed. Anything that gets under the skin will, in time, enter the blood stream. From this, it seems clear that the radiation formed products which account for the difference between radiation exposed and other parts of the skin, will spread to the entire body and will do some harm.

In the early parts of life this effect may be overshadowed by other factors like diet or economic differences, but with advancing years it adds up and finally becomes a controlling factor.

It would be easy to test the validity of this conclusion by having two parallel groups. One half would apply every morning to their skin a suntan screen solution; and the other half, a control group, apply a similar preparation without the suntan screen. This should be arranged as a double blind test. Until such time that this has been tested, proved or disproved, it would seem a good idea for persons without protective pigmentation to apply an effective suntan screen every morning as an after shave or makeup, as appropriate. This is not to be taken lightly because at age 84 the difference in maximum life span could be as much as 7 to 8 years. Obviously, the current fashion trend which dictates that all white persons should roast in the sun for hours on end is one which is working against improved longevity.

SENILE CATARACT

The effect of ultraviolet radiation in causing premature aging of skin was recognized by Unna (1894) and has received ample confirmation subsequently. J. G. Bellows and R. T. Bellows (1976) have studied and confirmed the applicability of this same aging mechanism (photo-oxidation) to the formation of senile cataracts.

Unsaturated fats are normally a part of all cell membranes. Strong light, such as fluorescents, splits these unsaturated fats and causes the formation of aldehydes and peroxides, both powerful crosslinking agents. These crosslinkers cause the aging of the inner parts of the eye, particularly of the lens and the retina.

Crosslinkage is also favored by an increase in protein concentration and loss of hydration of water. These bring the large molecules closer to each other which makes crosslinking easier.

These conditions occur as years progress, as discussed by Bellows. The eyes are embryologically like skin, formed from the original ectoderm. This fact makes the properties of skin and eyes similar.

Overlying cell fibers of the eye are increasingly pressed inward, and eventually join the central crosslinked masses. In time, the Lens structure becomes increasingly involved, so that it appears as a huge brown lump substantially without cortex. It is now a brown nuclear cataract.

The color has progressively changed from clear to brown, darkening progressively and even becoming fluorescent. A similar progressive change of color may be observed in the course of 1-2 years in hectograph rolls made from gelatin and glycerin, and crosslinked with small amount of formaldehyde, glyoxal or glutaraldehyde to increase their firmness.

This checks well with the observation of Uyama and Ogino, who have observed quinoid fluorescent crosslinking agents in connection with cataract. (The quinones are a class of reactive chemicals to which many powerful crosslinking agents belong.)

Prevention

The easiest way of reducing the probability of senile cataract is to minimize the exposure to light, particularly of the Ultraviolet rays. This is easily done by wearing tinted glasses - those do not need to be conspicuously dark to be effective. Further, the common fluorescent lights are quite rich in chemically active radiation. Where we have a choice, incandescent type light is preferable. Where this is not practical, it is recommended to use tinted glasses when habitually working with fluorescent lighting.

It would be of considerable interest to make a study that would find the correlation of the color of the lens of aged persons, as well as the occurrence of cataract, with the degree of exposure to fluorescent light in their daily work.

To a casual student of the eyes of squids, it would appear at first glance that the squid eye, which has the light sensitive retina as its outermost layer, has a better arrangement for sharp vision than the human eye, which has a light insensitive layer between the retina and the light. Before I became aware of this fairly recent knowledge, I used to wonder why the human eye is built as it is. To a casual observer, it may seem inefficient that the light sensitive retina is covered by an insensitive membrane in the human eye.

The explanation is now becoming apparent. The sensitivity to strong light is the cause. The outer film in the human eye apparently has the task of protecting the sensitive retina from too much active radiation, while in the squid, such radiation is absorbed by the water in which they live.

It has been theorized that Ultraviolet light is bad for the eyes because it induces free radicals. The free radicals are not the direct cause of cataracts. As you may recall, the process of crosslinking is a process of two steps, separated by a pause of at least several days. The life of a free radical is typically a small fraction of one second. The main crosslinking agents remain active for at least many days, and are therefore principal causes of senile cataract (some of these are formaldehyde, acetaldehyde, acrolein, glutaraldehyde, etc).

After exhaustive studies, Sundholm et al. concluded: "even if a free radical reaction might help produce a minor percentage of the crosslinkers other combination processes, the condensation between carbonyl compounds and amino groups is far more important in the crosslinking of autoxodizing lipid containing collagen."

This confirms that the principal factor in the aging of the lens and the formation of cataracts is in the molecular cross-linking and particularly in the condensation between carbonyl compounds (primarily aldehydes) and amino groups.

In any event, although this is not primarily a free radical effect, the Ultraviolet light helps produce aldehydes and peroxides, and is an important pre-disposing factor in cataracts.

CHAPTER 14

AN EXAMPLE OF OVERDOING

It is widely believed that sodium is so common that it is well nigh impossible to become sodium deficient. I decided to try how far one could go in that direction, and felt that there would certainly be warning signs before anything dangerous would happen. Both assumptions proved to be wrong. Only afterwards did I learn that a deficiency of either sodium, potassium or magnesium can predispose one to hemorrhage (spontaneous bleeding).

The day of reckoning was the day before Christmas 1980. As usual, I was spending the year-end holidays in Helsinki, where my wife is Chief Psychologist at a major hospital. My three younger sons, now all in college in the United States, were in their last high school years in Europe so they could learn languages. Without any warning sign whatsoever, I suddenly lost my orientation and became confused. Our family physician immediately had me admitted to the University Hospital, where Dr. Jorma Palo, an internationally known neurologist, placed me in intensive care. My BSF (Brain-Spine Fluid) contained 200,000 red blood corpuscles per ml. The diagnosis from this was clear: bleeding in the brain. "Cat Scan" and other tests showed no sign of sclerosis. The only thing that differed from normal was an extremely low sodium content in the blood. The diagnosis was: Bleeding in the brain which may be related to extreme sodium deficiency.

I was never in a coma, since I always reacted on direct contact. However, I was unaware of immediate surroundings and dreamed continuously day and night for a month. Subjectively, these were more than dreams, since they had a continuity and were etched indelibly into my memory. Actually, I believe my injured brain received garbled reports from its sensors. All this time I was fleeing, and I visited every country or place where I had ever been.

I shall here only tell the final events of this globe spanning flight: for some unknown reason an international spy organization wanted to capture me. I was sitting in a railroad car in tropical South America, thinking I had succeeded in escaping my pursuers, when at a flag stop I saw two of them boarding the train. I hid in a freight car behind two big crates and heard the two pursuers walking by. One said, "He could be hiding here." The other replied, "I don't believe he saw us, let's check the passenger cars first." The train had slowed in an uphill curve, so I jumped, landing in the brush which softened the fall. When the train was out of sight, I walked into the jungle. After struggling along for hours I came upon a jungle

path, which I followed.

After a while I saw a man in native garb walking ahead of me. I followed him, thinking he might lead me to some habitation. Suddenly he stopped, staggered, then fell, pierced by arrows from the jungle. I went up to the dead man, fully aware of the risk. I found his identification papers: Pedro Gonzales. Continuing along the path I came to a compound of large modern buildings. These would have been impressive anywhere else, but here in the jungle they were totally strange. To my horror I discovered that I had stumbled into the hidden world headquarters of the very spy organization I had been dodging in far flung flight. It was too late to turn back.

A security guard picked me up and asked who I was. I said, "Pedro Gonzales", and handed him Pedro's papers. He took me to his Superior who after a few questions said, "It is obvious that you are not Gonzales. Who Are you?" I replied, "Lamento mucho, Senor, pero yo soy verdaderamente Pedro Gonzales." (I'm very sorry, Sir, but I am really Pedro Gonzales.) The head of the guards ordered, "take this person to the Lab for a blood test." Blood was drawn in a routine manner, and analyzed. The lab man looked at the print-out from the analyzers computer and declared, "You are not Pedro Gonzales. You are Dr. Johan Bjorksten."

I was trapped. Continuous questioning around the clock followed. When they could not break me with questioning, they wired me up to a lie detector and fired "Yes - No" questions at me. The Chief Questioner stood behind me the entire time. I could never see his face. The galvanometer needle of the lie detector told the questioners when they touched on something important to me. By then I could sense what they were after but they wrested my secret from me word by word until there was only a single key word left, which was locked in the inner most recesses of my consciousness.

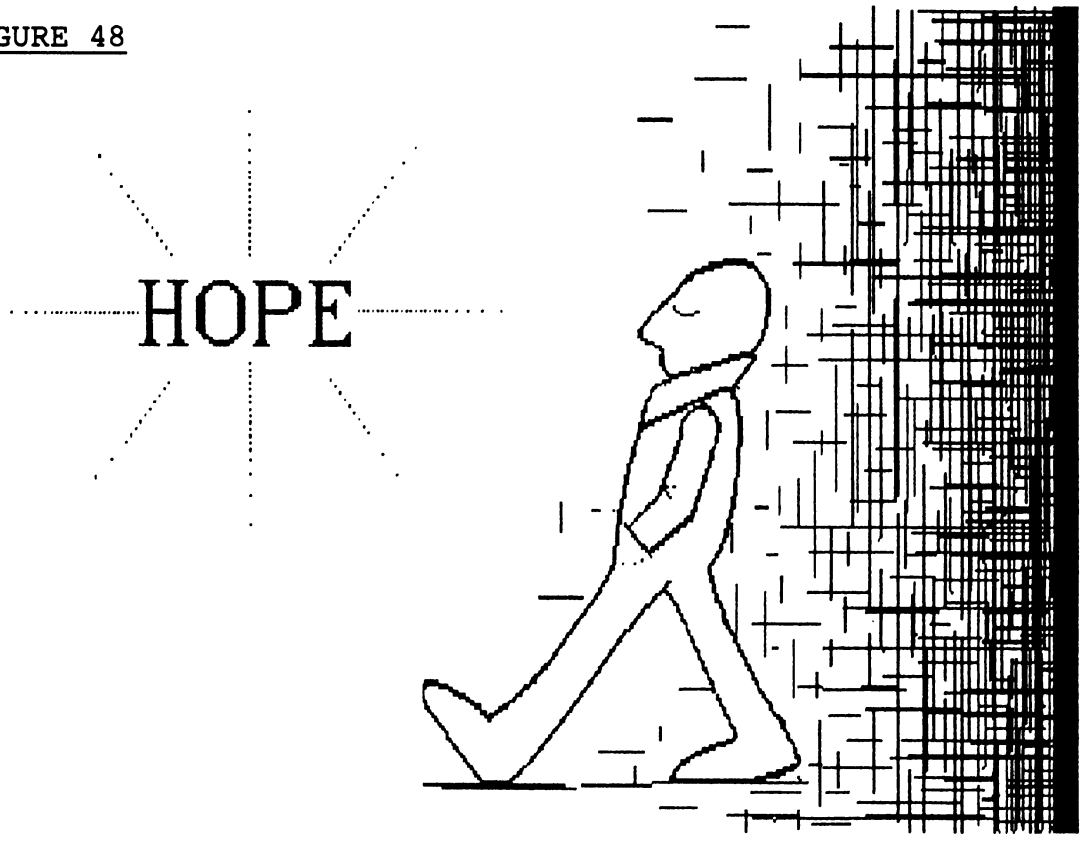
When the questioner finally pronounced this word I ceased struggling and said, "You win. I give up." I was exhausted, my mind a blank. I expected to be taken to an operating room for a lobotomy, a brain operation which would take away my power of initiative and make me either an obedient slave or a docile experimental animal. But nothing at all happened. Everything was silent. I turned my head and could see out of the corner of my right eye a dark heap lying on the floor behind me. The questioner had collapsed.

A great insight came to me then. This whole scenario fed on my own brain energy so that when I "gave up", that which I had fled and had struggled against was no more!

Then, what was real? As if to answer that question, the upper left quarter of my field of vision lit up, as by a spot

light. I saw my wife and three sons moving about, apparently unaware of me. I willed myself to join them. The scene before my eyes changed as in the movies when one picture fades and merges into another. I felt a great relief. The false reality was no more. I was free!

FIGURE 48



My recovery was rapid. It was not at all like the slow recovery expected after cerebral hemorrhage, but rather the fast recovery typical of a deficiency disease when the deficiency has been corrected. In a few hours, I was oriented and in a week I was up and about. In another week, after a very thorough check-up, I was released by the hospital as fully cured with the OK to drive my car and to travel alone. It was a close call. I started work on the book "Longevity, a Quest" in April and had it printed in September. This experience certainly taught me a lesson:

1. Don't ever neglect any of the essential nutrients.

2. Have variety in your diet.

3. Never give up hope.

CHAPTER 15

CHELATION

One approach to the removal of poisonous or harmful metals such as aluminum or lead from the body is the use of chelation. "Chela" means Claw in Greek. To chelate means to use a molecule, which is shaped somewhat like a claw, to grab hold of a metal atom and pull it away. The metal atom is usually carried into the bloodstream and to the kidneys or the liver for removal. Chelation is a process which occurs naturally in humans during exercise. Attempts to duplicate this process with certain chelators designed to remove specific metals such as aluminum and calcium (in the case of sclerotic disease) is still in the experimental stage. Some chelation treatments have been approved by the F.D.A. Questions as to the present status of this research and where we can expect to go in the future will be covered in this chapter.

Chelation by Infusion

EDTA (Ethylene diamine tetracetic acid) is one of the oldest and certainly the most common of the chelators. It is exceptional, in that none of it remains in the body. It is all excreted and therefore when using it, there generally is no danger of delayed after effects. However, it does not work well for aluminum removal. Salicylates do better. It might be possible that some of the positive effects of aspirin, which is a salicylate, could be depended on for removal of some of the aluminum in the body. In 1962, Hans Zinnser and I ran a comparison of chelators and found both salicylic and sulphamic acids to be more effective than EDTA for aluminum removal, at least in the test tube. Sulphamic acids are a class of organic compounds containing basic nitrogen in combination with some sulphur.

EDTA has been approved for treatment of poisoning with lead or with bone-seeking radio isotopes. However, its use to remove calcium in sclerotic disease remains controversial. With EDTA chelation discouraged in several states, many physicians have explored the use of sodium citrate solutions for the same purpose, reportedly with good results. However, for people in good physical condition, a similar increase of citrates in the blood can be achieved more comfortably by endurance type exercise. When the patient's physical condition does not permit this, her/his physician may consider chelation by infusion as one alternative way to remove unwanted metals from the blood circulation and from all other organs on which sclerosis has been a problem. Several other alternatives are now being tested.

Chelation by infusion is carried out by inserting a hollow

needle into one of the veins of the hand. The needle is supplied with the EDTA solution by gravity through a drop counter. The drop counter controls the rate of flow. Each infusion lasts about 3-4 hours. It is not painful, but it is not pleasant either. One can read or write while receiving the chelation in this way.

FIGURE 49 - ILLUSTRATION OF MAN UNDERTAKING CHELATION

In chelation treatment, not only the unwanted metals, but also some of the needed metals present in the body will be removed. While some of the chelators are selective to a degree, none of them is perfect in this regard. In particular, seizures can result if all of the calcium in the blood were removed. Therefore, it is a good practice to add at least some calcium, usually as calcium gluconate, to the last part of the chelator used in a treatment. Other essential metals may be similarly removed. They should then be replaced either as just mentioned, or in capsules or pills taken internally.

Usually three grams of EDTA is used in any one infusion. This amount can bind and remove 1.8 grams of either mercury or lead, or 1.1 grams of plutonium, or 1 gram of calcium or .2 grams of aluminum. However, some part of this removal capacity will be unavoidably lost when the EDTA removes some of the essential metals.

This loss is apt to increase as these essential metals are replaced. Some of the chelator is apt to consume these essential

metal additions still circulating in the blood. For this reason it will be somewhat more efficient to chelate every other day than to chelate daily. This is to give the essential metals more time to get out of the blood circulation, reach their destination and perform their function. If chelation treatments are too frequent, the chelator would be more apt to bind the essential metals just fed into the system after the previous chelation, instead of binding the harmful metals like aluminum. However, some other practical considerations may override this concern.

Because of the considerable time, inconvenience and cost involved in this treatment, efforts have been made to develop chelating agents which can be administered by injection or by mouth.

Almost all plants have some chelators in their roots. The chelators are needed to take up those nutrients from the soil which are present in very small amounts. Iron, magnesium and vanadium are examples of these elements. The mold Streptomyces polosus makes a chelating agent named "Desferoxamine" or "Deferal" (Sandoz) which is now being used to remove excessive iron. It has also been used experimentally to remove aluminum. It can be conveniently administered by injection into large muscles. However, it is not entirely free from side effects.

R. W. Grady and his co-workers have the important project of trying to create chelating agents which can be taken by mouth. They have achieved a considerable degree of success in animal tests with one class of chemicals, (hydroxamic acids.) Of these, one (Cholyl hydroxamic acid) looks promising, but so far as I know none have yet been approved for human use.

This group of chemicals have one drawback to their being studied. The chelated metals leave the body by way of the liver and the intestines which makes it very unpleasant for the analysts to test and check. In the EDTA chelation, the metals leave the body in the urine, which makes it easier to study and much less unpleasant to analyze and handle. Hundreds of compounds have been screened for use by mouth and the work goes on.

Thus, the infusion method, inconvenient though it is for the patient, is still the principal method of chelation. It is reasonably safe and is the best way we have for removing potentially damaging metal from the organisms. In cases of acute poisoning with lead, mercury, cadmium or with radioactive polonium, plutonium, strontium, or yttrium - there is no question that chelation is the best treatment, and its use fully justified.

However, opinions differ sharply when it comes to removal of calcium for treatment of sclerotic disease in aging persons. Each case is different from any other, just as no two persons can be absolutely alike.

The approval of new treatments is delayed by the justifiable, though sometimes exaggerated, requirements of extensive animal tests. These animal tests are then followed by clinical tests, which cost several millions of dollars for each new drug. Requirements that the tests be "Double Blind" substantially increases the cost of these tests. This is because of the added complication of the procedure, and the greater cost of getting "informed consent". "Double blind" means that neither those tested, nor the physicians or technicians who administer the test, know which persons receive the medication, and which the "Placebo" (a pill that looks and tastes like the medication, but which has no effect). The placebo is useful because in many cases people who receive a new medication expect a good result, and this can stimulate the patients enough to make them show some improvement. Yet, having a control group, which unknowingly gets only the placebo, makes the test more costly. It is easy to get sick people to volunteer for a test if they are promised a free trial of a new drug which might possibly help them. But when we tell them that there is to be also a control group which only receives a "fake medicine" and there is a good chance that anyone participating will be in the placebo group, most people will say, "No, I want to know that I'll get the real medicine or I don't care to take the test at all." Such resistance can be overcome by paying a great deal more money. However, paid participants in experiments are often harder and less desirable to work with than volunteers.

Natural Chelation

Even though chelation has achieved an appreciable place in medical practice, there are still many problems associated with it. The question has been asked, "Are there not in the body naturally occurring compounds which have a chelating action?" If so, wouldn't it be possible to mobilize and/or support the natural formation of such chelators in the organism. The answer to both questions is "Yes, to a certain extent and subject to certain conditions and limitations".

In fact, mankind has practiced chelation uses and enhancement long before anything was known about the nature of chelation. At least two of the substances every human produces in her/his life processes are important chelators: lactic acid, (including in this term also dilactic acid), and citric acid.

Lactic acid is one of the intermediate products which is formed on the chemical pathway that starts from starch or sugars and leads to water and carbon dioxide. Whenever a muscle does any work, some lactic acid is formed and energy is given off. When a muscle works hard, the amount of lactic acid in the bloodstream can be doubled for as long as the muscle continues

working. This high amount of lactic acid is registered by the brain in the form of tiredness (fatigue). Lactic acid can tie to several metals and chelate. When two lactic acid molecules connect with each other to form dilactic acid, their chelating efficiency is even better. When lactic acid production is stepped up through exercise, the chances of two lactic acid molecules joining to form dilactic acid is increased. Thus, we now understand why work or sports that call for continuous major use of large muscles produces such remarkable health effects.

Citric acid is also produced as an intermediate product on an energy pathway. Its concentration effects have not been studied as thoroughly as the lactic acids, but enough is known to justify a statement to the effect that it is an important natural chelator. When EDTA was prohibited in one of the USA states, citric acid in the form of its sodium salt was employed as a substitute, and in several cases gave favorable results.

Much can be said in favor of natural chelation agents in applications where other chelators have shown possible side effects.

The final decision of whether or not to use chelation by infusion in any of these cases should be made by a physician who knows the condition and health history of the patient.

By far, the most common case of close decision is with patients who suffer from advanced sclerosis which threatens to block vital arteries, but is still not so advanced that an immediate danger of death commands instant surgery. It is a fact that most scleroses are caused by deposits of cholesterol esters and a shortage of lecithins, and that the lime deposits might have been prevented by changes in food habits. Nonetheless, in a large number of well documented cases, dramatic clinical improvements have been achieved by infusion of calcium chelators through the veins such as EDTA or citrates. In no way can this be classified as quackery. It has in many cases gained for the patient critical years. Chelation has given many patients time to institute dietary improvements and other supporting treatment to improve underlying fat imbalances as well.

The remaining question then is: How long will it take before a chelator is developed that we can take by mouth, or by a few injections, instead of the time-consuming infusion? Could a life time habit of an hour or more of endurance type exercise together with some dietary control clear away calcium deposits as well as an EDTA treatment? These questions have not yet been answered. As of now, it seems probable that the second question might receive a positive reply. In the meantime, the final decision of treatment in any case of this type should be made by an M.D. physician who knows the condition of the patient, and her/his

health history, and who can ascertain the then current status of chelation.

To summarize: Exercise of an endurance type, for about one hour every day of your life would go far to protect from the accumulation of unwanted metals in your system. This amount of exercise would probably be enough to suffice. However, if even in the face of all these dietary and exercise precautions, you still suffer from a build up of unwanted metals, including excess calcium, your physician would probably advise medically controlled chelation. He will also know at that time if one of the more convenient methods of chelation has been approved for use. The time for it would be ripe.

CHAPTER 16

EXERCISE

The role and importance of exercise for health and longevity seems to be common sense to most people. The questions of how much and how far are somewhat debatable. Although most people would agree that exercise is good for you, many really don't understand why. The previous chapter gave one very good reason to exercise; to get the process of natural chelation started on a daily basis. This chapter will give realistic suggestions designed to lengthen the lifespan and give improved overall health; not to build big muscles which could become a liability later in life. Hopefully, this chapter will also go far to foster long term commitments to exercise instead of short-lived regimes which a person may fail to keep up.

There are scientists and health researchers who deny that exercise plays a vital role, in say cancer or longevity. Some have even gone far enough to suggest that exercise is bad for your health! The incident below is an example of that fallen school of thought.

A scientist wanted to make an animal experiment with rats to see if exercise would give them a longer life. He placed the rats separately in cylindrical cages. These cages were made to rotate so as to force the rats to run every day for an amount of time considered by the scientist to be necessary for good exercise. The rats which had to go through with this treatment died earlier than the control rats who had the same food, but were not rotated and forced to run. This was published and cited as objective proof that exercise was harmful.

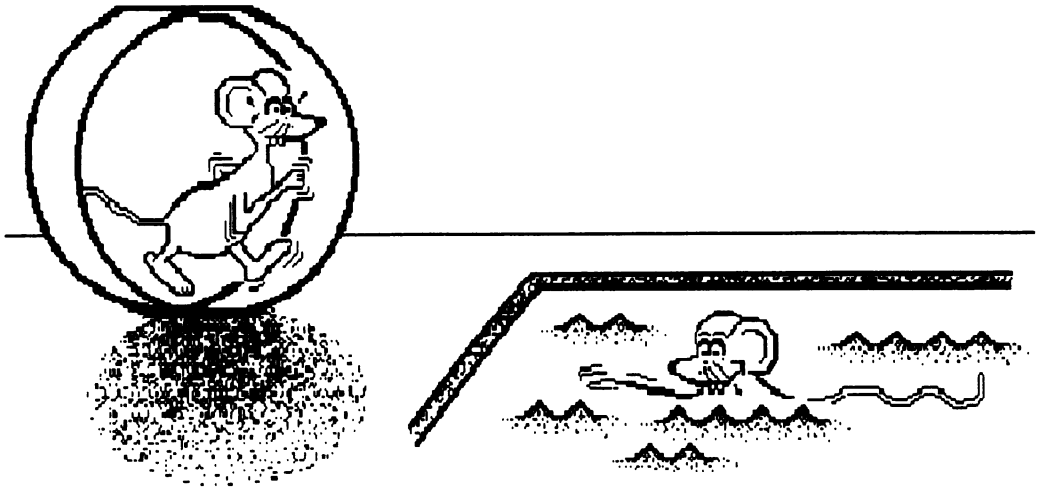
One of my fellow scientists brought up this study in a discussion. I said to him, "Before we draw any conclusions, shouldn't we try to think of ourselves in the situation of these rats? Suppose we were imprisoned, without any explanation, in cylindrical cells which rotated say two hours every day so that we would have to walk very briskly to avoid being tumbled. Do you believe that such treatment might possibly prove that you would not benefit from daily walks in some beautiful forest or park, at the time and pace you choose?" He conceded my question was a fair one. Nonetheless, the paper had been published and was cited as "proof" that exercise is not healthful!

One of the leading researchers then at the University of Miami, Dr. Morris Rockstein, made a more reasonable animal experiment. He started with very young rats and placed them at first in water of a pleasant temperature for only a few minutes. He increased the time of these baths slowly, until the rats got up to an amount of swimming which represented a good exercise.

Then he gave them a choice between a cage without bath and one with it. Every rat given this choice preferred the exercise to which it had become accustomed and apparently liked. These rats were stronger, healthier and lived longer than the controls.

Dr. Rockstein's excellent and thorough paper was also published. Intelligent researchers in the field will mostly see what is what - that is those of them who are interested enough to read both papers in full. But many people, including most journalists and abstractors, only read a press notice or a summary. For them, both articles may have equal weight, and those who wanted to "prove" a particular opinion would choose his reference accordingly!

FIGURE 50



EXERCISE AND CHELATION

The endurance type exercises maintain a chemical scavenging process. If the exercise is continued for at least an hour at a steady level, it will favorably modify the chemical balance in the body for some time even after it has ceased. Some examples of typical endurance exercise activities are walking, swimming, rowing, dancing, love making in its more strenuous aspects, skiing, sailing alone in a small boat and playing golf without excessive mechanization. At least one hour daily of endurance exercise will go far toward preventing stagnation and maintaining a healthy balance of the numerous interwoven chains of processes in the body. The increased level of lactic and citric acids in the blood during exercise will remove much of the metallic environmental poisons. A well-rounded exercise program should also include exercise of the brain by active interests. This keeps the brain stimulated.

These endurance type activities also give the benefit of maintenance of any activated site in the body and an increase in circulation of all principal organs.

A person who is unable or unwilling to exercise as suggested above, can still get some benefit from even the mild motion in a rocking chair. However, in such cases or where an already existing condition requires strong measures, chelation by infusion, injection, or ingestion may be prescribed by a physician.

COMMENTS ON PEAK EFFORT

An intense effort sustained only for a few seconds may help to build muscles, but will not contribute to longevity. A habit of physical efforts which cannot be sustained in advanced years is not recommended. Whenever a maximum effort exercise habit has to be discontinued, the large muscles, including the heart, become flabby. These muscles then become liabilities rather than assets.

I have watched many of my boyhood friends through the years. Several of them were very good at competitive sports and developed a great deal of muscle. When they reached middle age and could no longer excel in sports, they dropped exercise altogether. Their powers of resistance declined more than they realized. Few of them survived late middle age.

PITFALLS IN EXERCISE

1. Sports calling for short bursts of peak performance, such as throwing or jumping, greatly stress the organism without time enough for the benefits to develop. A longer lasting, lower level effort is therefore preferable.

2. It is unwise to start on a program that calls for so much time or trouble that you may find yourself unable or unwilling to keep it up for the rest of your life. If you get bored using one of the more typical endurance exercise programs, you can always make switches to other types of exercise which take similar time and effort. For example, you could switch between walking, dancing, skiing, swimming and rowing, etc.

3. Exercise is important not only because it develops circulation and the organs as a whole, but also because motion increases the production of lactic acid and citric acid in the body. Lactic acid is increased 100% in the blood, so long as the exercise continues, and drops back immediately after the motion has stopped. The most favored sports from the health standpoint are those which call for continued action for an hour or more at a time.

Brisk walking is the best single sport because it involves steady work of large muscles, and is not so strenuous that it would become a burden in later years. It could be varied by using other endurance type sports. Jogging is perhaps a bit too strenuous for the long pull. Marathon running is definitely overdone.

CHAPTER 17

CLAIMS OF EXTREME AGE UNRELIABLE

Over the years, considerable publicity has been given to three widely separated mountain communities in which inhabitants claimed to be over 150 years old. These communities were: The village of Vilcabamba in the Andes Mountains of Ecuador; inhabitants of Abkhaia in the Caucasus mountains in Grusia, USSR; and the province of Hunza in the Karakorum Mountains which is now part of Kashmir. In 1973 it was reported that a man in the Caucasus had died at 168 years of age.

All of these communities had in common a secluded location, very pure water from the mountain tops, a simple rural life, and the need for physical exercise which is part and parcel of the frugal life in the mountains. However, numerous other locations and settlements have the same, or very similar, living conditions without any such remarkable longevity.

Gerontologists generally were somewhat dubious about these claims, yet they could not be disregarded. These three locations might really have some hidden factor in common which had a dramatic life extending power. If so, no expense was too great to find out what this might be.

The allegedly super ancient persons in Grusia and the Hunza province of Kashmir had no proof for their allegations. Their claims were based entirely on hearsay, or on their so-called recollections of events in a distant past. One Grusian claimed that as a child he had seen some ancient memorable events. None of this evidence could be accepted as scientific, or binding.

However, the inhabitants of Vilcabamba did have baptismal certificates to substantiate their claims. The records of baptism were kept carefully and conscientiously by the Roman Catholic church. These documents were generally accepted as proving their claimed ages.

In 1978, a meeting was held concerning the Vilcabamba residents at the National Institute of Health in Bethesda, Maryland. The meeting was sponsored by the Fogert International Center and the National Institutes of Aging. Its organizers were Dr. Alexander Leaf of Harvard and Dr. Richard Mazess of the University of Wisconsin. Both had visited Vilcabamba, and reported their findings at the meeting.

The special interest of Dr. Mazess was to study the loss of calcium in bone structures, which often occurs in old age. For this he needed X-ray pictures of the bones of very old persons whose ages were known exactly. Dr. Sylvia Forman, a specialist

in quantitative anthropology from the University of California, helped him to determine the exact ages of the inhabitants by verifying them against records of baptism and death. In one instance, they found that a man who had claimed to be 127 years old was really 92. Dr. Leaf, on separate occasions, also became aware of the inconsistencies in ages from Vilcabamba. He had encountered a person in 1974 who stated he was 134 years old. However, just a few years earlier the same man gave his age as being 122.

The Mazess - Forman study found that it was not uncommon in Vilcabamba for the son to have the same name as his father, and that those claiming extreme high age generally had used their parents' birth certificates. This widespread practice became clear when the investigators began to inquire about the god-parents, who are also mentioned in each Roman Catholic birth certificate. With this new standard, all of the alleged extreme ages were disproved.

FIGURE 51 - ILLUSTRATION OF MAN SHOWING BIRTH CERTIFICATE

From Dr. Forman's statistical studies the conclusion can be drawn as to why there was such a high population of the elderly in these mountain communities. This is due largely to the migration of the younger people from the village and the return of elderly people to the villages of their childhood.

A few years ago, at the triennial convention of the European Gerontological Society, I had occasion to discuss these cases with some Russian colleagues. I told them about Vilcabamba and asked if they were aware of any evidence of extreme age. Their comment was that it is hard to tell and that obviously it was to the advantage of those individuals to present themselves as being older than they really were. This is probably universal.

CHAPTER 18

VITAMIN C

Many hundreds of antioxidants have been developed for various industrial uses, including rubber stabilizers and perfume antioxidants. Swift & Company obtained a patent, now long expired, on the use of Vitamin C as an antioxidant to keep bacon from getting rancid. Of the numerous antioxidants in industrial use, only a few qualify for human foods and drugs. Among these, Vitamin C (ascorbic acid) is very important. Vitamin C substantially enhances the antioxidant properties of compounds based on Vitamin E and Selenium, and several others. As we have learned, Vitamin C is also used by the immune system to ward off infection. This helps explain the broad spectrum of its beneficial uses.

Redundance, a key to survival

Redundance simply stated is: Many ways to gain the same goal. Just as evolution has given us alternatives for the most important bodily functions, in which most vital organs are duplicated, so also the body chemistry is provided with alternative resources. There are many things needed to maintain the human system, and we should keep it that way by varying our foods and our habits. This is wholly consistent with Le Compte's law: The rate of aging is proportional to the number of deficiencies, and to their severity. Any path or resource that is lost comprises one more deficiency in our system. Anything that is not used will weaken and may even be totally lost. A key to survival is redundance. Use all your resources, not only those you like the best.

Here is an example:

A Pathway Accident
Lost: An enzyme - and the ability to make Vitamin C ourselves.

All higher animals, with very few exceptions, can make their own Vitamin C. One of the exceptions is mankind. Why just us? A study has shown that humans have 10 of the 11 enzymes that form the pathway from starch to Vitamin C. It is only the enzyme for the last step that is missing. Its name is "gulono lactone oxidase".

It seems highly probable that since we have every enzyme necessary for the synthesis of Vitamin C except one, that we were once able to make our own Vitamin C. What time in our evolution did we have the ability and why then did we lose it?

In seeking an answer, we may ask: Are there any other organisms which also lack the ability to make Vitamin C? If so, which are they, and what do they have in common with us?

We find that, yes, there are indeed some others which share our fate in this regard. They are: a few big apes, guinea pigs, and a tropical fruit-eating bat. Does this make sense? Yes, and it tells us when and why it probably happened.

The natural home of the human race is described in the paradise legends of many faiths as a warm tropical setting with fruits and green vegetables in all seasons. In this setting there also lived some big apes, the guinea pigs, and a tropical fruit-eating bat. In this rich vegetation we all had the Vitamin C for free, so the pathways for making Vitamin C were not used at all for thousands of years. The enzymes earlier in the pathway found other uses, but the last one weakened and vanished.

THE DISCOVERY OF CITRUS FRUITS AS A CURE FOR SCURVY

The loss of our ability to make Vitamin C was felt in the colder climates, particularly so in times of hunger, war and long ocean voyages. Those completely deprived of Vitamin C died of scurvy. The knowledge that scurvy is caused by a deficiency of Vitamin C was slow to be accepted. Even as late as the American Civil War, 30,000 soldiers died from scurvy.

Let us go back to first known and recorded cases of scurvy, during the development of the East trade routes. The eastern travel routes had been developed to satisfy the great demand in european nations for the new spices as well as for the silk of China. The long trips were started by the Spanish and the Portuguese who concentrated on the Americas. The far eastern routes around Africa and India were even more time consuming and uncertain.

The Dutch were the first to perceive the importance of fresh vegetables on such long trips. Cape Town, located at the very tip of Africa, was founded in 1652 by Jan van Riebeeck, a naval surgeon employed by the Netherlands East India Company. This point served as a supply port, providing fresh fruits and vegetables for the East India ships. The English were lagging then. The long voyages took their toll in scurvy, which was a major hazard.

That the Netherlands East India selected a physician with naval training and experience to head their project is indicative of their resolve to attack the scurvy problem, and to solve it. Their plan was well thought out. All of their ships on the Java-East India trade would as a matter of course pause at Cape Town, whether East bound or West bound. They would take on provisions

for the next leg of their long journey. The Company, represented by van Riebeeck and later, his appointees and successors, could organize the supplies with meaningful additions and omissions, so as to find out which supplies would be most effective in preventing the dread disease. When a captain came in with several cases of scurvy he would naturally ask: "My colleague Captain van Ruypen just came in with the Timor and was out as long as I and had only two mild cases. What was the difference in our supplies?" Records were kept with usual Dutch care and clarity.

When something began to look promising, that ingredient was emphasized in one or two ships at first until optimal combinations of foods were determined. All participants were driven by powerful incentives: For the Company, the incentives were financial and political, for the captains and the ships' physicians, their own health and lives. Under these conditions it should not have taken them more than ten years, or at the very most twenty, to single out lemons and oranges as the effective nutritional anti-scurvy preventives. Since the Cape Town project was started in 1652 it seems safe to assume that the Company had the solution by 1672. This knowledge was kept as a carefully protected secret.

The Portuguese were then in a decline. The English did not get into India until some 70 years later, and then not primarily by the sea routes. Yet, the security at the Dutch shipyards was tight - it would not have been easy for a competitor such as an Englishman or a German to get in there, but when the shipyard was very busy with orders from the Company, they could see no danger in taking on a sturdy looking young Russian who applied for a job and seemed willing to work at anything. The man they took on gave the name Pyotr Michailov. What they didn't known about this man was that he was the Emperor (Czar) of Russia, later known in history as Peter the Great.

Peter had not been among the first in line to the throne, so he was never subjected to the extensive brainwashing to which many a royal person may be subjected. He was aware of many shortcomings. Above all he was interested in learning about ships. Holland was a leader in shipping, and had no interests adverse to Russia's, which England might have. He went to the shipyard, asked for a job and got it, no favors asked or given. He stayed with it until he had achieved a grasp of the elements of shipbuilding and had made friends he could never have met through diplomatic channels. In Holland, he had heard about scurvy, and how it was dangerous for a ship to stay too long at sea. He now learned that the Company's ships hardly ever had scurvy on board. Some old sailor must have guessed or learned the truth, and spilled it to the personable young fellow who was such a wonderful listener and often paid for the drinks.

Be this as it may, the fact is that Czar Peter bought from

Holland lemons and oranges by the shipload.

A few years later, Czar Peter was ready to start action to make a way for Russia to the wide waters of the world. The Baltic Sea was then dominated by the Swedish fleet and Sweden had possession of all the land surrounding it. In April 1703, Peter struck. Sweden had built a Fort at the place where Leningrad now stands, at the mouth of the Neva River. This river empties the Lake Ladoga into the Gulf of Finland which widens into the Baltic. This Fort was Fort Nyen, and had a garrison of 500. From Russia's viewpoint this was a wise choice. The sea was too shallow for the Swedish capital ships to enter. Peter attacked with superior forces, and in two storms fighting around the clock forced Swedish surrender.

The Swedish fleet which was sent to support the defense arrived a couple days too late, but did not know it. The Admiral anchored his fleet as close to the Fort as they could get, and sent two small ships, the brigantine Astril, commanded by Overlieutenant Kilian Wilhelms, and a sloop, Gäddan, commanded by Overlieutenant Wennersten.

The two small ships advanced into the immediate vicinity of the Fort, exchanged fire with large Russian forces, lost several men, and withdrew to report that the area was occupied by strong Russian forces.

This placed Vice Admiral Gideon von Numers in an awkward position. The report of the ships did not exclude the possibility that there might still be Swedes fighting somewhere in the vicinity, perhaps in the fort itself. They might be in desperate need of the ammunition and supplies he carried. Until he had clear evidence that the surrender, if any, was complete, he could not withdraw. And yet, there seemed to be nothing that the fleet could do. The Russians had no fleet at all that he could fight, and he could not get close to land with those big ships to bombard anything that mattered. He must have a certainty. Such must his thoughts have been as he received the report of the commanders of his scouting ships, the Overlieutenant Kilian Wilhelms of the Astril and the Overlieutenant Wennersten of the Gäddan. Lieutenant Emanuel Martin Werner, First Mate of the Astril, was also present when the two Overlieutenant Commanders made their joint report to Vice Admiral von Numers.

Lieutenant Werner was to be the only survivor of the following day. He relates the meeting with the Admiral as follows: Having heard the report, the admiral said: "Now you can move and shoot as you will and you shall immediately hoist your anchors and work your way back again to Nyens Fort". Both Overlieutenants declared "with one mouth" that this was impossible - but the Admiral repeated: "You shall go there even if no man comes back". "Yes" said then the Lieutenants, "If the Sir Vice Admiral gives

us a written order, we will go thereto." They went, sailing, rowing, towing, and sounding depths, for the Russians had removed all markers from the narrow and winding channel. From the fleet one could hear firing which lasted all night. Then long after sunrise, two strong explosions, and silence.

The Russian historian Borodkin informs us: "The Czar had been informed that the brigantine and the yacht which had earlier approached had returned. Rapidly the Czar assembled all available "lodyas", thirty of them, and filled them with guardsmen. The Czar himself, and Menschikoff were the only persons in this flotilla who had any sea experience, and they commanded it. (Lodyas were undecked flat bottomed barges, propelled by perhaps 20 rowers and with plenty of space for men or cargo.) They had no cannon, the muskets of the Guardsmen were the only artillery. There was no wind, and in the narrow channel the ships were immobile."

Both of the Overlieutenants died in this battle. Their last commands to blow up the ships were obeyed. Czar Peter wrote in a letter that he had lost only 8 lodyas in this battle. The estimate of the surviving Swedish officer was that the Russian lost 16 lodyas and 300 men.

Following this nights battle, the first in which Czar Peter took part, and perhaps the only one in which he demonstrated his personal great courage in a pitched battle, Admiral von Numers sent a junior staff officer, Tomas Wessling, with orders to contact the enemy under a white flag, and find out which of the Swedish officers were still alive. Lieutenant Wessling's report has been referred to by both Swedish and Russian historians, and was reprinted by a Finnish genealogist who in a quite different context ran across a copy of it in the Archives of the Swedish Nobility in Stockholm. Here follows a translation of the report, with omission only of some of the conversation with prisoners because it has no bearing on the discovery and first use of lemons and oranges for control of scurvy.

This is a translation of the report by Tomas Wessling, a young staff officer in a Swedish fleet under the command of Vice Admiral Gideon von Numers.

"In the year 1703, I was commanded by the well born Sir Vice Admiral Gideon von Numers to proceed with a small boat with two enlisted men (as rowers) to the camp of the enemy to learn whether our officers of the brigantine Astril and the sloop Gäddan lived and were prisoners of the enemy. At 4 PM I arrived at the wreck Astril and then was approached by two lodyas. I beat the drum, and let one of my men hold the white flag. Then one of the lodyas came in, and took me on board. I gave my hand and he took it in a friendly manner, and spoke in Russian. I did not understand. Then I talked with him who was in the other

lodya that he should not harm my two boatmen. Then the commander, who spoke German, answered that I need not worry about that. Then the commander of the lodya took off my hat and put a cap on me and tied a cloth over my face and tied my hands behind my back, and so I sat in the lodya until we arrived at the camp, upstream from Nyen. When I stepped ashore, two soldiers led me to Field Marshal Scherementieff's tent. Then my eyes were opened and my hands made free. Then he asked me what we want and who I am. So I replied I am an emissary from the fleet and handed him the letter from our Admiral, Sir Gideon von Numers. When he had read the letter he asked the soldier why he had tied my hands behind my back. He said: "I don't know," The Field Marshal spoke in Russian with him. Then two men came and took away his red coat and made him lie down on the ground. One man sat on his head, another on his feet, and they whipped him so that pieces of flesh flew around. Then the Field Marshal asked me if the man should hang. Then I took him by the feet and implored that the man be pardoned. So the Field Marshal answered me in Dutch that I only need to say a word, so I asked for his pardon and he was immediately set free."

"Then the Field Marshal asked me how strong our fleet was. I said that he certainly knew that much better than I. Then he asked how heavily armed? I answered 24 pair and 80 men, not counting the soldiers."

"Then they brought me to General Schaumburg, in his tent. There was before me Mans Orn, who was the late Overlieutenant Kilian Wilhelms personal servant, and a ship boy. With him I talked some about the officers, who were alive or dead. He said he did not know. And they immediately took Orn and the boy away. In the evening the General asked his personal servants to bring wine, and drank he to me a toast for his Royal Majesty, the King of Sweden. I drank this, and then responded with a toast to his Imperial Majesty the Czar of Muscovia - then he drank also likewise. Then he said: "The wine is here quite scarce, please ask your Sir Admiral to send me some". And then he asked me, if a few Dutch ships should arrive, that the Admiral would permit the passage of those ships which do not carry any war materials. So I answered: "Without a doubt would the Admiral do this".

"Then I went to the table, and throughout the meal we drank many toasts: to the naval officers, which he and I drank. Then I made a toast to all the officers who served in the Muscovite Army, which he also drank; and there was much talking which I can't recall. When we had eaten, he commanded tobacco and pipes and I had to smoke with him. Then he spoke here and there and I answered him well. Then he went to bed. With me remained a Major and a few officers, and I had to drink with them. Then it dawned (about 2 AM at that month and latitude) and they brought me to another tent, on linen damask cushions had they bedded for me."

"In the morning I went to the General's tent and asked him if he would be so kind and arrange for my return to the fleet. Then he answered me - he would talk with the Field Marshal about it, and got up and went to him. Then I went out with a field officer to learn how the late sir Overlieutenant Kilian Wilhelms was to be entered. And he was entered in the Swedish grave yard and the minister who was at Fort Nyen made the ceremony for him."

"I returned to the camp again. The General was still sleeping. I returned later and asked if the General would do me the favor of permitting me to talk with our prisoners, which he promised after the meal."

"Prince Alexander Menschikoff came riding with the Czar to the General's tent and asked me if I should like to talk with the commander of Nyens. I said: "Yes, I would greatly appreciate this". Said he to me: "There is my horse, seat yourself upon it". I replied: "I will walk there". He said: "Go and seat yourself on my horse". Which I did, and an officer with me, and we rode to our people."

(Here I skip a couple pages of the reports which deals with the conversations with Swedish prisoners of war, including the Swedish Commander of Fort Nyens. Although interesting, this is not relevant to the questions of scurvy and Vitamin C.)

Resuming the report: "I went with the General to the Field Marshal Scheremetieff, where I found ahead of me three of our prisoners namely Otto Frisk, Erik Reps and a man from Aland. The General asked if I knew them and I said: "Yes". I asked them if they knew which officers are still alive, and they said NO. I did not get to talk with them any more."

"The Czar stood there. Said I: "Lieutenant Killian Wilhelms had this sword you are wearing". He answered: "Yes, it is his sword, and I am wearing it as a memory because he was such a brave warrior". The Czar asked why they fight so desperately and then blow themselves up? I answered: "We have such rules, either sink or burn". Thereupon said the Czar: "One cannot give the soul without the body", and turned and went to some other officers. Then they took me to General Schaumburg's tent and ate there the evening meal. He <u>requested that the Sir Admiral should send him lemons and oranges</u>, and he would return favors appropriately. Then he retired, and I too."

"The 11th of May, I went to General Schaumburg's tent, and asked him if he would be so kind and get me back to the Fleet. Then he sent an officer to Governor Alexander Menschikoff to see if he was up. The officer came back and said that the Governor was up. Then the General said that I should go to the Governor and I would be sent on my way. I thanked him for all his

kindness and went to the Governor Alexander Menschikoff and said he to me that I should greet the Sir Admiral with his request that lemons and oranges finally should be sent to him and here you have your letter. He toasted me with a bowl of vodka and a glass of wine. Then I took farewell of him and rowed then with a lodya until I came to the outlet of the river, there they covered my eyes, and did not open them until we had reached the wreck of Astril. Then I thanked him and took leave of him. Then I sat myself in the boat, rowed away, and when I came out the fleet was not where it had been. The weather was misty. I rowed anyhow until I came to Retu Island, met a Galeja ship, and signaled with a drum. The Galeja took me to the General ship."

Dated, on the Brigantine Castor anchored at Nyen, May 13, 1703. Tomas Wessling.

Chronology: In 1652 Cape Town was founded by Jan van Riebeeck, a Dutch naval physician, in the employ of the Netherlands East India Company. The set-up was so favorable that it cannot have taken them much more than ten years to find out that lemons and oranges both of which they handled in commerce, prevented scurvy. At least, they must have known this by 1672. This closely guarded secret gave this Dutch Company a practical monopoly on the East India Trade, which lasted more than a hundred years. About 1700 Peter, later surnamed "the Great" came to power in Russia. He made a study journey in Europe and concluded that to become a powerful and advanced nation, Russia had to gain access to the seas of the world. He went to Holland and under the assumed name of Pyotr Michailov, got a job as carpenter's assistant at the shipyard of the Netherlands East India Company. He worked there several months, learning how a successful shipyard functions, and made friends with men he could never have met by any diplomatic channels. Peter spoke Dutch and certainly had opportunity to meet sailors.

(Upon going to press I received positive proof that the East India Company in 1600 used oranges and lemons to cure and prevent scurvy on their ships. (J. A. Nixon 1938))

In 1703, Peter personally led his first thrust to break through to the Baltic, which at that time was wholly enclosed by Swedish possessions. In May 1703, a junior Swedish officer came to the Russian camp, under the white flag. His orders were to inquire about prisoners of war. Surprisingly he was accorded very unusual attention and courtesies, and was in several days entertained by the Field Marshal, the Commanding General and the Governor, each of whom asked the young negotiator if he would not as a personal favor to them, ask his Admiral to permit the passage through the blockade of some Dutch ships carrying lemons and oranges and absolutely no armament or army supplies.

The report which this negotiator Lieutenant Tomas Wessling wrote on return clearly shows that the Russians went to extraordinary lengths to get these large quantities of fruits by indicating that if they could get their fruit there would be no trouble about the prisoners.

Nearly fifty years later

In 1747 James Lind, a physician's assistant on a British warship, independently rediscovered the efficacy of lemons and oranges as cures and preventives for scurvy. Even then, about fifty years passed before this was applied in the merchant marine.

The knowledge of citrus fruit as prevention for scurvy was slow to spread. Many remedies were suggested: Drinking salt water, fresh meat, a teaspoonful of tar. You name it: someone would advocate it.

Citrus fruit as a cure for scurvy was adopted very slowly. It was kept a secret by the English Navy (of course the Dutch and the Russians already knew) and indeed a veritable secret it was. Much later, during the period when Napoleon conquered all of central and southern Europe and threatened England, the British greatly benefitted from this knowledge. Napoleon could never subdue the English fleet because he had to take all his ships back to base every three weeks for a complete change of officers and crew, in order to avoid scurvy. The British had no such inhibitions for they knew by then that scurvy could be prevented.

There were many doubters. In the interest of saving space and avoiding spoilage, ship owners began the practice of substituting orange marmalades instead of fresh fruit. We now know that Vitamin C is destroyed by boiling, but back then the negative results with the marmalades instigated many claims that the whole idea of citrus fruit being of any use was false.

In the epic race to the North Pole between the British team headed by Scott and the Norwegian team headed by Amundsen, scurvy destroyed the British effort. Scott believed those who said that scurvy would be best controlled by having fresh meat. So he did not bring fruits. Instead, he used Iceland ponies to pull his sleds with the thought that on the way back they would have fresh horse meat. Amundsen had much lighter dog sleds and a good supply of citrus fruits.

Scott's expedition lost most of its men before reaching the pole. Scott himself fell severely ill before they reached the pole and found there the Norwegian flag left by Amundsen. He died on the way back, his body and diary were found many years later by another expedition.

THE ISOLATION OF ASCORBIC ACID

The active ingredient in the citrus fruit was identified in 1927 by Szent-Györgyi who called it ascorbic acid because of its function. It was a rather simple structure, and its synthetic manufacture followed soon. This gave rise to extensive clinical trials, claims, counter claims, rebuttals, and re-rebuttals. This continues even to this day though the need for this substance is general in all climates.

As the synthetic manufacture brought the price within the reach of everybody, more and more experiences were gathered. Many persons independently observed that Vitamin C was favorable in common colds and in other infectious diseases. Such multiple claims were instinctively resisted by the medical profession who throughout the centuries have seen that each illness has it's specific remedies and that claims for the same substance serving many purposes are too often a sign of quackery. So the claim of ascorbic acid (Vitamin C) being useful in many extremely different fields was met with a wholly understandable criticism and much doubt.

Dr. Ritzel in Switzerland made a very thorough study of the use of Vitamin C in colds at Swiss ski resorts where physicians were in residence. Careful and precise data was collected under optimum conditions, and with observance of all precautions. The results were clear and conclusive: The persons receiving a liberal dose of Vitamin C lost less than half as much time due to colds than did the group that received the placebo. Dr. Ritzel's basic paper was hardly noticed in the United States. This may have been due, in part, to the inclination of too many persons to read only the abstract of a paper and to infer that the text will not give a different picture as did the Ritzel paper.

Ritzel's paper contains an unusually thorough discussion of circumstances and precautions over the length of 10 closely printed pages before he comes to the gist of the experiments and tabulations. His summary is very brief, stating only that those receiving the Vitamin C had a substantial reduction of time lost to colds.

I can understand that a person with limited knowledge of German might find the long introduction and meticulous discussions somewhat tiresome. But jumping to the key parts of the paper found in the abstract does not suffice for a complete understanding of the unchallengeable care and completeness of Ritzel's flawless findings and arguments.

So it came to be that even today, there is a large body of people who should know better but who still keep questioning and requestioning ad nauseam the now so clearly established fact that Vitamin C is an essential factor in the immune system and that

anything less than optimal dosage of Vitamin C places the entire immune system under a severe handicap.

The human immune system is our heritage from the millions of generations who have fought and survived infections during the ages when hygiene was unknown and any mention of microscopic organisms was rejected as absurd. The immune system uses bursts of free radicals as its principle weapon in the fight against bacteria or anything that the immune system perceives as not belonging to the body, or out of place. The mechanism for creating the burst of free radicals is based on three things: An oxygen donor, such as a peroxide, a catalyst such as iron or copper, and an organic chemical of the group called enol dienes, of which ascorbic acid (Vitamin C) is an example. Vitamin C also has the unique ability of recharging the catalyst atoms so as to bring them back to the oxidation stage. In other words, it allows them to reload their guns so that they can fire their next load of free radicals selectively at their targets. These many necessary functions of Vitamin C are so basic that a broad range of its use is fully understandable.

The movements of Vitamin C in the body were carefully mapped by C. W. M. Wilson at the University of Dublin. Whenever an infection strikes, the Vitamin C supply of the white blood corpuscles will be rapidly exhausted. When the body receives a new supply of Vitamin C, it is brought immediately to the white blood corpuscles for reloading their guns. If there is a great excess of Vitamin C, then a reserve is created in the red blood corpuscles by first reducing ascorbic acid to dehydro ascorbic acid which packs better in the red blood corpuscles. While normally a daily intake from all sources of 500 mg for women or 1000 mg for men would suffice, this supply could be consumed rapidly by fighting a virulent infection. It is preferable to use it in smaller dosages through the day since singular large doses might be lost through the kidneys.

In cancer therapy, the undeniable efficiency of Vitamin C is limited since the immune system doesn't recognize the cancer cells as hazards and enemies. Therefore, the merit of Vitamin C will increase in performance once the immune system is alerted of these enemies through treatment such as the immunological therapy of Dr. Tallberg.

Dr. Linus Pauling has strongly advocated the importance of Vitamin C, and with Dr. E. Cameron has stressed its potentialities in cancer therapy.

CHAPTER 19

CHALONES

As we have learned, cancer is characterized by uncontrolled growth. Medical Research is now leaning toward the isolation and purification of growth-controlling substances capable of stopping cancer growth.

It is typical for all chalones that they are totally non-toxic, tissue specific and species non-specific. This means that a certain chalone only affects a certain tissue for any organism including itself. Thus, for example, a rat skin chalone would stop skin growth in a rabbit and a human as well; but it would cause no change in the growth of any other tissue, even in the rat.

The term " chalone" was originated by John C. Houck in 1974 as the name for an important group of growth controlling substances. They counterbalance the hormones in a negative feedback system of control. Hormones are messengers which tell cells and/or organs to Do something. The chalones are also messengers, but their messages are to Stop Doing. What makes the chalones such an unusual and outstanding group, is that a chalone which stops the growth of one certain tissue or organ in one animal will do the same for that kind of tissue or organ in any other animal, but will not change the growth in any other animal organ even in the same animal. The chalones are non-toxic.

The greatest difficulty in chalone research is the small ratio of chalones per tissue. This characteristic of chalones makes it very difficult to extract them. For example, even if you could get a ton of epidermal tissue (fresh skin), it would be difficult to separate very small quantities of chalones.

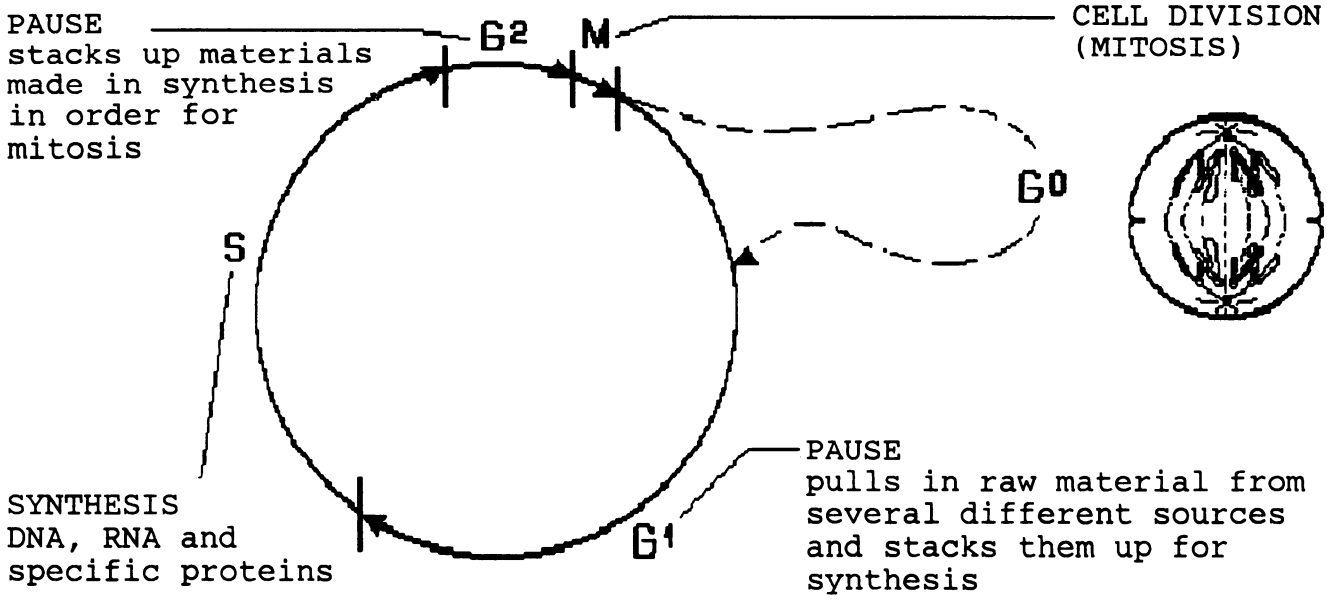
The flip side of this is that chalones are extremely potent. Very small quantities of chalone suffice to produce the particular inaction needed in any one case. Using the epidermal tissue example again; it has been estimated that the chalone which controls the growth of skin after a wound has healed is effective in a dilution of 1 milligram per 1000 kilograms of epidermis. That is in a dilution of one part to a million.

The chalones act by blocking mitosis (cell duplication) at either one of two defined pauses in cell division. These pauses are known as the G2 and G1 pauses. To make this clear, it is necessary to recall the mechanism of cell division.

This begins with a period in which needed materials are assembled and very little is seen in the microscope. This is Pause G1 (Fig. 52). Then follows the "S" period (synthesis), in which the materials assembled during Pause G1 are used to synthesize new DNA and other less well defined complex molecules. Following the "S" stage is a second "pause" G2, during which the new DNA and other materials are checked, assembled and brought into position for the cell division itself. After the G2 Pause, everything is in readiness and the actual cell division can start.

The Chalones have the power to stop action at either the G1 or G2 pauses, when no critical synthesis is under way, and the process can start up again without having to re-do or undo anything critical. This is the explanation of the total non-toxicity which is common to all chalones. Any disturbance at either the Synthesis period when the DNA is made, or in the mitosis itself, would cause great disturbances, most likely death or mutation.

FIGURE 52 - G2 AND G1 PAUSES (After M. Karkinen-Jääskeläinen, J. Wartiovaara, L. Saxen)



In 1976 J.C. Houck published a book, **Chalones,** (Elsevier Publ. Co.). Since then more than 300 papers have been published, and substantial progress made, but in spite of this the chalones

are not yet available in commerce.

More than 50 chalones are known already. It is indeed possible that a chalone exists for every known hormone. Chalones are specially useful when a certain hormone action is needed in several parts of a body, but must be avoided in one particular organ. In that context the chalone of that particular organ could locally block a hormone action, yet retain this hormonal action everywhere else. Quite generally, the tissue-specific efficacy of the chalones makes it possible to achieve localized blocking. This could prevent cancer from developing in a specific region of the body.

POSSIBLE USES OF CHALONES IN MEDICINE

The most attractive property of chalones is their total nontoxicity. Even when they stop growth, this action only halts cell division, it does not in any way affect the natural life span of even a single cell. Used as anti-cancer agents, they would still leave the immune system as strong as ever. An ex-cancer patient cured with a chalone would have a normal life expectancy.

Knowledge of the precise starting point of the cancer would be required. But with this information and an applicable chalone available, the chalone would be a very powerful therapeutic agent totally free from side effects. Only the scarcity of the chalones, i.e. their low concentration in available source materials, is slowing the progress along this line.

The next most interesting use for chalones is for control of rheumatoid arthritis which, like cancer, is characterized by uncontrolled growth.

Trophoblast chalones might stop cell division in a fertilized egg cell, and thus result in a very early abortion. Lymphocyte chalones might be useful for immunosuppression without any lasting damage to the immune system. Immunosuppression is necessary for transplanting organs from one organism to another.

In wound repair, a fibroblast chalone should prevent excessive cell growth which leads to keloid and/or to intestinal adhesions following operations.

All of these applications could become practical when the genetic codes for the chalones have been mastered. The best approach might be to use the few milligrams available of some chalones to determine their chemical composition. This knowledge could be used either for chemical synthesis, or for the application of molecular engineering techniques to transfer the genes for chalone production to some easily managed, rapidly growing

organism, of which there are many.

SCREEN FOR CHALONES

Having described how these act, I shall list the criteria used to recognize chalones:

1. A chalone acts only on a definite tissue.

2. Its inhibitory effects are non-toxic, thus with no immediate effect on the number of cells.

3. A chalone lowers the speed of progression through the process of cell division, thereby checking the increase in number of cells. The normal death rate of the cells then lowers their number gradually.

4. A chalone acts exclusively on its target cells. These target cells must belong to the same cell lines as the cells which produced the chalone.

5. No chalone has any effect on a cell from an organ system other than its own.

6. An extract from another organ, prepared in the same way as the presumed chalone, must have no effect on the cells from the line producing the chalone.

7. Non-chalone effects on the target cells must be excluded when testing for chalones.

Examples of some Chalones

Chalone	Cell state inhibited		Mole. Wt.
	G1	G2	
Epidermis	+	+	30,000-100,000
Ascites	+	+	
Erythrocytes	+	-	2,000-4,000
Fibroblasts	+	-	30,000-40,000
Granulocytes	+	+	3,000-4,000
Kidney	-	+	
Lens	-	+	20,000-30,000
Liver	+	+	
Lung	-	+	
Lymphocytes	+	-	30,000-50,000
Melanocytes	-	+	2,000
Sebaceous Glands	+	+	
Stomach epithelium	+	-	

G1 and G2 relate to the respective time lags as was discussed earlier. In these periods there is hardly any optically observable change, but instead intense chemical activity. These periods are therefore most vulnerable to chemical interference.

OCCURRENCE AND PREPARATION OF CHALONES

As research proceeds, it may well develop that every tissue has its chalone, although there have been some negative results in searches. Evolution has at an early stage found it necessary to keep the various growing tissues at peace with each other, preventing as far as possible contests within the same organism, and parasitism such as cancer. The chalones serve this purpose.

I already mentioned the major difficulty in the study of chalones, their very low concentration in tissues. The most studied among the chalones are those in which this difficulty is minimized by possibility of isolation of larger quantities from flowing liquids. Thus, the chalones of some blood cells have been relatively thoroughly studied. The prospect of using chalones in cancer therapy is under intense study and seems to receive a great deal of attention. So far, hardly any major therapeutic results have been published.

It is thus apparent that the chalones have great potentialities in therapy as well as molecular engineering. Before these are realized, some rather formidable obstacles have to be overcome.

Current status of research

In recent years, the effort on chalones has produced advancement in the techniques for quantity production of some chalones. The blood of swine proved particularly suitable for these studies. Not only is this swine blood readily available, but methods have been developed for separating the leukocytes (white blood corpuscles) in serum-free media. This makes it possible to avoid disturbances from unwanted impurities. The small size of this molecule, about 600 Da, gives us hope that the structure might be determined and this chalone produced synthetically.

Michael Kastner and his co-workers discovered that the swine white blood corpuscles greatly increase their content of chalones when they are first biotechnologically separated and then stored at a mildly elevated temperature under specified conditions. The 15-steps of this treatment are relatively simple, and are described in detail on page 640 of the Kastner reference. This would seem to permit substantially increased production of at least this chalone. This research could prove useful in the

treatment of some leukemias.

The next ten years should give us a complete clarification of at least the G1 Epidermal Chalone, and maybe a commercial production of the G2 counterpart by methods of molecular engineering. The production of the Porcine (from swine) white blood corpuscle chalone might come sooner.

The technology of chalone preparation is in a state of strong development. About 30% of all chalone development is from USSR laboratories, with particular emphasis on cancer applications.

Several review articles are listed among the references, two of these by J. C. Houck.

CHAPTER 20

ENVIRONMENT AND LONGEVITY

The word "environment" is one of the most meaningful words - it means so many different things to different people. Most people think of it as whatever happens to be around his or her particular place in the universe. The lawyer might think of it in terms of legal opinions and whatever might influence the interpretations of the law. The astronomer would say our environment is the Milky Way. The farmer would think more specifically of his own crops, weather and soils and maybe insects. The physician or the nutritionist might say the environment is what gets into us by breathing, eating and drinking. It includes microbes or poisons or radiations that might help or hurt us, and so forth.

The global environment includes everything which spreads in the atmosphere or hydrosphere (the interconnecting waters of the oceans in the world). Among these, acid rain is a result of the wide scale burning of fossil coal, which contains some sulphur, as well as the nitrous gases formed by exposing air to very high temperatures, followed by rapid cooling. These nitrous gases form nitric acid when they combine with moisture of the atmosphere. The resultant sulfuric acid and nitric acid in the rain has added a world wide corrosive influence which over centuries will modify both many kinds of stones and organic matter.

The hydrosphere will accumulate everything thrown into the rivers of the world. Much of that is then modified or removed without damage, but some of the chlorinated phenols and similar compounds are remarkably stable and may ultimately even poison the oceans. They may be concentrated by uptake of certain algae and enter the life chain. Some of these situations may pose delicate questions of priorities. For example, under some circumstances, epidemics might have been prevented by timely use of certain insecticides which could also have damaging effects when constantly available. Three or four or even ten generations might show the effects of such damage. Our knowledge is still quite limited, as is our wisdom.

All of these environments have some effect on longevity. Many of them have several effects so that the situation is truly complicated. Books have been, or will be, written about each of these factors. In this case, we might recall what a famous German chemist said in a similar situation: "The studies of numerous learned scholars have brought so much confusion and darkness into this field, that if they continue, we soon shall know nothing at all about it."

But keep your courage. Oliver Wendell Holmes wrote: "I would not give a fig for clarity before complexity, but I would give my life for clarity after complexity." That is the clarity we need and will get.

Returning to more tangible details I touched upon Selenium deficiencies in soil and water in parts of Finland, New Zealand, South Africa, and the Pacific Northwest of the United States. The attempts to introduce reindeer south of the arctic circle in Finland failed because the reindeer were all dying of heart failure shortly after transfer. Once P. Kurkela, a veterinarian with Lapland experience, had defined the deficiency of Selenium as the cause, the reindeer could be safely moved south. Already earlier, the advisability of supplementing the feeds of cows and pigs had become wholly accepted by the farmers in the Selenium deficient areas of the eastern and central parts of Finland. When the farmers observed how much better their cattle and pigs fared since Selenium supplement had been introduced, they were tempted to use it themselves until the medical authorities issued a warning. I understand the reason for this, for Selenium can be dangerous unless the dosage is well controlled, but it seems strange that it should take eighteen years for the successful animal therapy to be transferred or even approved for humans at a time when Finland had the highest cardio-infarct rate in the world.

These livestock problems in Finland were fairly easily solved once the problem was identified as Selenium deficient soil. Another example might suffice to relate the complexity of other environmental factors. The Japanese have a higher collective longevity than those living in the United States. Normally, one would automatically point to the decreased incidence of heart disease in Japan (1 out of 3 persons living in the U.S. can expect to die from heart disease while only 1 out of 9 in Japan). The Japanese have a higher intake of fish and complex carbohydrates than persons in the U.S. This factor alone has a considerable effect since Japanese living in California come closer to the U.S. Longevity.

But what about social environment? The Japanese are more likely to live in extended families wherein grandparents are an integral part. They have a secure key place as the personal centers of the extended family. This gives the grandparents an important central status, with respect, security, and a purpose in living on, which is much less often found in the Western World. In the United States, grandparents often live alone as long as they are able and then are sent to some institution to live out their last days in bad health. It seems common sense that an old person living with his/her family would be happier, healthier, and more well-cared for than an old person living alone with little or no social contact. But how much of an effect does this social factor have on longevity? More study and

solid data are needed to answer this question. The present state can be improved. It behooves us to analyze the experiences of those societies which have the highest percentage of happy and productive old people, and combine the best ideas, customs, diets, etc. to map out what appears to be generally most desirable and the best way to put these into practice.

CHAPTER 21

THE FUTURE - THREE POSSIBLE SCENARIOS

Scenario 1 - Economic Security for The Elderly

After the Great Barrier to life extension had been surmounted about the year 2050, medical progress came at a much faster rate than it did in 1987. However, it still took nearly 200 years before the average life expectancy of 150 years in good health and productivity was exceeded.

This gave governments and individuals enough time to plan and adjust for this newly evolved society of predominantly "senior" citizens. The work week was shortened to make way for the burgeoning working population. The retirement age was moved up with several scheduling options available. The most popular one was for healthy old persons to work on a half-time basis, working either mornings or afternoons, usually with a free lunch at the job between the two shifts.

On the individual level, people learned to plan for their own economic futures, thereby reducing reliance on the government for economic support later in life. This substantially reduced both personal and governmental economic stresses, and provided adequate earned income for healthy senior citizens.

The greatly expanded productive time of the population led to more leisure time, thus encouraging substantial growth and prosperity for vacation-oriented and entertainment industries. These increased opportunities for leisure included experimental facilities for those who liked to create, invent and launch new inventions or businesses. This gave gifted youths opportunities to develop and led to increased economic opportunities.

As is inevitable in any society, some problems persisted, but on the whole the average citizen was better off. Persons not only had more free time, but also had the economic resources to enjoy that free time in good health.

Scenario 2 - World War III

World War III came and 90% of the human race died. Of those surviving, the majority suffered damage, much of this genetic.

However, thanks largely to the gerontologic research in the years preceding the holocaust, it was possible to limit the damage, save enough of the science, and heal enough of the wounds

so that humanity could rise again to a new, and we hope, more wisely governed community of mankind.

Scenario 3 - A Critical Moment of Decision in the Unpredictable Future

World War VI had ended. The idea that peace could be maintained through a mutual capacity to make an overkill had backfired. We shall never know who set it off, for on earth's surface nobody survived.

Admiral Sharp of the Greenland Submarine Sector surfaced. The alarm systems signalled a lethal radiation so the "Astril" dived to safe depths. The Admiral took his flotilla to a well hidden submarine base at a depth of a thousand feet. This base had extensive repair and engineering shops supplied to satisfy all needs for 5000 persons up to a couple of years. It was a key center for submarine operations, including research. The base occupied a gigantic cave in a submarine mountainside.

The Signal Chief reported complete radio silence. The Chief Physicist and the head of radiation control agreed that it might be ten years before anyone could get to the surface and live.

Admiral Sharp summoned his Chief Biologist, "What is the status of your contacts with the whales? "

"We have made much progress since the last report, but knowing the heavy pressure on you, Sir, - ..

"Cut the formality, Bill. There is complete radio silence in the world. We may be the only survivors. Anything the whale can contribute could be utterly and unpredictably important to our survival. Tell me in as few words as possible where we stand."

"Through instantaneous computer translation devices, we are able to understand their complex language and have also been able to crudely simulate it. Through their enhanced brain capacity, we have already learned much about them and their environment. The key feature which distinguishes them from us is not having any fingers or even hands. The whales were never able to develop communication through reading or writing. To compensate, their brains are like computers - what you read or demonstrate to them they remember exactly, and can repeat without error even after a week - we don't know their limit yet."

"Our brain size is limited by gravity, and by the rigidity of the skull bones, which harden very early in life. When the bones harden, the brain can't grow. In humans, a heavier brain would require a much bigger head, and that would lead into

impossible skeletal and balance problems. The water mammals have no such restrictions, for in water, they are weightless. A whale's head is one third of his length and there is still margin for a great deal of expansion. So, the whales have brains already ten times bigger than ours, and unlimited space for further development."

"I have taught my counterpart on their committee on human contacts about 3000 words of Basic English. I ask your permission to introduce them to computers and have our communications engineers set up a whale sized screen with suitable controls for two way communication."

Admiral Sharp didn't need to think long about this request. In their current position, unable to surface, unsure about other super powers presence, or even if they could last as long as was necessary, the possibility of the whales' cooperation was one which could not be dismissed. "Permission granted. You have A-1 priority for men and materials. Report back in a month, or earlier if there is anything I should know. So long and good luck."

A month went by and Bill reports to the Admiral, "We have made progress. The two way computer communication is established. The whales would appreciate a top level meeting. Their Sector Chief and my counterpart would both like to come for an exploratory conversation with yourself, either here or at their headquarters as you may prefer. If you choose the latter, they will furnish transportation."

"Well done" said the Admiral, "Let them come here the day after tomorrow at 1:28 p.m. I want to see how closely they can keep time. If things develop we can go to them next time. I will order berths No. 27 and 28 in the light sub hangar set aside for them with proper markers and anything you can think of to make them feel comfortable, including communications and recording equipment."

On the appointed minute, two stately whales approached gate 27 of the Base, and a communication machine on the back of one of them said to the astounded guard: "Whale Admiral Klix of the NW Atlantic Sector and Humanist Nix are here to see your Admiral by appointment!" The gate opened, the whales entered and the Admiral and his advisors arrived and sat down in deck chairs, all facing a "whale sized" screen. After greetings and some introductory words they got down to the essentials. An outline for an agreement was reached, but would have to be ratified on both sides for final acceptance. The terms were these:

The whales, as represented by Whale Admiral Klix and Humanist Nix agree, subject to ratification, that they will cooperate with the humans at Greenland Base by refraining from disturbance,

allocating fishing grounds, designating hazards, and furnishing such information as might be helpful to the humans in their present situation. In return, the humans agree to teach the whales reading, writing, the use of tools and to help with adapting these tools to a whale's physiology.

Thus far the parties agreed. The whales further demanded for their fullest cooperation, that the base assign two berths to the whales with freedom of motion, that they devise a vehicle that can transport a whale comfortably on land, that they teach the whales robotics, in theory and practice, and that the base take on one whale as apprentice in the engineering department.

In consideration of this, the whales would further agree, through the use of their superb photographic memory, to give the information necessary for humans to map the ocean floor, designating the best land for farming and those areas rich with important resource materials for mining. They would also allow two humans with useful technical training and some experience in diving, to work with them, under their direction for a year.

The chief navigator decided to test their abilities and asked, "Can you show us a map of the territory where we are now?" Nix responded by drawing a map using the sliding "mouse" apparatus of the communication equipment. The map slowly took form on the screen. As he proceeded, the navigator stiffened and seemed deeply moved. Not only did the map show surface features at least as well as the best maps of the navy, but also showed topographical features of the ocean floor previously unknown even by the Chief Navigator. Indeed these whales held a wealth of knowledge and fantastic precision of memory and recall.

A distinguished silver haired gentleman from the State Department, who formerly represented his country as Ambassador to the imperial courts of London and of Kyoto, suggested that they meet again in a month, which would give Admiral Sharp time to assign a special committee to study the proposal and prepare for further negotiations, to create a base for the compromise which would appear necessary.

Whale Admiral Klix's response was immediate:

"We cannot understand the word "compromise". Either a thing is right and should be done, or it is wrong and should not be done. Either full collaboration or none. Between these is only confused thinking unacceptable to us. We expect your decision tomorrow at 1:28 p.m."

Back in Sharp's conference room, the men were vociferous in their opinions and could scarcely be contained.

The Ambassador said, "I have never heard "proposals" expressed with such finality. I can't decide if their method of reasoning is primitive or far advanced. One thing is certain, they meant exactly what they said."

The Colonel said: "We should immediately declare war on the whales. They must be exterminated. History shows that better brains give a military advantage. The whales evidently have better brains than we and their brains can freely develop to any size, while ours are locked into an unchangeable skull. It would be utter folly of us to teach them anything except possibly some religion. But to be on the safe side, we should exterminate them, as a hazard to humanity."

The Chief Physicist said, "Let's be practical about this. All of the evidence we have about post nuclear war is theoretical. We can only hope that the land at the surface will be arable again in 10 years. It could take much longer than that. We may have to live for generations under the sea and can ill afford to alienate these leaders of the Ocean. I say that we help them and if and when we are able to reclaim the land on the surface, we will have valuable and intelligent friends in the ocean ready to help us again if we need it. We'll have to worry about possible confrontation with the whales when we are in a better position to deal with it."

An assistant to the Biologist said, "How can we trust them? We could be sealing our own fate. Smite the human race to save our own individual lives? They already have a much higher brain capacity than we. Intelligence was what enabled us to evolve out of the realm of animals into beings of initiative. The whales could evolve into some sort of super human creatures with the artificial impetus of our knowledge and tools. What will we have to bargain with once they have developed the use of artificial hands? I'll be damned if I'm to become a hand servant to a pile of whale blubber!"

The Base Representative for IBM said, "I am horrified by the attitude of the previous speakers. The whales are peaceful, they don't fight each other, even at mating time, and they are no danger to anything bigger than a herring. I have never seen anyone grasp the computer ideas as fast as Whale Admiral Klix and Humanist Nix. I move that we accept their conditions with enthusiasm and abide with the letter and spirit of a treaty with them. Furthermore, IBM offers to employ two young adult whales for developmental work with computers at a liberal salary, whether payable in currency or in herring."

An angry young man, chosen to represent the ranks shouted: "Treason! He wants to sacrifice humanity for business interests!" A confused clamor ensued as several voices rose.

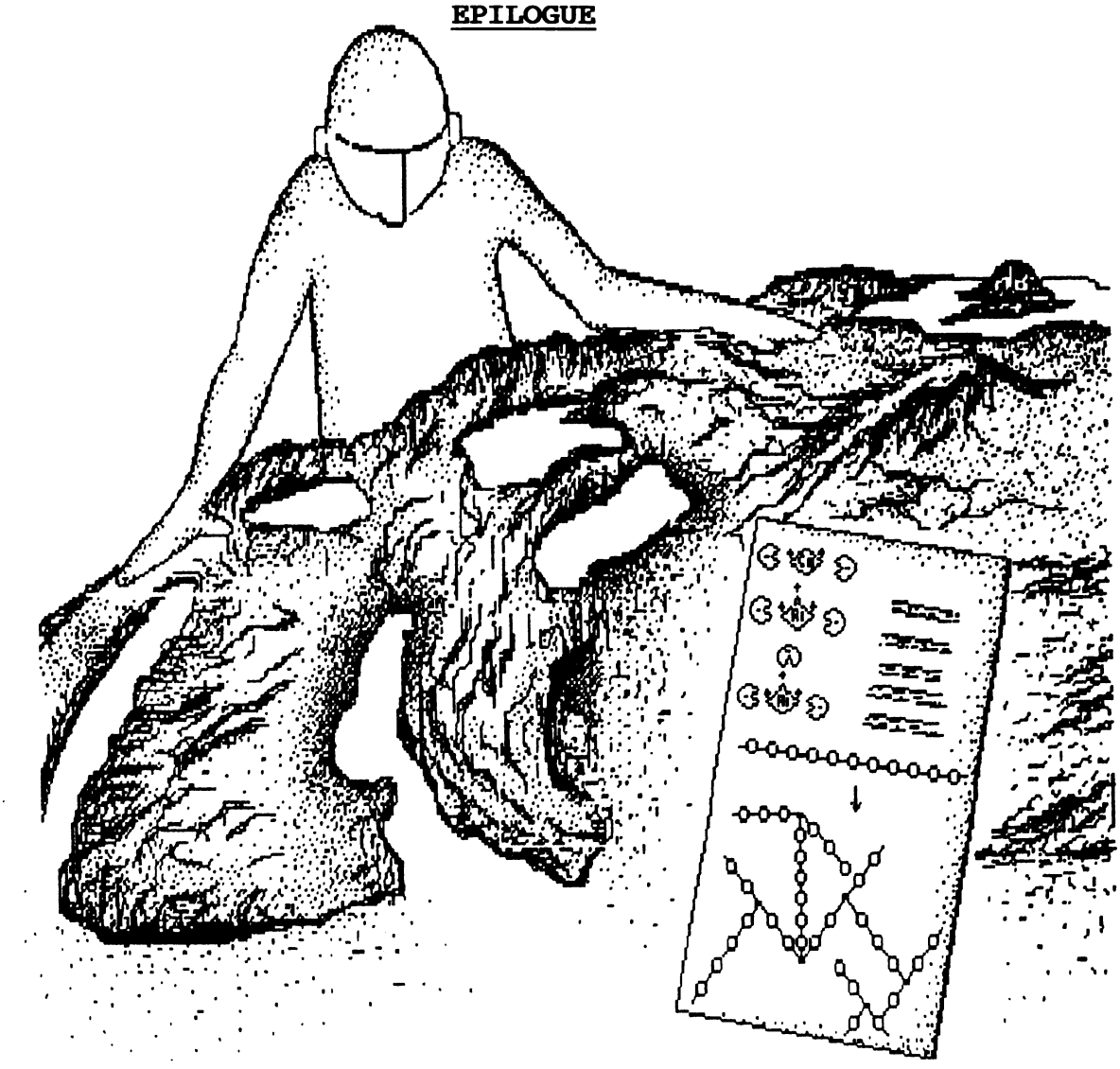
"Silence!", the Admiral barked. "No one is permitted to shout. You can submit your comments in writing and they will be noted. As I consider the gravity of this situation, I am reminded of an inscription at the Palace of the World Academy of Arts and Sciences:

> We are our own experimental animals, and
> can only hope that science will provide us
> with the insight that would be our salvation
> at critical moments of decision in an
> unpredictable future.
>
> Ragnar Granit

Such a critical moment arrives tomorrow at 1:28 p.m. As the ranking officer here, it is my duty to make this decision. I shall not shirk this duty."

Let us hope that in such "unpredictable" moments of decision, the decision makers will be able to settle problems without resort to violence.

EPILOGUE



Perhaps, when eons have changed Earth's face
that a traveler comes here, from Outer Space.
He circles the planet, and zeroes in
on my hidden place, far from cities' din.

My notes were stored under gases rare,
the symbols to him are crystal clear.
He says: "In that Age of Wars and Blood
this ancient Chemist yet understood
what has taken eons of time to bring
through labor, strife, and much suffering -
and yet, he was by the chance of birth
a lonely chemist, on distant Earth."

APPENDIX 1

For further details refer to Autoxidation in Food and Biological Systems (1980) Edited by Michael G. Simic and Marcus Karel Book available from: Plenum Publishing Corp. 233 Spring Street, New York, N.Y. 10013

The composition of the dietary supplement being used at present is:

Formulation GR 1358

	Parts By Weight
Lecithin	11,857.00
Dextrose	7,937.50
Inositol hexanicotinate*	1,184.90
Vitamin E, 400 IU (commercial mixed tocopherols)	473.36
Ascorbic Acid	295.47
Vitamin A, 25,000 IU	49.40
Riboflavin	13,84
Pyrodoxine HCl	16.70
Thiamine HNO_3	13.74
Calcium pantothenate	24.70
Vitamin B-12 (0.1% in Sugar)	4.94
Folic acid	4.94
Biotin	3.95
Rutin	19.67
Butylated hydroxyanisole	49.40
Sodium hydrogen selenite	0.40
Water	50.15
TOTAL	22,000.00

The antioxidants content is:

Ascorbic acid	1.34%
Vitamin E	2.15%
Butylated hydroxyanisole	0.22%
Sodium Selenite	0.0018%

*Hydrolyzes to 1,000 parts niacin and 263 parts inositol.

EXPERIMENTAL DETAILS

Before oxidation tests were started with the supplement, evaluations of the antioxidants in its absence under the specified test conditions were made:

Additives to Iron Catalyzed Linoleic Acid (Percentages)	Failure Time (Hours)
Vitamin E (0.25) + Sodium selenite (0.025)	21
Vitamin E (0.1)	40
Vitamin E (0.25) + lecithin (0.5)	44
Vitamin E (0.1) + lecithin (0.25)	64
Vitamin E (0.1) + ascorbic acid (0.1)	70
Vitamin E (0.1) + sodium selenite (0.025)	70
Vitamin E (0.1) + sodium selenite (0.025) + ascorbic acid (0.1)	98
Lecithin (0.25) + sodium selenite (0.025)	46
Lecithin (0.25) + ascorbic acid (0.1)	70
Sodium selenite (0.025) + ascorbic acid (0.1)	59
Ascorbic acid (0.1)	70

A dilution to 10% of the dietary supplement with linoleic acid, which gave antioxidant concentrations approximately in the same range as the above tests, had a 150 hour failure time. This indicated that an entity of the other ingredients is strongly synergistic, and this synergism increases sharply with increasing concentration. Further tests at lower and higher loadings showed that the oxidation

resistance increases with supplement as indicated in Figure 3.

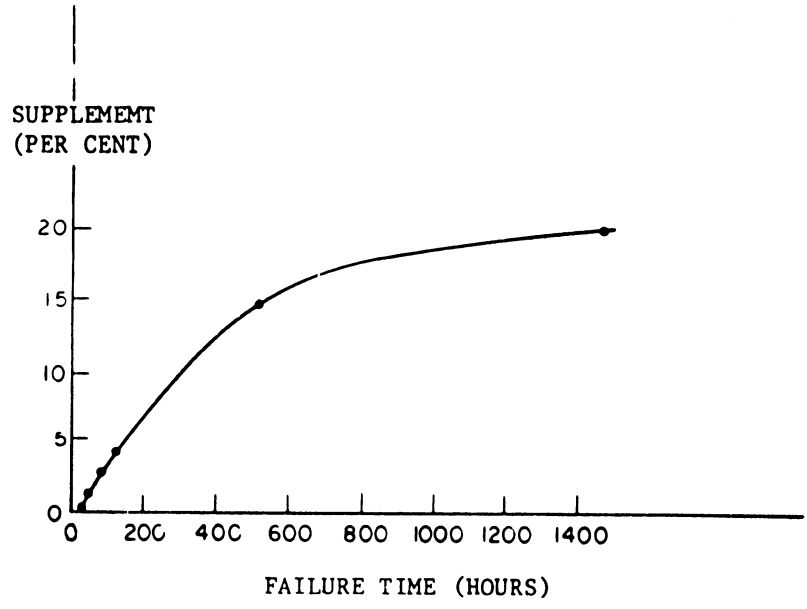


Figure 3. Increase of oxidation resistance with dietary supplement

The suggested daily intake of the formulation GR 1358 is 20 grams daily. In a conservative diet, this may be more than 20% of the unsaturated fats ingested the same day, so that the maximal protection figure of over 1,400 hours might apply.

Percent Supplement in unsat'd fatty Acid	Failure Time (Hrs)
0	12
1	24
2.5	48
5	110
10	150
15	560
20	over 1,400

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G L O S S A R Y

ACETALDEHYDE - An aldehyde found in cigarette smoke, auto exhaust, smog, and created in the liver from alcohol. Like all the simpler aldehydes it is a crosslinking agent, and as such reacts strongly with any protein it happens to encounter. It is also autoxidized (self-oxidized) by the oxygen in the air, or in blood, to form peroxides including some irritants in smog.

ALDEHYDES - A class of highly reactive organic compounds.

AMINO ACIDS - These nitrogen containing organic acids are the building blocks of which all proteins and all peptides are made of. One of the most basic building blocks in biochemistry.

AMYLOID - This word means "Starch like". It is sometimes used to mean just that and then is applied to anything that looks like starch. More often, particularly in medical connections it is used to mean some whitish, organic waste materials that cannot be removed by the body, but accumulates in the brain, kidneys and elsewhere until it begins to "gum up the works". No two analyses of it come out the same, so we conclude that it is a highly crosslinked mess which includes any large molecules that happened to be around and get caught in a web of other large molecules, which finally get crosslinked by aldehydes, maybe some free radicals, and crosslinking agents randomly present, until the mass gets so tied up that nothing available to the body can remove it.

AMYOTROPHIC LATERAL SCLEROSIS - A serious mental disturbance which could be favored by the inability of the particular patient's chemical systems to make some very long chain compounds required for maintenance of neuro-balance.

ANTIGEN - In immunology, anything that arouses the immune system to defensive action.

ANTIOXIDANT - Anything that prevents or slows down (retards) anything else from combining with oxygen. Antioxidants play a central part in food industries, perfumes, rubber and tire industries, and also in medicine and health. The principal antioxidants in life sciences are: The Vitamins E (Tocopherols), Selenium, phenolic chemicals TBH and TBA, Vitamin C. In industry many excellent antioxidants are based on Quinones, but some of these are not suitable for use in foods.

ATHEROSCLEROSIS - A common "degenerative" disease, often caused by dietary errors including excessive caloric intake, deficiencies in choline or lecithin, too high fat, and not enough antioxidant to protect unsaturated compounds from oxidations.

ATOM - The smallest possible part of an element.

ATP - Adenosine tri phosphate - The universal energy storage and transport molecule. Energy released during the oxidation of foodstuff is taken out in several successive steps since any excessive energy concentration must be avoided. Energy thus gained in excess of immediate needs, is usually in the form of ATP.

AUTOIMMUNE - A state in which a persons immune system mistakenly turns against normal healthy organs, or against intentionally implanted organs from outside. Rheumatoid arthritis, multiple sclerosis, and failures of heart transplants are examples.

AUTOXIDATION - An oxidation which happens by itself, like rusting of iron, drying of linseed oil and butter turning rancid.

CANCER - Cells which have lost control of growth and keep on growing by cell division.

CARCINOGENESIS - The process of causing cancer.

CARCINOGENS - Cancer causing substances, usually crosslinking agents or irritants.

CATALASE - An enzyme which splits off the extra oxygen contained in hydrogen peroxide. When you put hydrogen peroxide onto a scratch, it foams up due to the catalase in the blood speeds the decomposition of hydrogen peroxide more than a hundredfold.

CATALYSIS - Something that makes a chemical reaction go easier, like a carriage rolls more readily downhill if you lubricate its bearings. Enzymes can very greatly speed up chemical happenings which go by themselves anyway. They can't cause anything to happen that does not go by itself, no matter how slowly.

CENTRAL NERVOUS SYSTEM - The Brain, Spinal Cord, and other structures enclosed within the special membranes surrounding the brain and spinal cord. Nervous elements of ears, eyes, pituitary and pineal glands are examples of this.

CHALONES - Chemical messengers that carry commands to stop some particular action. Thus they are antagonists to hormones with the power to cancel orders brought by hormones. All chalones are totally non-poisonous, organ specific, species non-specific. This means for example that the skin chalone from a mouse could not only stop the growth of skin in a mouse (for example: when a wound has healed), but could also do the same for a horse, or for a person. Also, it could only control the growth of one thing, not of any other organ at all. Chalones are not yet available commercially because they are so extremely dilute in all natural sources.

CHELATION - The process of binding a metal very strongly to a claw-like molecule which partly surrounds the metal atom in a firm grip. This is used in medicine to pull out and remove unwanted metal; in mining for extracting valuable metals from their ores.

CHOLESTEROL - A solid steroid alcohol occurring widely in nature.

CHOLINE - This is a vitamin which is an essential part of lecithin, and which in itself has important functions in the communication system within the body, and particularly in brain and nerves. As a part of the lecithin molecule it makes possible the transport of water insoluble hormones and vitamins A, E and D in the blood, and is an essential part of both HDL and LDL lipoproteins.

CHOLINERGIC - A chain of chemical reactions which needs choline for at least some of the energy part of its action. Acetyl choline is a common form of choline in causing muscle fibers to contract, and also in control of mental concentration, as well as in memory and long range planning.

CILIARY GANGLION - A mass of nerve tissue which is needed for the proper function of the eye.

COLLAGEN - Nature's all purpose glue, easily modified to fit a wide range of conditions, from water soluble gelatins to a hard cement that holds together inorganic molecules (calcium phosphate, etc.) in the bones and gives these a far better shock resistance than would be possible without collagen. Excessive, progressive crosslinkage of proteins is an underlying process in aging. The insight in this fact stemmed from studies with collagen (1942). About one-third of all body proteins are collagens.

COMPLEMENT - A system of protein molecules produced by the immune system which kills antibody-tagged foreign cells by making holes in their cell membranes.

CONTAGIOUS DISEASE - A "catching" disease, passing from one person to another either directly, or indirectly through carriers. These may be dead things, or other life. It took a couple hundred years for this idea to be accepted. From the first microscope in mid sixteen hundred until 1840 when anatomy professor Friedrich G. J. Henle wrote: "The material of contagion is a live one and is indeed endowed with a life of its own, which is, in relation to the diseased body a parasitic organism."

CONTROL - A technique for evaluating test results, by comparison with a set-up which omits whatever is being tested, but is otherwise in every respect the same.

CROSSLINKING AGENTS - Any substance capable of tying two other molecules together with a "bond" or "bridge". This includes many myriads (tens of thousands) known compounds - any molecule with two reactive sites of any kind, or with one poly-reactive site is a crosslinking agent. In life processes, when aging is concerned every reaction must be counted with, which causes anything to be formed that cannot be broken down and removed. It is necessary to count with reaction times equalling the maximum life span of the organism, for humans 100 years. Examples of crosslinking agents are thus fast acting, such as formalin and acetaldehyde, aluminum, ozone, mustard gases, all of the principal mutagens--and slow acting such as molecular oxygen, poly chloro- and poly oxy-compounds, anything that left standing with a protein solution for 70 years will cause more insoluble material to form than in a part of the same solution to which nothing was added.

CYTOCHROMES - A group of blood proteins, which easily can take up and give off Oxygen. The most commonly encountered of about 35 known cytochromes, is cytochrome C, often encountered in connection with cell breathing.

CYTOSTATIC - Substances which stop cell growth.

CYTOTOXIC - Cell poison.

DEMENTIA - Loss of mind, insanity.

DOUBLE BLIND - A technique in testing used to ensure that the results are not changed by the hopes or beliefs of those who make the comparison. Markings and distribution of the tests are arranged so that neither persons on the test, nor those who conduct the tests, can know which individuals got what sample, until the results have been recorded.

EDTA - Abbreviation of ethylene diamine tetracetic acid, a strong chelating agent used for extracting metals either in medicine or mining. In medicine it is officially approved for treatment of poisoning with lead, or with radioisotopes including strontium, polonium, plutonium, etc. It is not very efficient for aluminum. Its use for removal of calcium from sclerotic arteries is still controversial, although several qualified physicians are using it and have reported encouraging results.

ELECTRONEGATIVITY - Electric charge present on the surface of an atom.

ENCEPHALOPATHICS - Encephalon means brain. Pathic means sick. A person who is encephalopathic has a brain disease.

ENZYME - Substances which can increase the speed of chemical reactions enormously, subject to the following limitations: Each enzyme is effective on one kind of reaction only, to which it fits "like the key to a lock". The enzyme can only speed reactions which can go without it, however slowly. The enzyme works on a reaction like a lubricant on a wheel, which causes the wheel to turn a lot more easily, but cannot cause it to roll uphill. Enzymes are widely present in all living organisms, indeed, it is difficult even to imagine any life without enzymes. The enzymes are proteins. They are not consumed in the enzyme reactions any more than a lubricant would function to drive a car.

EPITHELIAL - Skin in a broad sense, expanded to include also the linings of internal organs, and further organs which in the embryo were formed from a skin fold; in such a broad sense the brain and most of the nervous system is of epithelial origin.

ESTERS - In organic chemistry, the product formed by combining an alcohol with an organic acid.

ETHYL ALCOHOL - The chemical name for ordinary alcohol.

FACTORS - Any biologically active substances that do not fully meet the definitions of hormones, chalone, or whatever else may be in question.

FIBROBLASTS - Connective tissue cells that form the fibrous tissues of the body, such as tendons. Fibroblasts are the most important type of stationary connective tissue cells. Fibroblasts are divided into three groups: the collagen producers, the cartilage producers, and the osteoblasts, which produce the crosslinked bone collagen, which gives bones a degree of elasticity which greatly contributes to their impact strength.

FREE RADICAL THEORY OF AGING - The theory that aging is largely caused by the impact of free radicals. This might well be a cause of 10-20% of the aging. Free radicals could do damage by three different mechanisms: by splitting essential large molecule, by sheer impact of hitting, and by causing crosslinkages, which render essential molecules insoluble and inactive. The splitting ("fission") type reaction generally gives rise to smaller molecules, which mostly are soluble and thus unlikely to cause permanent harm. To the extent that it depends on crosslinking, this theory is a subsection of the crosslinking theory of aging which was published 13 years earlier.

FREE RADICALS - Atoms or molecules with at least one unpaired electron, which means an unsatisfied binding force, ready to connect to anything it encounters. Generally the free radicals cannot remain free for more than a small fraction of a second, if in that time they have not connected to anything else, they connect to another free radical so that they satisfied each others free binding force and thus are no longer free. There are some long lived free radicals, but these usually have a large bulky body or are otherwise hindered in their motion so that they are no longer truly "free". Cells of the human immune system use bursts of free hydroxy radicals to destroy foreign invaders. For effects in Aging, see **CROSSLINKING.**

FRUCTOSE - A simple sugar, commonly occurring in fruit juices and honey. Chemically combined with glucose, fructose forms Cane Sugar which is the ordinary sugar of commerce. Taken alone, fructose is inferior nutritionally to both saccharose and glucose, since the ability of human metabolism to handle fructose is somewhat limited. As a sweetener, it is superior to both of the two other sugars mentioned. It is about twice as sweet as cane sugar and is about three to four times sweeter than glucose.

GLUCOSE - A simple sugar, and the only sugar which the brain can process directly. Glucose is evidently the sugar chosen by millions of years of evolution to be the most basic for animal metabolism on earth. In comparisons with other simple sugars in animal experiments as well as in tests with humans, it has given the best survival curves and the least formation of blood cholesterol. The only carbohydrate sources which give better results than glucose are those complex carbohydrates which are actually large numbers of glucose molecules linked together: boiled starch, dextranes, glycogen. These form glucose when digested. Unboiled starch is not favorable, because it resists the enzymes of the upper digestive tract and essentially feeds the bacteria in the colon, at the end of the intestines.

GRANULOCYTE - A common name for three kinds of white blood corpuscles, which have granules in their cell plasm. They are named for the dyes with which they can best be stained for recognition. At the present, they are one of the more promising raw materials in the search for chalones.

HDL - High density lipoproteins, which transports water insoluble substances in the blood stream. It contains about twice as much lecithin as does the "LDL" and accordingly can pick up undesirable water insoluble substances such as cholesterol, from the arterial wall, and carry them away for example to the liver for removal or re-working.

HORMONE - A chemical messenger, that is transported (often by the blood stream) a relatively long distance from its source to the cells it affects. Insulin, vasopressin, male and female sex hormones, and cortisone are some examples.

HYALINS - Any of several translucent nitrogenous substances.

HYDROXYL RADICAL - A very reactive free radical formed when a superoxide radical reacts with hydrogen peroxide, or when an enol diene such as Vitamin C reacts with hydrogen peroxide and an iron or copper catalyst.

IMMUNE SYSTEM - Our protective system, Leucocytes (White blood corpuscles) of various kinds and specializations, killer cells (T-cells) controlled by the Thymus gland, n-cells formed in the bone marrow, complement and interferon. The immune cells must multiply very fast to keep ahead of bacteria and cancer hazards, and are therefore susceptible to damage from chemical anti-cancer poisons or from X-rays.

INFARCT - Tissue which has died due to lack of oxygen resulting from a blood clot blocking an artery.

INFUSION - The continuous slow introduction of a solution, usually into a vein.

INSOLUBLE - Something that will not dissolve. A highly cross-linked substance is insoluble in <u>any</u> solvent without decomposition. Example: Sugar is soluble in a cup of coffee.

INTERFERON - A class of protective proteins produced by the white cells and fibroblasts which prevent viruses from penetrating body cells and which may also help to regulate cell development.

ISCHEMIC - Localized tissue anemia due to hindrance of the inflow of arterial blood.

LDL - Low density lipoprotein, which contains only half as much phospholipid (lecithin) as the high density (HDL) lipoprotein. Therefore the cholesterol it transports is held loosely, and is easily deposited in the arteries.

LECITHIN - The most common and typical of the phospholipids.

LEUCOCYTE - Scientific term for white blood cell. There are several types of leukocyte - see also **IMMUNE**.

LIPIDS - Fats and oils. Saturated fats are solid at body temperature, while unsaturated fats have a lower melting point and are often oils. Especially important are the lipids found in the cellular membranes. Polyunsaturated lipids are particularly sensitive to damage by oxidation and in any comparative experiment should be adequately protected with antioxidants.

LIPOPROTEINS - Substances found in the bloodstream, which make it possible to transport water - insoluble substances in the blood, including for example Vitamins A, D, and E, many steroid hormones, and many prostaglandins. To make such transports possible, all lipoproteins contain phospholipids ("Lecithins") which have strong attraction both for water and for oils and so make such usually difficult transport possible, and even easy. HDL lipoproteins have a high content of lecithin which enables them to firmly grip their burden and bring it away, while the LDL lipoproteins contain only half as much lecithin, and thus have a light grip of their burden (often cholesterol) and are likely to dump it in the tissues.

LONGEVITY - 1. a long duration of individual life. 2. length of life.

LYMPHOCYTES - These are white blood cells, formed in lymph glands, spleen, thymus or bone marrow.

MACROMOLECULE - A very large molecule.

MELANOMA - A type of often deadly skin cancer characterized by dark color.

METASTASES - Additional positions of a malignant tumor. A change of position, state, or form as transfer of a disease producing agency from the original site of the disease to new parts of the body.

MITOCHONDRIA - The principal power plants of the cells. They oxidize food to water, carbon dioxide, and energy, which is partly taken out in the form of high energy phosphate ATP. Free radicals are a normal and necessary part of mitochondrial oxidation.

MOLECULES - Smallest possible combination of atoms which can be made and still be the same substance.

MUTAGEN - A chemical which causes mutations. Haddow showed in 1946 that crosslinking is a prime cause of mutations, and Peter Alexander showed a few years later the generality of this fact. It now appears that all mutagens are agents which can cause co-valent bonds between the two strands of DNA.

MUTATION - a genetic, <u>inheritable</u> change.

NECROPSY - Dissection and examination of a corpse, to determine the exact cause of death, or to increase medical knowledge.

NEURITE - Anything growing out from a neuron, usually referring to the long Axones, and the short and branching Dendrites.

NEURONS - Nerve cells.

NGF - Nerve Growth Factors. Substances essential for the growth, health and repair of nerves. Liquid from wounded human brain has been found to support growth of rat nerves or of embryonal chick nerves. This makes it appear possible that NGF from animal sources might become important in medicine, which also has considered human placentas as a possible source. This is an important frontier in current medical research.

PARKINSONISM - A chronic nervous disorder that is marked by muscle rigidity but without tremor of resting muscles.

PHAGOCYTE - A cell, as a leucocyte, that typically engulfs foreign materials and digests them, thus removing debris and killing foreign bacteria.

PHOSPHOLIPID - Molecules which are of three parts: an hydroxyl substance (usually glycerin), some fatty acid molecules, and a water-loving substance (usually choline). This general theme can be varied by changing any one of these three components. This manyfold possibility of combinations enables the fine-tuning of life processes to match each of a great many needs.

PLACEBO - In a clinical study when new medicines are tested, the hopes or beliefs can influence the results. To avoid this some of the patients will receive no new medication, but only a pill of the same size and taste as the remedy being tested. Such a pill is called the placebo. Neither the patients nor the physicians will know who received the placebos until the test is over and the results recorded.

PLAQUES - Solid and indigestible remains of dead cells. Typically plaques contain some of every large molecule in their environment, both of fatty and protein nature, all crosslinked together to a tight, indigestible and insoluble mass.

POLYMER - A chain of the same molecule. Example: Starch is a polymer of glucose.

PRECIPITATE - 1. a substance separated from a solution or suspension by chemical or physical change usually as an insoluble amorphous or crystalline solid. 2. a product, result, or outcome of some process or action.

PEROXIDE - Highly oxidized compounds, like hydrogen peroxide, which can directly oxidize many unsaturated fats and oils thereby starting some free radical type chain reactions which normally are stopped by antioxidants.

PROTEASES - Enzymes which breakdown proteins. A very large number of proteases are known, some of them are highly precise in their action in breaking only particular bonds, others are "broad spectrum".

T-CELLS - Thymus-derived white blood cells which kill and eat foreign bacteria, viruses and cancer cells. The thymus glands controls the production and activities of the T-cells. These use as ammunition bursts of free hydroxy- radicals.

THYMUS - Thymus derived white blood cells which kill and eat the breast bone. The thymus instructs the T-cells when to mature or reproduce, and what targets to attack. This gland is even in advanced years essential for resistance to disease. It is sensitive to X-rays and should be protected by a lead shield if X-ray therapy is to be applied in its area in excess of needs for a small number of X-ray photographs.

TOCOPHEROLS - A family of natural antioxidants known as the Vitamin E. Some of the oxidation products of tocopherols are pro-oxidant, and the use of high dosages of Vitamins E therefore are not desirable. Vitamins E are the mainstay of natural antioxidants. A key question of Longevity is: "How much of an antioxidant can be taken without making the necessary oxidations too slow?" Vitamin E is the natural answer to this question, and may be judiciously improved by combinations with Vitamin C, and lecithin as natural additives, and with care and medical counsel cautiously supplemented as physician may be recommending in special cases.

TOXIC - Poisonous. Toxic effects depend importantly on the dose, the state of health, other foods or medicine taken, and so forth.

UREMIC - Urea in the blood. Urea is a principal form of disposing unwanted nitrogen compounds in the urine. When the kidney's fail, Uremia or gathering of Urea in the blood follows. A Uremic person is in need of dialysis treatment.

VALENCE - Binding force (an unpaired electron). Bi-valent means two-binding forces, poly-valent means more than two valence.

WATER - Same as hydrogen oxide. More people have died from water than from any other liquid. The quality of water depends on small amounts of salts or other substances dissolved in almost any water. More than half of the human body weight is water. The water content of the body declines with age, due to continuing crosslinkage of large molecules.

Adenosine Tri Phosphate (120)
Aging pigments (52)
    See also Amyloid, Lipofuscin
Alfrey (50), (80)
Aluminum (39), (49), (59), (150)
    accumulation (69)
    aluminum-calcium relationship (51)
    as cause of Dialysis Syndrome (80)
    as dominant crosslinking agent (57)
    as outcast element (137)
    atom (59), (61), (62), (63)
    clinical effects (83)
    content in brain (82)
    content in water (50)
    content increases with age (61)
    in AD brains (67), (68)
    in aortas (78)
    in crosslinking (52)
    in non-ischemic dementias (36)
    in public water supplies (69), (81)
    natural defenses against (63)
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    role in non-ischemic dementias (50)
    showing valence (84)
    tanning of leather (77)
Alzheimer Brains
    crosslinkage status of (65)
    protein accumulations (68)
Alzheimer's Disease (1)
    as Deficiency Disease (68)
    definition (36)
    neuronal defenses against (64)
    overdose of aluminum (63)
    personal prevention (70)
    prevalence in U.S. (36)
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Amino acids
    food sources (127)
Amyloid (52), (72), (83), (89)
    See also Lipofuscin
Amyotrophic lateral sclerosis (36)
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CURVES AND DIAGRAMS

Certain diagrams have been adapted and clarified by Alisa Myers.