APPROACHES AND PROSPECTS FOR THE CONTROL OF AGE-DEPENDENT DETERIORATION

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What can I, an unsophisticated industrial chemist, contribute in this august gathering? Groping for a justification, I can find only that there is perhaps some difference in viewpoint between academic science or the citadels of power of our Government and an industrial chemist who is a playball for many forces vastly more powerful than himself.

If I have any place here at all, it will be to expose to your judgment some concepts that are forced on entrepreneurs whose only choice is to produce results or vanish.

When we approach an industrial problem, the first steps are:

1. Get the target in clear focus.
2. Know what the competition is doing.
3. Reduce the history to charts.
4. Keep it simple.
5. Find the most generic of the possible solutions; in other words, kill as many flies as you can with each swat.

In the following presentation I shall apply this outline.

I. The Target:

To give as many people as possible as many more healthy, vigorous years of life as possible.

II. The Competition:

This is represented by the other principal research activities that use money and manpower: the military, the space effort, nuclear science. These competitors can also at times be allies, but for present purposes the competitive aspects come to mind. What have they given for the money spent? How can we produce results that, judged by the criteria of public good, can justify a higher priority than they now enjoy?

III. Reduce History to Charts:

FIGURES 1–3 show the acceleration of power available to man. What, then, have all the workers on the extension of vigorous, productive life accomplished for the money spent? FIGURE 4 gives the answer.

IV. Keep It Simple:

When I look at the last curve in FIGURE 4 and, as a simple-minded industrial chemist, contemplate the lack of progress that it shows, I recognize a very familiar situation. Only the time scale differs. Change the years to weeks, and this curve could be the sales or production curve of any industrial product whose research has been ineffectual or has long passed the point of diminishing returns.

With this kind of chart I can hear the voice from the other end of a long-

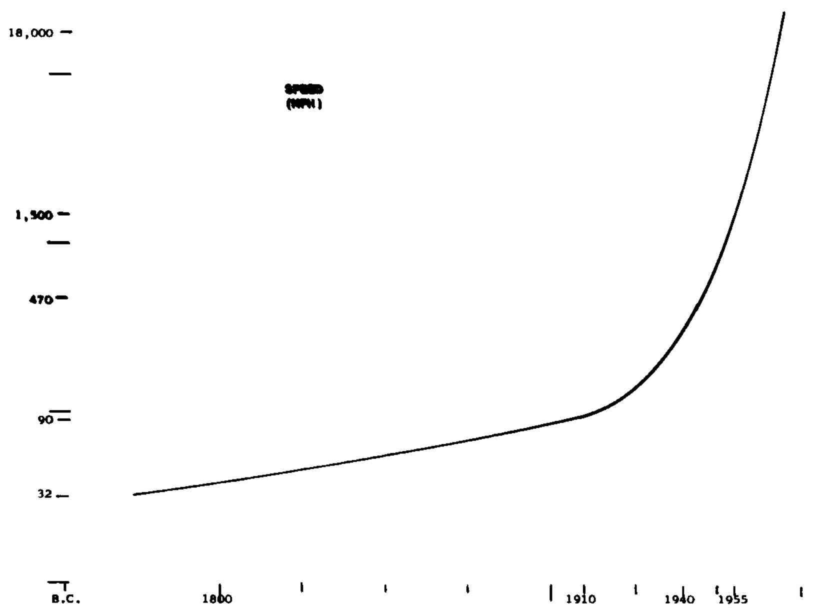

FIGURE 1. The increase in speed available to man and its logarithmic acceleration due to systematic, well-supported-and-directed efforts by the U.S. Air Force, NASA, and supporting organizations.

distance connection: "If you people don't get busy and produce results in the next three time units, you will be *out*."

We have heard that and met the challenge enough times to have remained in business 25 years, so it doesn't alarm us unduly.

What, then, are the possibilities?

In FIGURE 5, A is the present American mortality curve. Curve B is the curve that would result if a cure were found tomorrow for the principal killing diseases of today: the present curve would be moved over about 15 years. The person who did not die of a coronary at 90 would, at age 105, be so much weakened by general aging that he would fall victim to the slightest ailment. Curve C, the flat line, would result if no progress were made on any

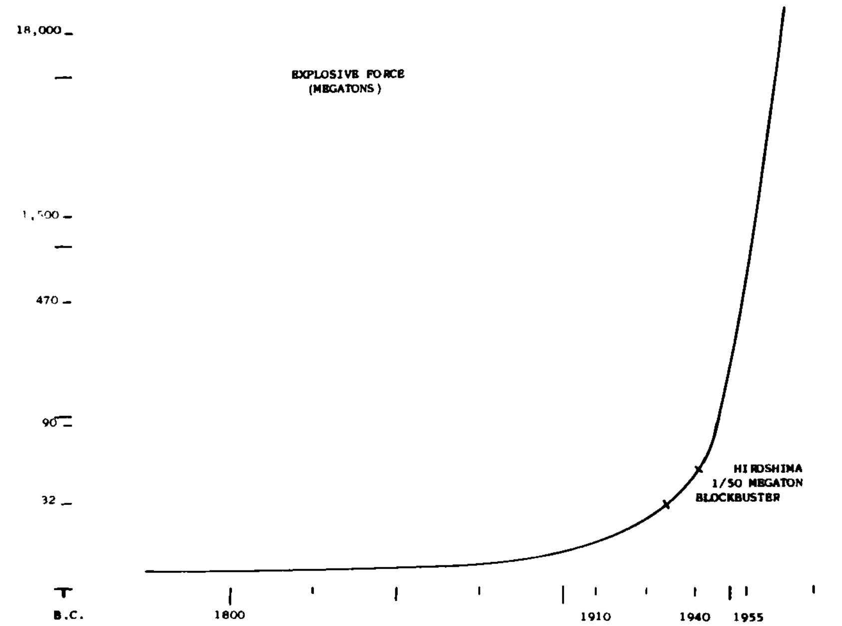

FIGURE 2. The increase in explosive power available and its logarithmic acceleration due to the research activities of the military, the AEC, and supporting organizations.

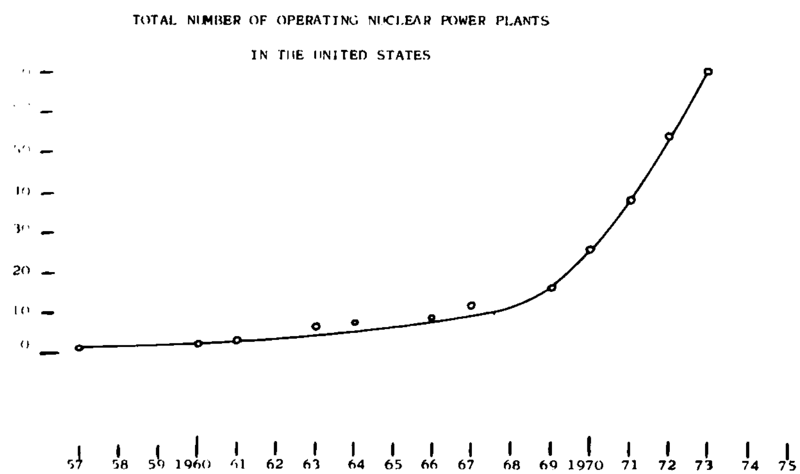

FIGURE 3. The increase in nuclear power generation and its acceleration due to the research activities of the AEC and industry.

FIGURE 4. Life expectancy at 60 for white males from 1789 through 1967.

of the prevalent diseases per se but the problem of progressive deterioration due to aging were solved. It is evident that the gain would greatly exceed any of the common predictions.

A near-100% success is not unknown in medicine—diseases have all but disappeared—smallpox, plague, most recently, perhaps, polio. But let us be conservative. Few will argue with the notion that a 10% success is a reasonable expectation where systematic, well-directed research is brought to bear. A 10% success in control of aging might be expected to result in curve D.

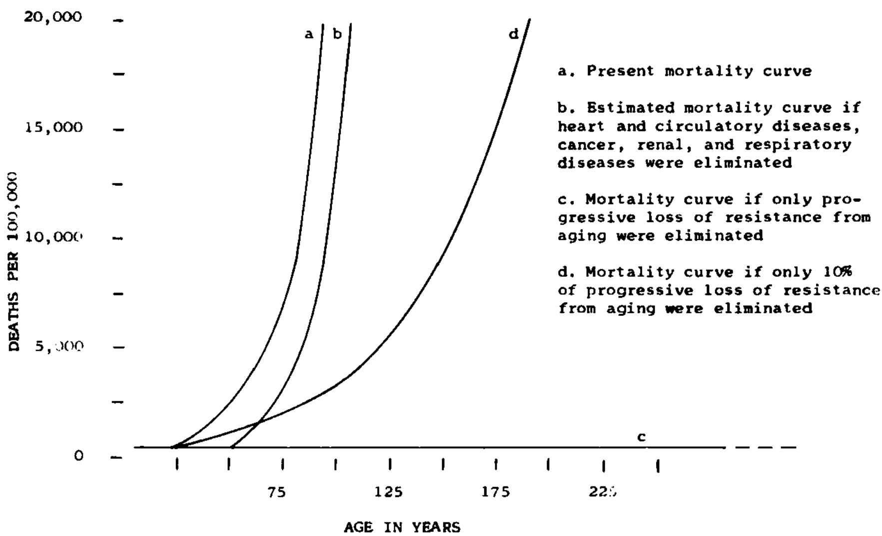

FIGURE 5. Present and projected U.S. mortality curves.

This would lead to a far more tangible result than if all of the research were directed to all of the specific diseases.

V. Kill as Many Flies as Possible with One Swat:

The age dependence of mortality from all diseases is further illustrated by FIGURE 6, from data compiled by R. R. Kohn and published in the Journal of Chronic Diseases (1963).

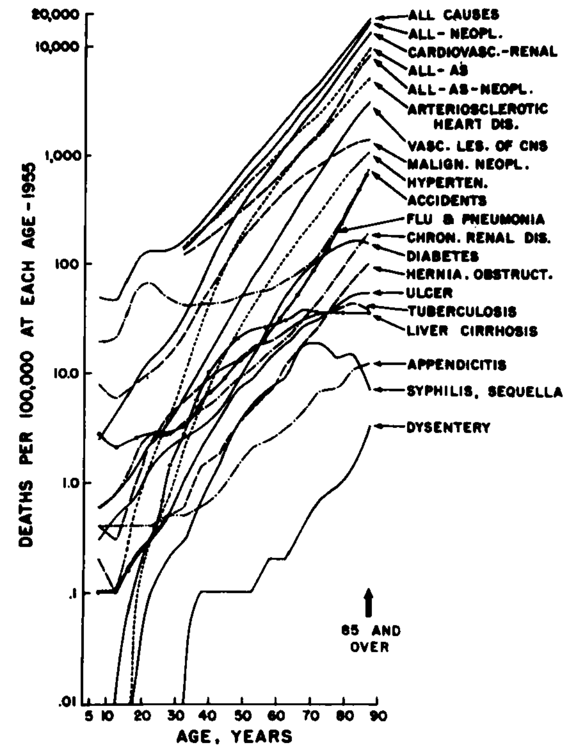

FIGURE 6. Mortality from selected causes by age. Plotted from data compiled by R. R. Kohn and published in the Journal of Chronic Diseases (1963).

We see here that every one of the major diseases tabulated is age-dependent. To attack the problems of these diseases separately, as is now the preponderant course of action, is akin to trying to stop a hemorrhage by closing all of the capillary vessels separately rather than ligating the main artery. It would seem that the present policy of directing most of the medical research to the specific causes of death rather than to the underlying cause or causes of aging and their prevention might benefit from reconsideration. Not only is research aimed at the braking of aging potentially vastly more rewarding, but it may also be easier to pursue. The old fields have been plowed over and over. The field of direct aging research is far less crowded; gold may still be found close to the surface.

The Advantage of a Newer Approach

A few words about recent research, previously unpublished, may serve to illustrate the multiplicity of approaches that can be taken and to show how the field of aging is open to the application of modern research tools and methods.

We fed a pregnant rat a total of 40 millicuries of tritium shortly before it gave birth to a litter and during the first days of lactation. The offspring never received any other radioactive material. One of the litter was sacrificed 621 days later. The tritium still remaining had been fixed in compounds or positions that could not be pried loose by the metabolic forces available to the organism. It was now possible to determine in which form those compounds that contained tritium had been immobilized from birth to far beyond the middle age of the animal.

We did this. The predominant amino acids that had remained fixed in the organism are shown in FIGURE 7. No other radioactive amino acids were found in the separatable peptides.

You will note that these are those amino acids which have side chains (underscored) sticking out from the backbone of the molecule, with a reactive group on the end. If we gave a child toy models of all amino acid molecules and asked it to build a grid, it would pick the amino acids we found. Otherwise there were considerable differences between the fractions. For example, in the liver, the water-soluble radioactivity we found was present in a single peptide composed only of the amino acid serine and a carbohydrate fraction containing ribose. Although the ribose was only 0.05% of this peptide, it contained 90% of the tritium.

The phospholipid fraction, extracted from the residue, was free of amino acids but contained a portion of the tritium administered at birth in the form of unsaturated lipids. It was surprising to us that something as easily oxidized

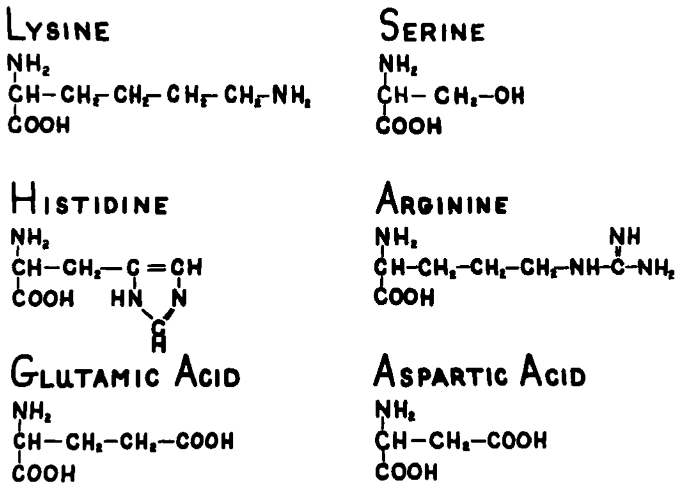

FIGURE 7. Fixed amino acids in 626-day-old rat whose mother was fed tritium during late pregnancy and early lactation.

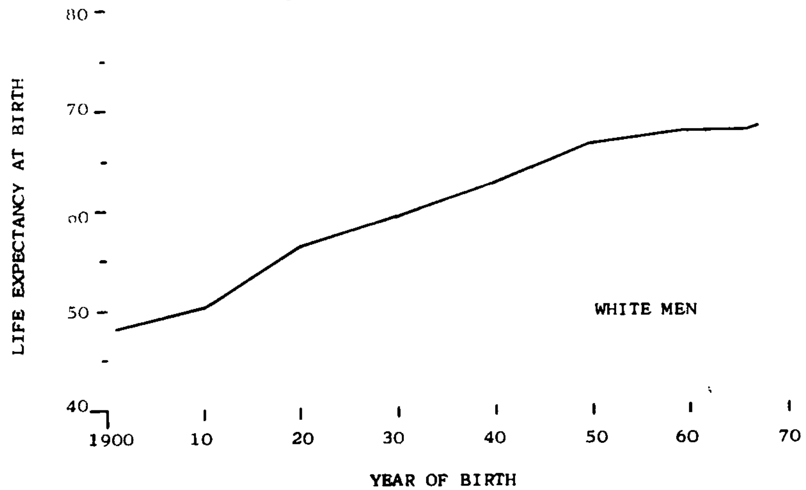

FIGURE 8. Life expectancy of American white males according to year of birth.

as these lipids could remain fixed through life. These were also found in the corresponding fraction of the brain.

On hydrolysis, at body temperature, of the residue from extraction with water, acetone, and phospholipid solvents, we obtained three polypeptides, of which one consisted of all the amino acids mentioned above and two consisted of the same amino acids except histidine.

The residual matter resisted all milder hydrolysis treatments and was insoluble in all the commonly used biological solvents: 8n urea, urea plus detergents, 6-N guanidine plus detergents, acid and alkaline salt solutions, dimethyl sulfoxide, acetamid, formamid.

It still contained a large share of the total radioactivity present in the animal at death. This is under investigation, but one finding may be mentioned here. We dissolved some of this intractable material in hydrazine-hydrate (95%), passed it over a Dowex-50 column, and eluated a glycopeptide. This substance—80 mg—was hydrolyzed to release the sugars and subjected to further column chromatography. It contained ribose and RNA, and this fraction contained a radioactivity comparable to that of the ribose in the very first water-soluble fraction.

Were these two ribose fractions orignally the same? Was the ribose found in the first, soluble fraction connected with that RNA present at birth which remained functional through the years, and did the ribose found in the last, extremely insoluble, fraction stem from that RNA which was immobilized and rendered nonfunctional by crosslinkage, so as to form insoluble conglomerates or aggregates with other macromolecules?

These findings from our recent work show how results of some significance can still be obtained with ease in the chemistry of aging. Organ transplantations, mechanical or electronical implants, new antibiotics or other drugs, remedies for specific syndromes and diseases—none of these will reach its full potential utility until the progressive loss of resistance due to aging is brought under control.

Even the curve of life expectancy at birth (FIGURE 8) shows that medical research has reached a point of diminishing return. The life expectancy at 60 of a white male was in 1967 only 1.1 year higher than it was 178 years earlier. Planning must be reassessed. The time for action is at hand. Efforts should not be dissipated on attempts to solve the problems of each disease separately. Their common stem, aging, must be attacked with means and a will at least equal to those applied to problems of space, atoms, or degenerative diseases—which, after all, are only tertiary by-products of aging.

Acknowledgment

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BRONK: As this very interesting paper was being given, I was continually reminded of the fact, familiar to biologists, that anything we do with regard to the process of aging will reveal some of the most important biological processes and understanding of them that we can hope for, because aging and life and the maintenance of life are all part of the same picture.

When reference is made to the tremendous increase in the power available to people with progression and time, I am reminded of one of the frustrations of the present era. While a great deal has happened since the time when man first was able to exercise more force by the use of a lever until the present, when, by turning a switch, he can gain far more power from nuclear-energy procedures, nevertheless, the use of the lever has given to man, as a man, greater power, and it still is available, whereas the vastly greater power of which you spoke is not available to man as a man, but as one of a vast aggregate of people.

I think of the same analogy in regard to communication from the days when man first used signal fires to communicate greater distances than he could communicate with his own, unaided voice, to now, when we use Telstar. But man as a man cannot communicate by Telstar, but only as one of a vast number of people, and that, I think, was the historic significance of that historic sentence uttered by the astronaut when he first stepped upon the moon, "One small step for man; a giant stride for all mankind."

So while we tend to think of a vast increase of our energy into communication and all the devices that technology has conferred on mankind, individual man still is limited to a very considerable degree.

Next is Dr. Kurt Hirschhorn.