Volunteer takes test to measure nerve conduction changes that occur with aging.

PROBING THE AGING PROCESS

GRC scientists are seeking not the Fountain of Youth but ways of helping us all live to a healthy old age

BY JOAN AREHART-TREICHEL

A modern four-story Gerontology Research Center adjoins the backside of the Baltimore City Hospitals. For eight years it received relatively little attention from the outside world. But during the past few months it has moved into the national limelight. In fact, it may eventually become a household word.

For, in July 1975 it was named the in-house research program of the new National Institute on Aging (SN: 10/2/76, p. 214). And thanks to the gerontology mania that has been sweeping America of late, it is being heavily courted by the electronic and print media for information on what's going on in aging research, and whether GRC researchers can help us all live indefinitely.

Alas, Methusalah is *not* on their agenda. But the GRC's 70 senior scientists and 80 supporting staff *are* trying to find ways to help us all live out our genetically programmed lifespans, and in the richest manner possible. And that means conducting research from the clinical level on down through hormones, immunity and eventually to genes.

An example of the interesting research going on at GRC, at least from a practical viewpoint, is the Longitudinal Study of Aging, where researchers keep track of human volunteers to see how their bodies change with chronological age. The study actually started 16 years ago at the Baltimore City Hospitals, before the GRC had its separate research facilities behind the hospital. The study includes some 650 men between ages 20 and 95. Most of the volunteers are well educated and highly motivated to stay in the program as long as they live, both to help science and to help themselves, since they get exhaustive physicals every two years.

Although the study has been underway for quite some time, the results are coming in only now, because it takes much longer to get research from humans than from shorter-lived experimental animals. The study is showing, for instance, that while older people may be just as active as younger ones, they expend less energy in the process. As people age, they also tend to replace muscle with fat. Exercise, of course, may help counter this trend, Arthur Norris, study administrator, acknowledges. He and his colleagues have simply not studied the effects of exercise on this trend yet.

Lung function likewise declines with age, Norris and his co-workers are finding, but this decline seems to level off after age 70. High levels of cholesterol in the blood, which are risk factors for heart attacks, seem to peak around age 55. Subjects up to age 55, on the average, showed an increasing amount of cholesterol in the blood; those who survive beyond age 55 showed a decrease and may be at less risk of a heart attack from this factor than the young. The study is also providing some practical results for physicians. It has told them what normal glucose tolerance and normal creatinine clearance (indicating whether the kidneys are diseased or not) are for various ages.

Another GRC study that holds promising practical results concerns receptors and their role in aging. It has been long known that hormones are chemicals that circulate in the blood and signal cells to do different things at the right time, such as metabolize fatty foods or adapt to stress. Only during the past few years, however, have researchers learned how these hormones pass messages to target cells—through tiny protein receptors on the outside or inside of cells. They have also learned that the receptors can be decreased by obesity and that receptors can be blocked by diabetes (SN: 8/16/75, p. 110).

These findings prompted George Roth and his co-workers at the GRC to study whether hormone receptors are also altered by aging. They found that there are indeed changes, at least in lab animals. There is a loss in receptor number with age. Explains Roth: "We feel that this loss of receptors is an important mechanism in the aging process."

They are now trying to see why the receptors dwindle in number. There are several possibilities. The receptors are normally made and broken down in the life cycle of the cell. So one explanation may be that the receptors are made more slowly in the old cell than in the young cell, or that they are broken down more rapidly. Or perhaps receptors simply stop functioning properly as they age. Certain enzymes, which are also proteins, are known to change in function and possibly in structure with age.

They are likewise studying receptors in humans. They took lymphocytes, a type of white cell, from the blood of some of the men participating in the longitudinal study and found that hormone receptors on these cells decrease in number with aging.

And most intriguing, they are trying to see whether certain chemicals can bring the number of receptors back up in old cells in hopes that it might reconstitute some of the hormonal effects that are lost with age. Caleb Finch of the University of Southern California already has evidence that increasing the number of receptors in old cells is indeed possible. When he gave female mice estrogen shots, the shots increased the number of estrogen receptors in the mice's uteri. If ways can indeed be found to restore the number of receptors in old cells, Roth says, the technique might hold practical benefits for older people. In other words, it would be

a form of hormonal replacement therapy, but at the molecular level.

While Roth and his colleagues explore the effects on the endocrine system, Albert Nordin and his co-workers are studying the effects of aging on another system of the body—the immune system.

Ordinarily, antibodies fight infectious agents, and antibodies are made by bone marrow-derived cells called B cells. B cells are helped in their fight by another population of cells derived from the thymus—T cells. However, the body's resistance to infectious agents declines with age. Nordin and his team wanted to know exactly what effect age has on these particular immune fighters. They have found that the deficiency may be due not to a decline in the number or function of B cells but rather to a defect in the function of helper T cells. This decline may be the result of certain other T cells suppressing the immune response.

They now want to confirm these test-tube findings in experimental animals. For instance, can they detect two separate populations of T cells—helper T cells and suppressor T cells—in animals? If so, then they can further explore the interaction of the two and their precise roles in the aging process.

And in still another GRC lab, Gunther Eichhorn and colleagues are getting down to more nitty-gritty: What happens to the genetic machinery of the cell during aging? Specifically, they are exploring the impact of one ubiquitous environmental factor—trace metals—on DNA, RNA and aging.

First, they have found that the content of trace metals in cells changes with aging, mostly increasing, thus suggesting that trace metals may be a vital factor in whether cells live out their genetically programmed lifespans or not. Second, they have found that metal ions can sabotage the transcription of DNA into RNA. (For example, platinum complexes can hook onto a DNA molecule and keep RNA from copying a correct message from it.) They can also alter the specificity of enzymes that act on DNA, produce cross-links between DNA chains, or even degrade RNA. (The ions, however, do not appear capable of degrading DNA, which has led to the postulate that DNA may have been chosen over RNA as the primary bearer of genetic information because DNA is not susceptible to metal ions.) Finally, the researchers point out that metal ions can mess up the translation of RNA into proteins in unforgivable ways.

For instance, they knew from two other scientists' work that at low levels of magnesium ions, there are few errors in the incorporation of the amino acids into protein chains. But as magnesium increases in concentration, there are more errors. They devised an elegant hypothesis to explain the phenomenon, which went something like this:

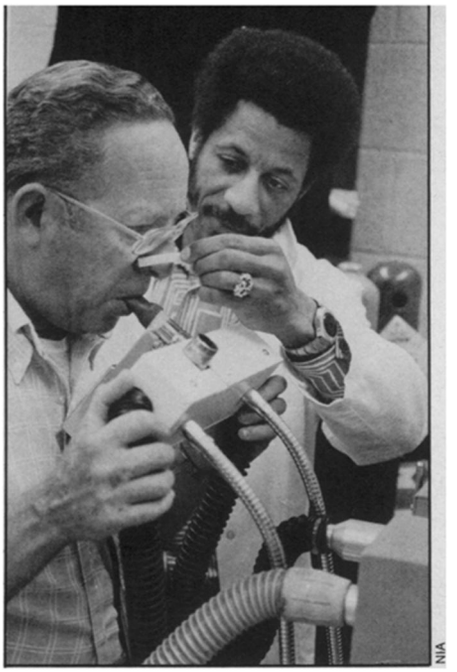
In protein synthesis, base sequences on the messenger RNA that carries the message for specific amino acids must be recognized, through base pair formation, by base sequences on transfer RNA molecules that carry the amino acids. When the base pairs are formed in a complex between mRNA and tRNA, a series of negative charges on the phosphate groups of these molecules come very close together and therefore repel each other, thus making a weak complex. The complex can be strengthened by neutralizing the mutually repulsive negative charges by positively charged magnesium ions.

When only a few magnesium ions are present, so the hypothesis goes, the mRNA-tRNA interaction is so weak that only the strongest base pairs (those that lead to correct incorporation of amino acids) are possible. In contrast, when the interaction is strengthened by the presence of more magnesium ions, the formation of weaker base pairs becomes possible. The mating between tRNA and mRNA is then no longer so sensitive to the strength of the bonds between the base pairs and incorrect amino acids are incorporated.

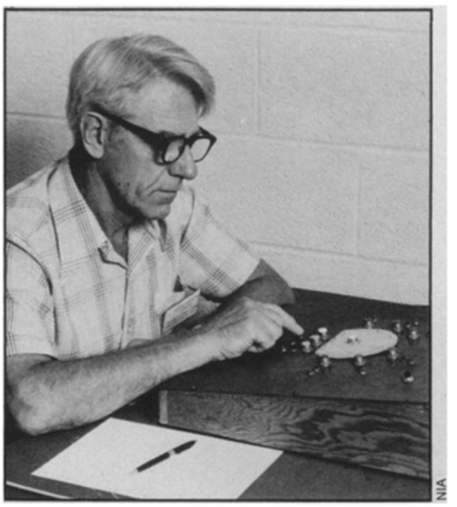
They tested the hypothesis that metal ions can cause mispairing of bases and found that it was correct. A high concentration of magnesium ions led to more mismatching of bases than did a low concentration of ions.

These findings are many a nucleotide throw from offering ways of preventing trace element-induced aging. But they should eventually lead to some practical results, Eichhorn believes. For instance, another researcher has already found that inhibiting metal ions with metal complexing agents increased the lifespan of rotifers, tiny cold-blooded creatures that live in ponds and that look like specks of salt. If these results are applicable to humans, people might eventually be able to take metal-complexing agents as they now do vitamins in order to inhibit those metal ions that promote aging, yet not those that are essential for the health of cells.

Obviously, the results discussed here are only a smattering of the many that are emerging from the GRC. Undoubtedly many more will be pouring forth in the next several years now that aging is, at last, becoming a glamour area of biomedical research with the concomitant infusion of generous research funds. □


NIA

Testing lung changes due to aging.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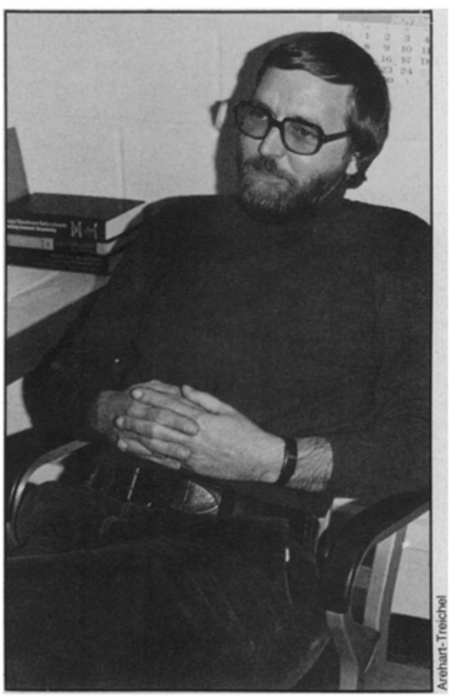
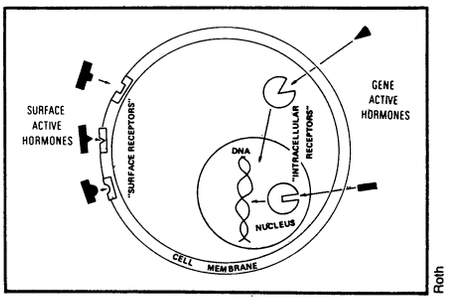
Exploring the effect of aging on logic.


Arehart-Treichel

Nordin says T cells culprits in aging.



Roth

Hormones pass messages to cells via protein receptors. The number of these hormone receptors decreases with aging.