Eugene Roberts, Ph.D., has been a leading figure in neurochemistry for more than half a century. Currently a Distinguished Scientist at the City of Hope in California, he received his doctorate in biochemistry in 1943. In the intervening years, he worked on the Manhattan Project determining the safe levels of exposure to uranium dust. Dr. Roberts performed cancer research at Washington University in St. Louis where he discovered the neurotransmitter gamma-aminobutyric acid (GABA). And in 1954, he founded the Department of Biochemistry and the division of Neurosciences at the City of Hope.

For much of the last decade, Dr. Roberts has been studying steroid metabolism and has been instrumental in reviving interest in pregnenolone and DHEA as potential therapeutic agents. At age 78, he remains an active researcher, theoretician, and member of the National Academy of Sciences, still trying to climb such "Mount Everests of science" as cancer and schizophrenia.

I spoke with Dr. Roberts about his latest research regarding the biochemistry of pregnenolone and its therapeutic effects. I was impressed by his very lively mind, which easily leaps from one idea to the next, and the vast range of his knowledge. Additionally, he's warm and perceptive, with a highly creative perspective, a person who seems to really be having fun in life.

David: What aroused your interest in pregnenolone?

Dr. Roberts: Originally, I was interested in DHEA and DHEA sulfate because these steroids have been shown to decrease monotonically with age in both males and females after a peak in their early twenties. About 30% of DHEA and DHEA sulfate in the blood of males comes from the testes, and the rest comes primarily from the adrenals. In females, it comes largely from the adrenals. In both sexes, small contributions of these substances may come from other tissues.

Subsequently I got interested in pregnenolone, the substance from which all other steroidal substances are formed. That's how it came about, sheer curiosity.

I looked into the early history of pregnenolone which was very interesting to me. It's a shame it was dropped so soon as a potential therapy for rheumatoid arthritis back in the 1940s. It probably was a function of the sensational effects of cortisone, which was discovered around the same time.

Generally, the clinical reports of yesteryear indicated that pregnenolone could exert marked improvements on various symptoms of rheumatoid arthritis. [Editor's emphasis.] It also seemed to affect other autoimmune conditions, e.g., lupus. The results were interesting in that they indicated pregnenolone or substances formed from it could exert similar effects although dissimilar in structure.
The work of Hoagland and his colleagues on the effects of pregnenolone on fatigability was most interesting, particularly since fatigability often precedes the symptoms of rheumatoid arthritis. *Normal individuals showed significantly decreased fatigability when working under stress when they were receiving small oral doses of pregnenolone; and their performances improved as well.* [Editor's emphasis.] Individuals working under relaxed conditions, little change was noted.

![Eugene Roberts, PhD with important molecule](image)

After oral administration of pregnenolone, pregnenolone sulfate is rapidly formed in the intestine and liver and enters the bloodstream. Thus, oral administration of pregnenolone largely results in an elevation of pregnenolone sulfate in the blood.

Many physiological tests in animals have found that pregnenolone sulfate has excitatory effects on nerves which in turn enhance the effects of known excitatory neurotransmitters such as glutamate. Upon penetrating the blood-brain barrier pregnenolone has an excitatory effect. Since the blood-brain barrier is lowered (more permeable) in regions of the hypothalamus and pituitary gland, at the minimum, pregnenolone would be expected to have a major action on the release of various hormones, such as those arising from the thyroid, adrenal, and pituitary glands.

It is possible that pregnenolone ingestion increases alertness for the latter reason; meaning that it gets into the hypothalamus and pituitary more easily. However, the effects must be much more complicated because pregnenolone sulfate, pregnenolone, and the substances derived from them are known to have effects at many sites, including membranes and in the gene transcription process.

**David:** What are you working on currently?

**Dr. Roberts:** There are two major areas related to pregnenolone. One is related to memory. Experiments performed with James Flood gave results that were just amazing. Poorly trained mice learned to avoid a foot shock by going to the correct arm of a T-maze. Immediately after training, small amounts of pregnenolone sulfate were injected directly into several regions of the brain, the amygdala, septum, mamillary bodies, hippocampus or caudate nucleus. The ability of
the mice to perform the task successfully was measured one week later. When less than 150 molecules of pregnenolone sulfate was injected into the amygdala, the mice had significantly enhanced retention of the correct response. From this result, **pregnenolone sulfate appears to be the most potent memory enhancer yet reported in animals**, and the amygdala seems to be the most sensitive brain region for memory enhancement. [Editor's emphasis.]

In order to prove to ourselves that we hadn't made a mistake, we had separate dilutions made in another laboratory and we got the same results.

Now, I'm trying to figure out how only 150 molecules can have such an influence. It appears to be similar to a pheromone-like effect, such as when a few molecules of sex-attractant from a female moth informs a male moth a mile away of her location. There are a number of possible mechanisms for this effect in which a cell is signaled by a particular substance to produce more of itself in greatly increased amounts.

Thus, a few molecules of pregnenolone sulfate liberated endogenously (from inside the body) or furnished exogenously (from outside the body) may cause glial cells in the brain to produce millions of molecules of pregnenolone and liberate them into the environment. Solving how this happens may give us a handle as to how to greatly enhance memory capability with the administration, for the most part, of naturally occurring substances.

Another great current interest for me is the area related to the attenuation (lessening) of spinal cord damage. Tens of thousands of individuals injured in the last earthquake in China are today hospitalized as paraplegics or quadriplegics. There is urgency in developing a practical means for avoiding this in California, where a major quake could occur at any time.

Lloyd Guth (a researcher at William and Mary College in Virginia) and I found that **pregnenolone, when combined with Indomethacin (a nonsteroidal anti-inflammatory drug and a stimulator of cytokine secretion), could attenuate damage to the spinal cord** if rats were treated immediately after the injury. Control animals receiving saline alone showed marked spinal cord degeneration and paralysis. [Editor's emphasis.]

The combined treatment reduced **histopathological changes** (abnormal changes in cells or tissues), spared tissue from secondary injury, and increased restoration of motor function. In fact, of the 16 animals treated, 11 were able to stand and walk within 21 days after the injury; 4 of them were nearly normal. These positive effects were never observed in experiments where pregnenolone was absent from the treatment regimen.

It now has been found elsewhere (unpublished, personal communication) in similar experiments that continuous administration of pregnenolone sulfate gave better protection compared to any experiment ever observed previously. This approach may prove to be applicable not only to spinal cord injury, but also to nervous system injury in general and perhaps to injury to other tissues as well.

We are now exploring means to develop a transdermal preparation that will be effective, since spinal cord-injured individuals often have difficulty swallowing. And under chaotic post-quake
conditions, injecting solutions can be problematic. Our goal is to devise a preparation of pregnenolone or pregnenolone sulfate in a tube which will be widely distributed in earthquake first-aid kits. Anybody should be able to apply a cream or gel to an individual with a spinal cord injury. Of course this approach also would be applicable to injuries resulting from accidents of all sorts.

Among other interests, the above projects are keeping me fully involved.

David Jay Brown earned his master's degree in psychobiology at NYU, and researched learning and memory while in USC's doctoral program in Behavioral Neuroscience. He is the author of Brainchild, and co-author of two volumes of interviews with some of the most fascinating people on the planet - Mavericks of the Mind and Voices from the Edge. David is currently researching the unexplained abilities of animals with British biologist, Rupert Sheldrake, and writes regularly for publications all over the globe.

References