Chemical clues to schizophrenia

Researchers announced last week what they termed "the first direct understanding" of the symptoms of schizophrenia. Philip Seeman and Tyrone Lee of the University of Toronto reported that key areas of the brains of schizophrenic patients contain about twice the normal numbers of receptors for a chemical, dopamine, that carries signals between nerve cells. They speculate that schizophrenics are thus oversensitive to their own brain signals and are flooded with unusual thoughts, hallucinations and illusions. A variety of previous observations have implicated the transmitter dopamine in schizophrenia, but this research specifies its nature.

Seeman believes that his results lead to new approaches to curing schizophrenia, which affects more than one percent of the U.S. population. A blood test for schizophrenia may also be a result of the experimentation on dopamine receptors.

The rationale behind the recent discovery, Seeman explains, is to find just where the effective antischizophrenic drugs work. That information should reveal where schizophrenia is generated.

Scientists from four countries cooperated to obtain postmortem brain tissue from 48 people, including 20 schizophrenics, who died of heart attacks, car accidents or suicide. The dopamine receptors were counted by measuring the amount of a radioactively labeled drug, haloperidol, adsorbed to different regions of the brain. Haloperidol is an antischizophrenic drug that binds specifically to dopamine receptors, according to Seeman.

Lee and Seeman found an increased number of receptors in only two brain areas, the limbic region (an area responsible for "emotional thinking") and the caudate nucleus (an area that modulates body motion). Seeman and Lee believe that the difference is directly related to the disease and is not merely a consequence of its treatment. The researchers found the substantially increased number of dopamine receptors in six patients who had never received any drugs.

The suggestion that schizophrenics have too many receptors is consistent with earlier data implicating the dopamine system. Amphetamines, which trigger dopamine release, can produce symptoms of schizophrenia, as can too high a dose of L-dopa, a chemical precursor of dopamine administered for Parkinson's disease. At first, researchers thought the problem was one of too much transmitter chemical, but Oleh Hornykiewicz of the Clarke Institute of Psychiatry in Toronto and the University of Vienna demonstrated that the brain content of dopamine is normal in schizophrenia.

There is, however, another disease caused by abnormal dopamine levels. The brains of people with Parkinson's disease lack many of the dopamine-producing cells. Those patients are treated with L-dopa. However, Hornykiewicz, who introduced L-dopa therapy, had kept frozen brain samples of patients from before the treatment was discovered. Frequently, when there is a deficit of transmitter in the nervous system, the receiving cells increase the number of receptors—as if to increase their chance to detect the weak signal. Seeman has analyzed the brains of five patients who had received no drugs and found that the receptor levels were higher than normal, as high as in schizophrenics. This, Seeman says, "closes the jigsaw puzzle."

The results on dopamine receptor number have not yet been confirmed by other investigators. Solomon Snyder and colleagues at Johns Hopkins University, using a different technique, have observed more variability in receptor number among schizophrenic patients and among controls, and no consistent differences between the two groups. Lee told the scientists that he could not yet rule out a tighter binding between the antischizophrenic drug and an altered receptor. Seeman cautions that the results rest on a sometimes uncertain diagnosis of schizophrenia. "This is just a beginning," he says.

A report of more preliminary research, also presented at the meeting of the Society for Neuroscience in Anaheim, Calif., suggested a different chemical basis of schizophrenia. Frank Ervin of the University of California at Los Angeles and Roberta Palmour of the University of California at Berkeley identified a peptide in the blood of several schizophrenic patients. The peptide is nearly identical to a pituitary hormone found in normal people. The researchers report that the peptide—called leu-endorphin—dropped one hundred fold in concentration after 16 dialysis treatments when the patients were approaching normalcy. They have also observed high levels of leu-endorphin in patients who relapsed after several weeks. When partially purified leu-endorphin was injected into animals, it caused convulsive patterns in brain wave tracings. According to Ervin, this result indicates an effect on the limbic system, one region assumed to be involved in emotional disturbances. Other scientists are skeptical of this peptide being a specific schizophrenia toxin. More experiments will be needed to rule out the possibilities that the chemical is a response to the stress of dialysis or to the suspension of drug treatment. The substance might also represent a reaction to the abnormalities of schizophrenia, rather than its cause.

Whether or not the extra dopamine receptors and leu-endorphin turn out to play key roles in schizophrenia, the research indicates that new techniques of radioactive drug assay and biochemical analysis are valid tools in the search for clues to the basis of mental illness. □

Chasing Chinese chicken cancer

Rural planners in China's Ho-nan Province did not know it in 1967, but their massive relocation of workers to dig an earthen canal laid the groundwork for what may be one of the largest medical experiments in history.

In one fell swoop, party officials inadvertently solved a logistical problem that confronts disease researchers all over the world. Their transfer of 50,000 peasants fortuitously created a test group (and a control group in those left behind) large enough for scrupulous statistical analysis. When they ordered the peasants to leave their chickens behind, they also unwittingly isolated a major clue to the origin of cancer of the esophagus—the leading cause of death in that corner of the world. These two quirks of fate may provide scientists with new leads to the natural causes of cancer, report a group of U.S. researchers just returned from the People's Republic of China.

Robert W. Miller, an epidemiologist with the National Cancer Institute, said his scientific group toured Linh-sien County, the site not only of the Red Flag Irrigation Canal but also of a variant of esophageal cancer unique to that area but not to humans. "Their chickens have a remarkably similar carcinoma in the squamous cells lining their gullets," Miller told Science News.

Chinese medical scientists have long believed that the chicken and human tumors are analogous, but prior to this decade they could not tell which came first—the chicken or the human cancer. As Miller noted, it is virtually impossible to sort out the myriad carcinogens and other pathogens which dovetail to provoke tumors. "They didn't know if the disease passed from human to bird, from bird to human, or from an outside influence to both populations concomitantly."

But the local "barefoot doctors"—a kind of paramedic peculiar to China who combine simple surgical procedures with a knowledge of medicinal herbs—monitored the chicken flocks the peasants purchased when they resettled. Two and a half years later they found a chicken with gullet cancer. Since then, 12 chickens in the new flocks have shown the disease, while the neighboring, parent flock of 2,400 birds has never had a single case.

Chinese epidemiologists began putting these clues together. The disease had passed from humans to chickens in a previously "no-risk" area for chickens. So it was not the environment—not the previously suspected chemicals in the water, nor a shortage of trace elements such as molybdenum in the soil, nor foodstuffs per se—even though the only direct connection between the chicken and human populations was table scraps fed to the chickens. However, since the settlers brought little with them except their special living habits and customs, the problem could be the way they processed their food. Perhaps, the researchers reasoned, it was the result of a special recipe. They were right.

"It's called pickling, and it's a dish with chopped willow leaves, sweet potatoes chopped fine, sesame seeds, turnip greens, and maybe some spices," Miller said. "I'm not clear on this, but it seems the only processing they do is to boil the food for a while." The vegetables stay in large earthen pots for as long as six months, eventually developing a fungus.

The preparation of the dish makes it highly suspect. But there were nitrosamines in the food as well (a type of molecule that has recently been implicated in stomach cancer in the United States). A recent article in THE CHINESE MEDICAL JOURNAL said tests showed that a combination of the nitrosamines and the mold produced precancerous cells in chickens.

Chinese party members are working to upgrade water quality and improve food-drying techniques to quell molds—and are discouraging "pickle" eating. But they do not expect the rate of esophageal cancer to decline in the near future; like many other tumors, it can have a latency as long as 30 years. But by manipulating the chickens' diet, they hope to erase gullet cancer by trial and error soon, signalling an end to carcinogenic exposure and foretelling a time when human generations will be unafflicted.

Miller and other cancer researchers in this country are closely monitoring the Chinese progress, albeit informally, and are running further tests to determine the pickled foods' mutagenic properties. "Even though the United States has no cancer exactly like the Chinese strain, the opportunity they [the Chinese] have to isolate a natural cause of cancer may very well help us better understand the neoplastic process." □

Electricity and natural healing

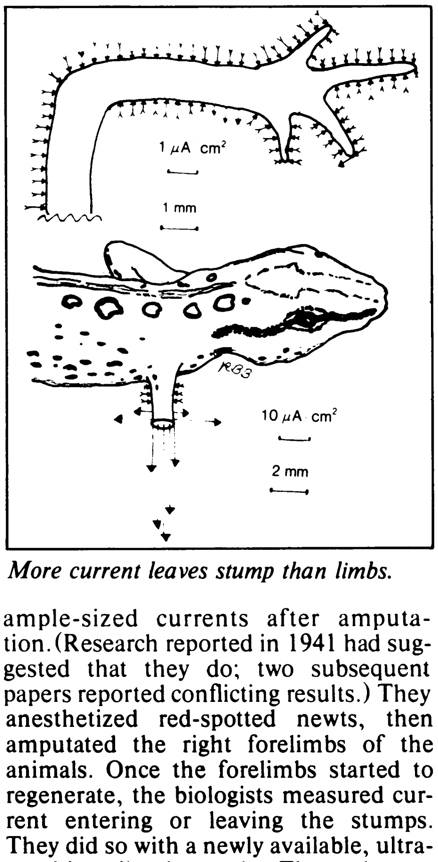
The chemistry of the human body and the effects of chemical compounds on the body have been explored, but what of the electricity naturally present in the body and the effect of electrical currents applied externally to the body?

Insights into this largely unexplored area have surfaced in recent years. For instance, certain cells and tissues are electrical conductors (SN: 9/11/71, p.179); electric fields weaker than electroencephalogram readings may be intrinsic to the brain and may regulate nerve firing, which is both a chemical and electrical event (SN: 7/17/76, p. 41); and externally applied electrical currents can regenerate amphibian limbs, help heal human fractures and ulcers and even partially regenerate mammalian limbs (SN: 5/4/74, p. 287).

Now research reported in the October PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES shows that limb regeneration occurring naturally among amphibians is driven by electrical currents present in the animals' skin. These experiments also suggest that skin-driven electrical currents might promote natural healing or limb regeneration among vertebrates, including humans.

Recently, Richard B. Borgens, Joseph W. Vanable Jr. and Lionel F. Jaffe of Purdue University showed that, in the process of regenerating amphibians' limbs with external electrical currents, current must be pulled out of the stump in order to induce regeneration. Inward current actually induces degeneration. This suggested that electrical current present in amphibians' limbs might be involved in natural regeneration.

The researchers have now attempted to determine whether normally regenerating amphibian stumps generate



More current leaves stump than limbs.

Borgens, Vanable, Jaffe/NAS

ample-sized currents after amputation. (Research reported in 1941 had suggested that they do; two subsequent papers reported conflicting results.) They anesthetized red-spotted newts, then amputated the right forelimbs of the animals. Once the forelimbs started to regenerate, the biologists measured current entering or leaving the stumps. They did so with a newly available, ultrasensitive vibrating probe. The probe was also used to measure currents leaving or entering newts' intact forelimbs.

Specifically, they measured for current around intact forelimbs and found that current entered at almost all locations, but left regularly only at the base of the first digit and occasionally only at the fingertips (Fig. A). In contrast, far larger currents (50 times larger) were found to leave the recently amputated stumps than left the intact forelimbs, and current entering the stumps was much less than that entering intact forelimbs (Fig. B). Thus it appeared that large currents do escape from naturally regenerating amphibian limbs and might very well be the drive behind the regeneration. Borgens, Vanable and Jaffe also found that the peak current densities coming off stumps one week after amputation were very high, but that they dropped dramatically as the stumps showed development of new limbs.

With the role of electrical currents in limb regeneration fairly well established, the biologists began to search for the source of the currents. First they removed the motor and sensory nerves from newt limbs and amputated only some of the limbs. The denervated stumps generated larger currents than did the denervated intact limbs, suggesting that the regenerating currents were nerve independent. Next the researchers ran tests to see whether the regenerating currents were sodium dependent. When they increased the sodium concentration in the solution surrounding the newt stumps, current leaving the stumps always rose. When they lowered the sodium concentration, current leaving the stumps always declined. Thus, limb regeneration appeared to depend on sodium input. But where might the currents arise? The biologists thought they might come from the skin covering the stumps. Three different chemicals were used to keep sodium from entering the stumps. All three agents drastically reduced current escaping from the stumps, showing that the sodium-driven currents do arise in skin over the stumps.

But how could sodium-driven currents in the skin over a stump actually bring about regeneration of that stump? Recent cell research advances, the investigators believe, suggest an answer. The advances show that drops in current across a cell membrane can move certain molecules in the membrane. Sodium passing through the membranes of skin cells over a stump, the scientists believe, might well alter large molecules in the membranes of these cells as well as in the membranes of nerves penetrating the skin, thus promoting wound healing and limb regeneration.

All these experiments, the researchers conclude, present a good case for the role of electrical currents in natural amphibian limb regeneration. But the experiments raise an even more provocative question. Might there be skin-driven electrical currents that promote healing or even regeneration in other vertebrates, including humans? Yes, the investigators reply, pointing out that as far back as 1860 and 1910 there were reports of large currents leaving injured human skin.

"Our new results encourage reinvestigation of these old findings," Borgens, Vanable and Jaffe say, challenging fellow biologists. □