PSYCHOBIOLOGY

Lithium vs. Manic-depression

A common salt presents paradoxes at the basic neural level.

by Patricia McBroom

Twice a year, 14 scientists from the United States, Canada, Norway, Denmark, England and Switzerland travel to such pleasure spots as Nassau and Majorca to spend two and a half days talking about mental depression.

The group has no name, no agenda; its funds come from a former victim of depression who contributes some $10,000 a year so these specialists can meet.

During one recent meeting, the group decided to run an international experiment with lithium carbonate—a mineral that shows promise of being the first effective treatment of recurrent severe depression.

Some 10 researchers in five countries will use the same regimen, the same materials and the same criteria for testing lithium over a period of three years. All data will then be analyzed at Rockland State Hospital in Orangeburg, N.Y., under the direction of Dr. Nathan Kline, from whose patient comes the funds to support the meetings.

Lithium carbonate is an inexpensive white powder that has been under investigation in Europe for some 15 years. It is only now beginning to attract attention in the United States (SN:4/15).

If the experiment is unusual, the drug being tested is no less so. Lithium has already proved itself effective against mania, often, if not always, depression's opposite number. Taken on a daily basis, the mineral virtually reduces the manic's euphoria to normalcy. That it may also work against depression seems paradoxical. Stranger still, lithium has little or no therapeutic effect after depression has set in, but seems capable of forestalling depressive attacks. At least some Scandinavian work—claiming 80 to 85 percent success with lithium as a preventative—points in that direction. Should the international group find the same results, lithium will be established as effective treatment against manic-depressive psychosis, a major mental disease and an important element in 25,000 suicides in the United States each year.

The curious effects of lithium reflect the mysterious activity of ions or electrolytes deep within the living nerve cell.

So far as scientists can tell at this point, sodium ions, instrumental to the firing of nerve cells, are pathologically elevated during both mania and depression. Because lithium appears to substitute for sodium in the cell, it has become a wedge driving open an entirely new field of biochemical research —called electrolyte or mineral metabolism—and may offer new understanding of the biological basis of mental illness.

In fact, lithium often inspires more enthusiasm as a research tool than as a drug for treating illness; and, as a drug, the Surgeon General of the U.S. Public Health Service recently promoted it before the Congress as a breakthrough in mental disease.

Lithium belongs to the same chemical family as sodium and potassium—minerals whose ions are basic to nerve cell operation.

Theoretically, normal neurons possess a very thin membrane with an unequal distribution of sodium and potassium ions on either side. On the outside are 10 times as many sodium ions as potassium, while the reverse is true on the inside. When sodium pushes through the membrane, it sets off an electric current that fires the nerve.

But in manic-depressives a team of English investigators three years ago found this ionic distribution to be severely disordered. During mania, cell sodium was increased three times over normal; during depression, it was elevated by 50 percent. At the same time, the depressed patients had lower potassium concentrations.

These changes, Dr. David Murray Shaw, one of the team members, wrote last year, are "gross to a degree seen up to now only in advanced cancer and similar wasting diseases." (SN: 8/13/66).

The English scientists found that upon patients' recovery from manic-depressive psychosis, their sodium ions returned to normal. Lithium, says Dr. Shaw, profoundly altered the ionic distribution. He suggests it might have therapeutic effects by blocking the passage of sodium through the membrane.

The English work stirred great interest, and the sodium clue has now become a major line of investigation. A few weeks ago, for example, it was speculated that the excess sodium could be restructuring water molecules within the cell and, in effect, bloating it.

But so new is this field and so intricate are the workings of nerve cells, that no one is staking his money on any theory.

"We don't know what's going on," says Dr. Heinz Lehmann, a professor of psychiatry at McGill University in Montreal and one of the international group.

No one knows which is more important, he says—electrolyte balance, cell membrane permeability or the structure of cellular water. Nor can anyone judge whether the nerve cells in manic-depressives are more or less excitable and what effect either condition would have on behavior. One suggestion is that the nerve cell itself is abnormally excitable, while its synapse, or link with other cells, is unusually dull.

"This electrolyte thing is just opening up," says Dr. Lehmann. It does not seem to him to make sense that sodium ions would be pathologically increased in both mania and depression. But, he comments, "there it is."

Broadly speaking, the new studies signal a shift in psychiatric research emphasis from biochemistry—which has held the center stage for the past ten years—to physical chemistry at the molecular level. Where mental diseases are concerned, that represents a major scientific step.

Though the action of ions is still mysterious, biochemically, the action of lithium is more understandable because of the work that has been done on tranquilizers and anti-depressants; lithium resembles the depressants.

Dr. Joseph J. Schildkraut at the National Institute of Mental Health drew this conclusion by tracing lithium's effect on norepinephrine—one of the four major transmitter substances that work at the synapse, where nerve cells communicate with each other. Most of the drugs that affect emotions also affect norepinephrine levels. The euphoric drugs, like cocaine, seem to increase it while the depressants lower it. According to Dr. Schildkraut's work, lithium lowers it.

Whether this is a basic mechanism in emotions or a mirror image of some other system, such as ion transport, he doesn't know. In the micro-world of the nerve cell, basic mechanisms will be incredibly difficult to find—but the search is on.