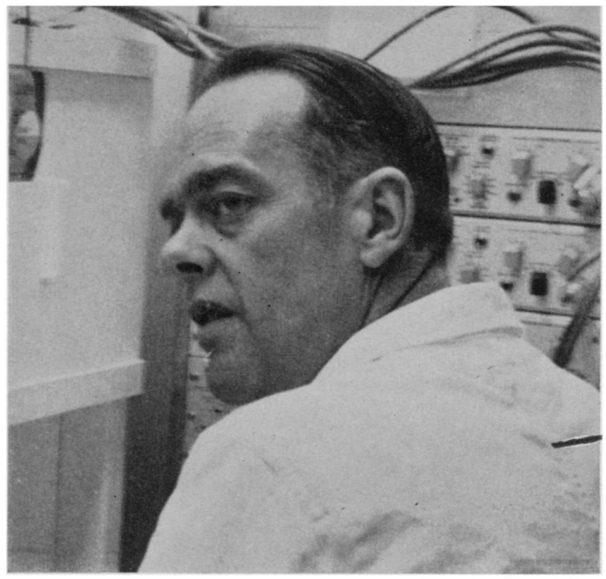


Worcester Foundation

Bergen fits pieces into patterns.

BIOCHEMISTRY

Target: the alpha 2

Brain and blood chemists are after a globulin, and perhaps an associated molecule, as a biochemical clue to schizophrenia

by Patricia McBroom

Scientists have been panning the blood and urine of schizophrenic patients for 15 years, looking for biological clues to the disease.

There is now a fair-sized river of body fluid coursing through laboratories, leaving bits and pieces of information which so far lack coherent pattern. But among the isolated pieces are some nuggets of gold.

From these bits, scientists have begun building speculative theories to explain schizophrenia. The one intriguing them at the moment is the leaky membrane theory, based on suspicion that something in the blood of schizophrenics causes brain cell membranes to leak chemicals in and out with unusual ease. A leaky membrane could cause chemical misbehavior both outside and inside the cell. On one hand, it could give rise to dangerous antibodies; on the other, it might distort brain metabolism as well as nerve transmission.

Clarification of these theories awaits further work with a chemical that might be causing the membranes to leak: the alpha 2 globulin.

A blood protein, this globulin has been found consistently elevated in roughly 60 percent of the schizophrenic patients studied. Three separate laboratories—the Worcester Foundation for Experimental Biology in Shrewsbury, Mass., the Lafayette Clinic in Detroit and the U.S.S.R.'s Institute of Psychiatry—now believe they are working with the same agent. The agreement represents a significant advance over past conflicting evidence on schizophrenia.

No one knows yet what the alpha 2 globulin is, nor whether it is the schizophrenic agent itself or a carrier of some other potent chemical.

Proteins of the alpha 2 class all look very much alike, says the Worcester Foundation's Dr. John Bergen. Isolating the protein is like trying to select from a family of identical sextuplets.

Also, the globulin could carry the true agent around in the form of a small attached molecule. Globulins carry many kinds of chemicals through the bloodstream. Aspirin, for instance, is difficult to find because it combines with globulins. At some site, says Dr. Bergen, it must detach from its carrier and do its work. The same may be true of some agent of schizophrenia.

Dr. Bergen and a colleague at the Blood Research Institute in Cambridge, Mass., Dr. Robert B. Pennell, have some evidence of such a molecule attached to the alpha 2. The molecule could be one of the indoles, a class of chemicals that includes many hallucinogenic drugs such as LSD.

But so far other investigators have not confirmed his lead.

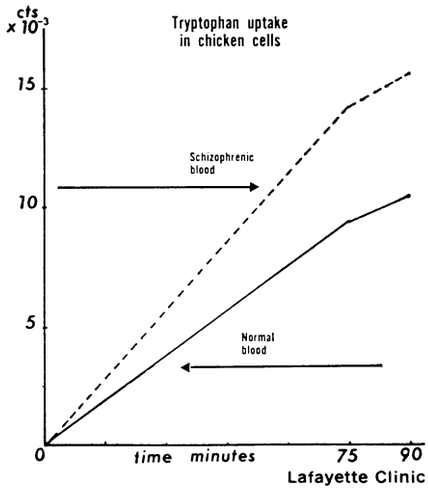
Evidence drawn from the blood fits logically into other work being done on the urine of schizophrenic patients, in which several investigators have found hallucinogenic-like substances. DMPEA, the so-called pink spot, isolated from urine of schizophrenics but not normal people, is a mescaline relative. Three other hallucinogens, including bufotonin, have also been found in urine.

". . . this globulin has been found to be consistently elevated in roughly 60 percent of the patients studied."

"We must find out whether the alpha 2 is bound to a small molecule that resembles DMPEA," says Dr. Bergen. He favors the DMPEA link because that substance and the blood factor he found have similar effects on animals.

At the Lafayette Clinic the intact alpha 2 globlin is being treated as the active agent, possibly a stress hormone, in schizophrenia, rather than as a carrier. If it is a hormone that moves through the bloodstream carrying stress signals to the brain, then it can be expected to vary with levels of stress.

That seems to be the case. Alpha 2 increases with physical exercise and from the stress of cold or a psychological test, says Dr. J. S. Gottlieb, clinic director. He suggests that the globulin is also present in normal individuals, but is out of control in the schizophrenic patient.



Lafayette Clinic

Leaky membranes may be the clue.

In the brain, an excess of alpha 2 could be making cell membranes unusually leaky, so that substances move across the barrier with greater ease.

Soviet scientists report that brain cells taken from a rat become fragmented and swollen when incubated with the blood of schizophrenics. The Lafayette group has also found increased permeability in chicken cells,

. . . a biochemical target

although not from the brain, when treated in the same way.

"It would appear," says Dr. Gottlieb, "that substances are passing through the membranes of neural tissue with greater facility in patients with schizophrenia than in normal controls."

If chemicals are leaking out of cells into the bloodstream, the body might see them as foreign intruders and defend against them with antibodies. Such antibodies would be potentially capable of harming brain cells.

"They certainly would harm brain cells if they came in contact with them," says Dr. Peter G. S. Beckett, associate director at the Lafayette Clinic.

Worldwide, a variety of reports, primarily from the Soviet Union, claim to have found antibrain antibodies in samples of blood from schizophrenics. And last year, the leading proponent of the antibody thesis in this country, Dr. Robert G. Heath of Tulane University Medical School, New Orleans, went much further in reporting actual traces of antibody action in the brains of deceased patients. He says he has located the effects in the nerve cells of 14 schizophrenics 10 hours after their deaths.

The Heath work has not been confirmed elsewhere. "We don't have any evidence on that," says Dr. Beckett, but the Lafayette group believes that antibody action may be one part of the disease.

On the other side of the membrane, substances leaking into cells could start a companion abnormal process.

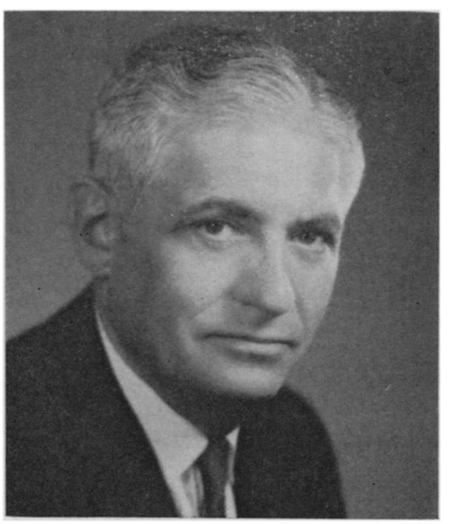
To get rid of excess chemicals, the cell may be driven to speed up metabolism, producing either abnormal chemicals—such as hallucinogens—or abnormal amounts of a normal chemical essential to nerve transmission.

In the presence of alpha 2, the chicken cells studied by Lafayette scientists did, in fact, take up excessive amounts of some chemicals. One of these was tryptophan, a normal amino acid derived from food. Tryptophan breaks down into serotonin. Too much serotonin would distort nerve signals, since that chemical plays an important role in regulating transmission within the brain. Moreover, serotonin can be converted into hallucinogenic substances, such as bufotonin. Brain cells might use these abnormal metabolic routes to get rid of excess tryptophan.

Confirmation of these theories depends on the identification of alpha 2 and its effects. For the moment, says Dr. Bergen, no one can say whether the presence of the globulin is a result of schizophrenia, a cause or a completely unrelated phenomenon: "Once we have something really pinned down, we can start forming theories on which to base rational treatment," he says.

Dr. Heath, whose work remains controversial, is now almost alone in dissenting from the thesis that alpha 2 has a role to play in schizophrenia. He believes the agent in the disease belongs to another family of blood proteins, the gamma globulins, and this spring he presented evidence of such a protein crossing capillary walls into brain cells.

In 10 years of research, Dr. Heath has built the most detailed body of biochemical evidence on schizophrenia that exists anywhere. He has injected both monkeys and human prison volunteers with the schizophrenic blood agent he calls taraxein, and believes he has pinpointed its effects in specific brain areas (SN: 2/11/67, p. 141).



Tulane University

Heath holds in the face of skepticsm.

But others have been unable to reproduce his results, partly through lack of money and opportunity. Dr. Bergen has now begun to duplicate the Heath experiments, with the hope of fitting their results into the crazyquilt pattern emerging elsewhere.

Meanwhile, many scientists remain skeptical of all the evidence on blood and urine, including the alpha 2 lead. For instance, Dr. Seymour Kety, former chief of clinical science at the National Institute of Mental Health and now at Massachusetts General Hospital, criticizes the work for insufficient controls, which if followed rigorously might wash out the evidence.

Moreover, scientists have long looked for single enzymes to explain complex mental disorders without success. That does not mean an enzyme will never be found, says Dr. Kety. But past failures create skepticism.