

Testing the Spoor of the Gray Behemoths

—The Schizophrenias

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As a child you may have watched the public circus parade which always featured the elephants lined up, trunk hooked to tail, following one another with a slow waddling gait. These gray behemoths with their gold and red trappings were the apogee of all that was formidable. The lead elephant would have a small turbaned mahout perched on its broad and massive head. For sanitary reasons and comic relief, the last in the parade was the white garbed dyschondritic dwarf who pushed a two-wheeled cart. With his side shovel he ceremoniously picked up the elephant droppings and placed them in his cart, closed the lid, and everybody laughed.

Since the turn of the century, research in the schizophrenias has been like the circus parade. In my biological dreams the parade of gray behemoths represents the schizophrenias while the dyschondritic dwarf represents the biological scientist collecting the spoor of the schizophrenias. Other problems occur for the biologist in that all elephants are not alike. The spoor collected at the end

of the line of gray behemoths can come from any one of the six or seven schizophrenias (elephants) in the parade. The biologist needs to keep constantly in mind which schizophrenia supplied the spoor.

For example, the pragmatic biologist has determined in a safe manner the body temperature of the elephant by the prompt insertion of a rectal thermometer into the fecal ball. In real elephant hunting the elephant boy sticks his finger into the spoor to determine the degree of heat at the center. This will tell his educated finger exactly the distance to the game and the solution to the problem of elephant hunting. Also, in the forest are the dung beetles which make smaller balls of the large ball and roll them off to nurture more dung beetles. In my dreams these are the non-biologically trained therapists who study grantsmanship in order to employ technicians to negate and neutralize the findings of the biological scientist—the dwarf without the grant.

In the past, the microbiologist, biochemist, nutritionist, and pharmacologist have made discoveries by the study of the spoor of the "schizophrenic" patient.

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Occasionally the urine or blood was also examined. These studies enabled biologists to separate eight different entities from the schizophrenias. A plural hodgepodge of disease entities still exists in the schizophrenias. The motivated biologist finds the spoor more difficult to acquire now that the psychiatrists have learned the bare fundamentals of statistics which they apply freely to their heterogeneous schizophrenic populations as they study me-too drugs.

As a biologist in 1929 at the University of Wisconsin, I first became interested in the schizophrenic when I saw a catatonic patient temporarily recover when given carbon dioxide inhalations by Dr. Ralph Waters. In this instance, Ralph Waters and Chauncey Leake were the biologists while Bill Bleckwenn (the psychiatrist) supplied the schizophrenic patient. This group later extended their findings to intravenous sodium amyral as an agent producing a lucid interval. When given carbon dioxide, or the depressant sodium amyral, a catatonic patient may "come to" and relate episodes of his past life and his present ward life, and the clarity of detail astounds the listener. This early demonstration convinced me, and should convince others, that the severe schizophrenic who is frozen with schizophrenia into a wax-like statue still has a normal brain anatomically and only the physiology, or function, of that brain is in biochemical imbalance.

Later as an intern at the Wisconsin General Hospital I wanted as much anesthesiology as possible. We were allowed to trade off services so I got three months of anesthesiology and four months of neuropsychiatry, a service that nobody wanted. This balance toward neuropsychiatry shaped my career.

I recall one of my patients who was continuously psychotic with status epilepticus. I gave him sodium pheno-barbital, 100 mg intramuscularly every hour all night long. He was restrained because of his violence. At 5:00 a.m. he appeared to be better and asked for a cigarette. I hesitated, and he boasted, "If you'll give me a cigarette, I'll make smoke come out of

my ears." A restraint was loosened, and he got his lighted cigarette, took a big puff, held his nose, and smoke came out both ears! Chronic holes in ear drums on both sides! As an unemployed epileptic he made a living in the local bars demonstrating this trick.

I learned early that psychiatrists are not to be trusted in the study of biochemicals. A nose drop preparation produced a drop in body temperature. We found some antischizophrenic effect with this preparation. A psychiatrist friend wanted to use this on a problem patient. He left it with the ward nurse with written directions: give 10 drops and take body temperature every hour. The nurse gave 10 drops every hour and took body temperature likewise. After six hours the patient was extremely uncomfortable with goose bumps, pallor, and a heart rate of 30. When the medical team arrived the patient who was just schizophrenic and not stupid said weakly, "I think electroshock therapy is better than this new therapy." The patient recovered uneventfully, and the nose drops are no longer marketed. As one enlightened government official once said, "For research in schizophrenia, the psychiatrist should be on tap but not on top." A psychiatrist trying to do biological research is like an aborigine who is handed a new boomerang. The poor fellow spends the rest of his life trying to throw the old one away!

From 1948 to 1957 we ran a research ward for the chronic unresponsive schizophrenic at Manteno State Hospital in Illinois. We examined the spoor of the schizophrenic, and we continuously gave the patient many naturally occurring biochemicals which we thought might mimic the action of carbon dioxide.

The human ethics committee was myself, the biological scientist, and the interested graduate students who applied the good Golden Rule by trying on ourselves the biochemicals which we planned to use in the patient. We were not trying new drugs, but other pure biochemicals. These biochemicals were used to overbalance or optimize a chemical reaction in the human body—ours or the patients.

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These smart biochemicals, which we hoped would know where to go and what to do in the brain, included methyl guanidine, pyridoxine, multivitamins, choline, methionine, glutamine, glutamic acid, aspartic acid, L-tryptophan, calcium, magnesium, potassium, guanidine, ACTH, and cortisone—to name but a few. Hydrazides produced effective thalamic epilepsy for convulsive therapy. The simple antidote was the intravenous injection of the vitamin pyridoxine. However, this convulsive therapy which started in the thalamus was no more effective than EST which originated in the cortex, and EST was much more convenient.

The period at Illinois 1945 to 1954 was one of intense learning under the tutelage of Warren McCullough, Fred and Erna Gibbs, Percival Bailey, Paul Bucy, and Lasslo Meduna. The graduate students under Klaus Unna, Ted Sherrod, and James A. Bain contributed as they prepared and defended their theses. We were all interested in the brain and how it worked.

In 1950 Martin Pilot perfected the absolute eosinophil count under our direction. The schizophrenic patients had such low counts, 11 to 22 per cu mm (stress), that we couldn't use the eosinophil lowering effect of ACTH to compare the patients with normals who have an eosinophil count of 150 to 250 cells/cu mm. This showed us that the physiological state of the schizophrenic was one of constant stress.

We were also innocent bystanders in 1950 when Morris Lipton and Nat Apter had Charles Huggins remove the adrenal glands from six schizophrenic patients. The adrenal glands, which were tested in vitro by the Hoagland group, were normal and none of the schizophrenics got any worse or any better. The patients might have improved if the adrenolutin theory were correct and might have improved if schizophrenia would respond to the tender loving care that was bestowed on these patients. Neither happened! The patients were maintained thereafter on DOCA, cortisone, and extra salt in their diet.

Since schizophrenia (Waste Basket Diagnosis) was not modified by the removal of the main source of catecholamines—the adrenal—we developed a distinct prejudice against the adreno-chrome-adrenolutin theory and the whole catecholamine (dopamine) theory of schizophrenia. One weekend in 1956 as a clincher we got pure adrenochrome from a nearby pharmaceutical firm and injected recovered alcoholics who volunteered for the study. We told the men that some form of the "DTs" (delirium tremens) might occur with the injection. The individual dose rose gradually from 0.5 mg to 7 mg intravenously. There was no effect on the blood pressure or pulse rate, but with the larger doses the purple adrenochrome came through the kidneys into the urine. No DTs, no adverse effects, and we concluded that if adrenochrome would not be destroyed it would be excreted harmlessly in the urine. This convinced us even more that catecholamines had little to do with the schizophrenias.

In 1954 we showed that arecoline with its acetylcholine-like effect would also produce a lucid interval in the severe schizophrenic patient protected by methyl atropine. Arecoline is the active ingredient of the betel nut—a mood-elevating chew for the Asians.

The choline and arecoline research did lead us to Deanol which is the tertiary amine precursor of both choline and acetylcholine, a known neurotransmitter in the brain. In our open studies, Deanol had as great an effect in the schizophrenias as did Vesprin, one of the me-too tranquilizers then available. But, as usual, only a small but definite proportion of these patients responded to our new smart biochemical. Should we fight for our new smart biochemical, or should we continue the search for the main cause of "schizophrenia"? We chose to follow the elephant's spoor to see what else might be hiding in the medical forest and masquerading as the true schizophrenia. Some scientists may make their reputation by learning more and more about less and less. If we chased the disease schizophrenia we

might learn more and more about elephant spoor, but not much else! Furthermore, by chasing the spoor of a disease we were labeled scientific diletantes—hardly deserving of grant support.

In the fall of 1959 (October 17), I had a massive heart attack, and as I lay in the oxygen tent breathing rapidly as my lungs filled up with fluid I decided to give up my teaching and my administrative duties and study schizophrenia for the rest of my scientific days. Accordingly, I resigned my directorship at Emory University Medical School and sought a post in psychiatric research —Head of Neuropharmacology at the New Jersey Neuro-Psychiatric Institute which planned to develop a research ward for male schizophrenics. Joseph M. Tobin was the Director, A. Arthur Sugerman was Head of Psychiatry, and we all shared medical duties. The years 1960 to 1965 were convalescent and staff and equipment building years. Dr. Leonid Goldstein showed for the first time by quantitative EEC methods that the chronic male schizophrenic was constantly over-aroused even when stiff with catatonia. No wonder carbon dioxide or amytal worked! Some sort of natural depressant was thus needed. Contrariwise, what would cause the brain to be continuously over-aroused? Could it be neurohumors, hormones, or ion? If so, which, how, and where in the brain?

In August and September of 1966 we made a discovery—the chronic male schizophrenic was much lower in blood histamine (27 ng/ml) than comparable normal males (47 ng/ml) and, furthermore, the histamine rose to normal as the patient improved with an effective antipsychotic drug. We requested financial help from the National Institutes of Health to study this finding. The grant was refused because histamine had no effect (at the dosage used) on the transcallosal pathway of the cat brain, a special but enigmatic laboratory preparation used interminably by one of the scientists of the reviewing panel. Histamine is certainly one of the most important

neurotransmitters in the brain.

This action is overlooked by the dopamine and serotonin workers who multiply like rabbits when nourished by their tax-supported grants. At a recent international meeting a young scientist flippantly discussed the neurohumors of the brain, but failed to mention histamine and many others.

Left to our own financial and our own aging neuronal resources, we did what we could with our new knowledge. Outpatients volunteered to be tested for their blood histamine levels—72 of them. A new test, the Experiential World Inventory, devised by Doctors Osmond and El-Meligi, was used to assay the dysperceptions, paranoia, depression, and impulsivity of our outpatients. A normal score was 15, and a highly dysperceptive individual outpatient might have a score of 220. The study was open. Would the blood histamine rise as the numerical score of psychopathology went down? In our 22 successes, the negative correlation coefficient was a modest -0.28. The significance was such that this would only occur once in a hundred times by chance! We *were* on our way; a blood sample might now tell us the degree of improvement in a given low-histamine patient.

We analyzed our outpatient group and found some patients with very high (above 100 ng/ml) blood histamine levels. With these patients the blood histamine slowly came down with therapy. Their individual correlation coefficients might be as high as +0.66 compared to an equally significant -0.88 for a histapenic or low-histamine patient. We discovered many more of the high-histamine patients, so we coined the word "histadelic" for their type of illness. Thus histapenic and histadelic patients are equal in their degree of thought disorder and overarousal, but the histapenic patient has hallucinations and paranoia while the histadelic patient is severely depressed and usually compulsively involved with one type of suicide. They also have other compulsions and abnormal fears. The changes in histamine (low or very high) only occurred in about two-thirds of the

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schizophrenics—so we continued to study the spoor of many more patients.

In 1970, when we found that most or all of the blood histamine occurred in the basophils of the blood, we sent the paper to **Nature** magazine and got it back within three days as being too specialized for **Nature**. We then sent it to **Science** magazine and had it turned down with the comment that high and low histamine occurred in only two-thirds of the schizophrenics. When were we going to tell the world what the other third might be? This unfair criticism spurred us on to learn more about the other third of the schizophrenias.

In the 1960's one jolly dung beetle thought he might learn something by giving a single big dose of acid (LSD-25) to an elephant. He literally killed the golden goose that dropped the colossal dung. The zoo elephant was shot with a dart containing millions of doses of LSD. The elephant promptly had a grand mal epileptic seizure and died. If a smaller dose had been given and the elephant showed hallucinations, the study might have had scientific merit. An artful paper was written on this tragic episode and published in **Science**.

In 1968 we decided that the only biochemical event which could provide histapenia and histadelia would be the mechanism of the storage of histamine in the basophils, which in turn would depend in part on some trace elements such as copper, manganese, calcium, or zinc any of which could be in excess or in under supply in the body. The inner core of the elephant spoor was getting warmer to the tip of the index finger!

To make a long story short, the schizophrenic patient in general was found to be high in serum copper. They excreted less copper than the normal controls. Excess copper could be removed by giving zinc and manganese by mouth. With zinc and manganese, some patients improved in their extremes of histamine and also their extremes of behavior. We were most happy when zinc gluconate and manganese gluconate appeared in the health food stores. Now the druggist would no longer label our

Ziman drops (zinc, 10 percent, manganese, 0.5 percent) **for external use only**. Now, the FDA could no longer breathe down our very vulnerable necks.

In 1970, we found that patients excreting the mauve factor had significantly more zinc in their urine than did a group of

schizophrenics who did not have the mauve factor. Dr. Arthur Sohler also showed that mauve factor patients excreted more coproporphyrin than did the control, non-mauve factor patients. Donald Irvine at Saskatoon unraveled the chemical structure of the mauve factor, and Dr. Sohler at my suggestion found that the kryptopyrrole would react avidly with pyridoxal phosphate, but not with pyridoxine. At long last our index finger in the warm spoor indicated that kryptopyrrole urinary excretion would take with it pyridoxal and zinc to produce a double deficiency; namely deficiency of a vitamin and an essential element. Zinc is a trace element needed by 20 enzymes in the human body. For instance, zinc is needed by the brain to produce RNA and DNA, those nuclear substances which deal with cell reproduction and perhaps the storage of memory. We were now making definite progress with histamine and trace metals while the aggressive and well-financed dung beetles were rolling up portions of the spoor and even the cerebral spinal fluid to look for abnormalities in catecholamines and serotonin.

These mauve factor patients have stress-induced mental difficulties frequently starting at age 17 because of zinc deficiency. They grow showers of metabolic white spots in their fingernails, and because of their B6 deficiency they fail to recall their dreams. With enough B6 they again remember their dreams. When they ask why we want them to recall their dreams we answer "dream recall is normal and we just want you to be normal." One pyroluric patient called excitedly to relate that the first dream was about the terrible time he had had in the mental hospital (a real Id catharsis). He asked if I had planned that for him. Because of my usual busy day I said, "Yes!" and went on to the next dreamless

patient.

Another 13-year-old young lady who had had only nightmares in the past two years found that now she had pleasant dreams. Her only comment was that "some of my dreams were awfully sexy." I responded by saying pragmatically that at least she wouldn't get pregnant from dreams. She replied, "Oh, I wouldn't go that far even in my dreams!"

Yet another 17-year-old patient had her nightmares changed to pleasant dreams. Her psychoanalyst protested that nightmares were useful for the elimination of aggression and that the change to pleasant dreams was a step backward!

In our book, **Mental and Elemental Nutrients**, we summarize the three common types of schizophrenia, namely histapenia, histadelia, and pyroluria. If we now add the disorders which masquerade as schizophrenia, namely hypoglycemia and cerebral allergy, we will probably include 95 percent of the present disorders which can easily be separated by the competent clinical laboratory connected with an outpatient clinic (Pfeiffer, 1976). With these five main variables we can for the first time calculate and list the combinations of disorders which have been labeled schizophrenia. Since histadelia and histapenia represent the extremes of a single variable, the combinations amount to only 23 possible combinations. This may appear large, but the parameters are measurable. In contrast, psychiatric theory which might blame parents or sibling consists of intangibles as numerous as the lightning flashes in a summer storm.

The single area which requires a sharper focus is the field of cerebral allergy. Dohan has shown

that 4 percent of hospitalized schizophrenics react adversely to wheat gluten. Singh and Kay (1976) have confirmed Dohan. T. Randolph has pioneered in the study of many allergens as the etiological agents in mental disease. The advent of RAST radioactive antigen sensitivity testing may help take the witchcraft out of allergy testing and place the testing in the laboratory where it belongs. By present methods a single blood sample can be tested for 10 or more of the common antigens which cause cerebral allergy. These tests should now become routine at each Brain Bio Center. At present the diagnosis of cerebral allergy is a last resort effort in the diagnosis of the schizophrenias.

The spoor has now been analyzed, but the circus parade of behemoths continues from one psychiatric hospital to yet another wherein the spoor cannot be analyzed or the analyses interpreted. The community mental health center stuffed with sociologists guided by a psychologist in residence and an analyst on call is hardly the answer to the problem of schizophrenia. The Brain Bio Center, a clinic with a diagnostic purpose, may provide the answers if allowed to thrive and proliferate. A new delivery system for the diagnosis and treatment of mental disease is needed, and the Brain Bio Center is exactly that.

REFERENCES

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