Out of the Quicksands

F. H. Kahanl

I. ONE STEP FORWARD

The year 1951 was a dismal period in the history of psychiatry. Between 1940 and 1950, research in psychiatry, particularly physiological research, was in the doldrums. Analytic theory had expanded markedly, especially in the United States, and psychological and psychiatric analysts led the field in research. The main objective was not to find out more about schizophrenia, man's most common illness, but to fit the facts of schizophrenia to Freudian theory. Few questioned the basic theory itself, and practically no research was attempted to test the ideas emanating from it.

Saskatchewan, with a population of about 1,000,000 people living in 200,000 square miles of inhabited prairie and parkland, did not seem to be a promising place for psychiatric research. Toronto and industrial eastern Canada are 1,500 miles or more away. There was no psychiatric research of note being done within a radius of 1,000 miles.

[1] **2716 Sinton Avenue, Regina, Saskatchewan S4S 1K1.** **The author acknowledges with gratitude the generous assistance of Dr. A. Hoffer whose records, correspondence, technical advice, and guidance made this history possible.**

There was no tradition of psychiatric research to follow, and the need for it was buried beneath other needs. Thousands of miles of highways had to be built or improved- Old buildings had to be replaced by new. Government services in education, health, and welfare had to be expanded and improved.

The Director of Psychiatric Services, too, was having problems. His main preoccupation was to change obsolete and grossly overcrowded mental hospitals into habitable places for those human beings forced into them in large numbers. The Weyburn hospital alone, built to accommodate 1,000 patients, held over 2,500. Yet research developed. It started haltingly, with very few clues and little money. Many things could have prevented it starting at all.

One day a young doctor in St. George's Hospital, London, England, read an article on peyote, a sacrament used by many Indians in their religion. Dr. John Smythies thought that the effects of peyote were similar to experiences reported by some schizophrenics and mentioned this to his colleague, Dr. Humphry Osmond.

The two doctors learned that mescaline, a substance capable of changing the way people perceive their world, was a

component of peyote. They also learned, from a biochemist who was then a medical student at St. George's hospital, Dr. Julian Redmill, that mescaline resembles adrenalin structurally.

They have since discovered that this was known for years. Many European authors, including H. H. de Jong, C. G. Jung, and W. MacDougall, had suggested for 30 years before this that a toxic substance, usually thought to be an amine, might be responsible for schizophrenia. But no one had been led to formulate a hypothesis which would start a systematic search for the compound.

At first Dr. Osmond and Dr. Smythies thought that an idea so obvious must have been scrutinized and rejected long ago. Dr. Smythies made a survey of the literature and consulted with Dr. Harley Mason, an organic chemist in Cambridge University, England. He and Dr. Osmond decided to pursue their line of thought and suggested that in certain circumstances the body produces a mescaline-like compound which they called M-substance for short. They began looking for this substance which, they said, had to be able to produce changes like schizophrenia and which had few easily detected, physiological side effects.[2]

They were encouraged by the fact that other scientists, besides Dr. John Conolly, had long before noted physiological differences in schizophrenia. F. M. Shattock, in a monograph on "The Somatic Manifestations of Schizophrenia," had reported, among other things, collapsed and odd shapes in capillaries, marked pigmentation of the skin common in chronic female schizophrenics, and phasic hyperglycemic levels common in acute schizophrenia.

Hopefully, they began experimenting with mescaline on themselves and volunteers in what was to become the first serious investigation of the world of schizophrenia ever undertaken.

One day, a subject, listening to another subject describe his mescaline experience on tape, remarked that things like that sometimes happened to him. This subject was a severe asthmatic and took adrenalin to help him control his affliction. If he took very large amounts of adrenalin, as he sometimes did, the world changed. He had colored visions with his eyes shut and feelings of unreality.

This was an important clue, but there were others. When the effects of mescaline were compared with the effects of schizophrenia, it was found that the former produced mild changes which are often found in schizophrenia. Pupils became widely dilated, and there were various changes in the skin, such as blushing and sweating at first, leading to pallor and dryness. The heart rate and blood pressure appeared to be raised at first, but both soon fell.

These and other observations raised a host of new questions. It was certain the relationship between mescaline and adrenalin had to be investigated further. An agent to counteract the toxic effects of mescaline had to be found in the hope that this would lead to a treatment for schizophrenia.

Dr. Osmond tried to arouse interest in this idea in England, but was unsuccessful. This was one of the reasons why he came to Saskatchewan, late in 1951, to become clinical director of the Weyburn mental hospital, then one of the worst mental hospitals in the world.

Here he and Dr. Abram Hoffer met. Dr. Hoffer, tall, forthright, self-confident but trusting, a son of Saskatchewan pioneers, had just been appointed Director of Psychiatric Research for the province, and was interested in mescaline after learning about it from Dr. Heinrich Kluver of Chicago.

"Dr. Hoffer was just beginning to think about establishing a type of research program, but had not yet decided what particular project he would undertake. Dr. Osmond's idea sounded sensible and on careful investigation he found it had a great deal of merit. They therefore began to work together and gradually arrived at

2 The word hallucinogenic was first used in a Journal of Medical Science paper, 1954, by Hoffer, Osmond, and Smythies, to describe substances like mescaline which have the ability to produce hallucinations and other disturbances of the senses in normal people.

a plan which was carried out for the next several years.

From the day they met, Dr. Osmond and Dr. Hoffer worked together in one of the most fascinating and prolonged hunts' ever conducted in biochemical research, and against great odds.

Dr. Hoffer's first office was in the basement of a rambling brick building attached to the Regina General Hospital, known as the Munroe Wing. It was just big enough for a chair, a table, and a little folding bed which he had built into the wall because there was no room on the floor. The bed was not needed for psychoanalysis, he explained, but for physiological testing of patients. He was testing blood and urine samples of schizophrenic patients and normal volunteers and comparing for differences.

Seventy-three miles away, on the outskirts of the city of Weyburn, Dr. Osmond began tackling research and institutional problems in the monstrosity known as a mental hospital.

From the beginning, Dr. Osmond and Dr. Hoffer believed that schizophrenics were patients who were sick and not weak people who were living a deviant way of life. This disease, they said, had psychological, sociological, and bio-chemical components. To ignore any one of these was detrimental to the patient. But while psychiatrists were ready to see the first two areas, they had persistently refused to look for the chemical pathology which Dr. Hoffer and Dr. Osmond believed could be found.

Since they could not persuade chemists just by conviction, they had to provide them with guidelines and hypotheses. The information they had was scanty, but enough to start with. The evidence pointed strongly to adrenalin as the Pandora's Box of schizophrenia and was given further confirmation by a Regina anaesthetist, Dr. E. Asquith, who told them that during the war, in England, pinkish adrenalin was used during anesthesia and when the patients revived they had disturbances including hallucinations.

Dr. Hoffer and Dr. Osmond could only speculate on what was going on in the body—perhaps a methyl group was going on to the wrong compound, in a process called transmethylation, and producing substances like mescaline, which has methyl groups on it.

Late in 1951 they submitted their first research proposal for a grant of $25,000 to the Committee on Research of the Mental Health Committee of the federal Department of Health and Welfare.

They were convinced that there was something in the body producing the clinical picture of schizophrenia, but how to find it? Where to start? Psychiatry was in a state of befuddlement and even then Dr. Hoffer and Dr. Osmond did not have a reliable guide for diagnosis. Exactly what was schizophrenia? They didn't know for sure. They didn't even have standards of recovery because too much depended on the psychiatrist's opinion and interpretations.

While they waited for news about their application, they studied the literature for clues. Could schizophrenia be treated by increasing the blood sugar level and by pituitary extract? Why did the mental state of a schizophrenic patient improve after he sustained severe burns covering nearly a third of his body? How does one account for the disturbance of liver function noted in schizophrenia?

Then, too, there was the immediate and urgent matter of improving conditions at the Weyburn hospital. Together they acquired donations of old journals, pictures, chairs, and other items which would help cheer up one of the basement wards.

One day the late Dr. Griff Mc-Kerracher, the provincial Director of Psychiatric Services, told them that two members of the committee to which they had applied, Dr. Defries, of the Con-naught Laboratory at the University of Toronto, and Dr. Young, a chemist, were coming through Regina, and suggested that it would be valuable for Dr. Osmond and Dr. Hoffer to meet them so that when their application came before them they would at least know who they were.

The four men met in Dr. McKerracher's office in the old public health building. Dr. Defries wasn't very encouraging. It was highly unlikely, he said, that any set-up in which he was interested would give them a grant for the work they wished to do.

"You could tell that after half an hour to an hour, Dr. Defries, an epidemiologist, was getting bored to death," Dr. Hoffer remembered. "He excused himself and went out, leaving Dr. Young to talk to Humphry and me.

"Now Dr. Young and I had been classmates in biochemistry, and so we knew each other from our university years. Dr. Young listened, and as we developed our theme he became more and more excited. An hour later Dr. Defries came back and when he saw how enthusiastic Dr. Young, Dr. Osmond, and I were, he also became enthusiastic. So we outlined our ideas to them, and before they left they both promised that they would do what they could to help us.

"As with many committees, new and strange ideas are often unacceptable, and our ideas seemed more strange than most. The chairman of the grant committee was Dr. Charles Roberts, who at that time was head of the mental health section. Dr. Roberts is a nice person, and he felt that it would be a good thing to have each province doing research in mental health. Some of the provinces were using the research money available to them, but Saskatchewan was not. He thought that it would generally be a good thing to encourage research in Saskatchewan.

"However, the vote ended in a tie. The three psychiatrists, Dr. E. Cameron, chairman at the Allan Memorial Hospital in Montreal, Dr. A. Stokes, professor of psychiatry and chairman at the University of Toronto, and Dr. E. Hobbs, professor of psychiatry at Western University, voted no, and the three scientists, including Dr. Young and Dr. Defries, voted yes. Dr. Roberts could have broken the tie but he didn't want to because, / think, he didn’t want to alienate the three top psychiatrists in Canada. Yet he wanted us to get the money. So he came up with a brilliant idea. He said to the committee, 'Would you allow me to send this proposal to Dr. Nolan D. C. Lewis in New York?' Dr. Lewis is the dean of American psychiatry and was then head of the New York Psychiatric Institute."

No one objected. Dr. Hoffer speculated that the psychiatrists were certain that Dr. Lewis, also a psychiatrist, would side with them, and the scientists, having done their duty by voting in favor, couldn't have cared less what happened to the grant after that.

"Meanwhile," Dr. Hoffer went on, "we were sitting back here, January, February, March of 1952, not hearing anything from Ottawa. We were getting very impatient and one day I complained to Griff McKerracher, asking him when we would hear from them. Dr. McKerracher phoned Charlie Roberts in Ottawa, and Roberts told him the thing had gone to New York for examination. So Griff phoned Dr. Lewis in New York. It was late Friday afternoon, five o'clock our time, seven o'clock New York time, and Dr. Lewis had left his office for his farm estate for the weekend. The message came back that he would be back Monday morning."

Eight o'clock Monday morning Dr. Hoffer was in Dr. McKerracher's office, and the latter put a call through to Nolan Lewis. Dr. Lewis said, yes, he had received the grant application.

"What do you think of it?" Dr. McKerracher asked.

"I have circulated it among my top staff," Dr. Lewis said. "We have gone over it, and we have just written to the government of Canada that not only must these men be given the two years' support for which they ask, but they must be given 20 years' support."

"Dr. Lewis," said Dr. Hoffer, "is one of the very unusual intelligent psychiatrists. He is one of the most creative world psychiatrists, and he favors ideas above method.

"So now Charlie Roberts had what he

wanted; the referee in the United States had said, 'Give them the money,' and this let him off the hook. He had handled it right. I discovered from Nolan Lewis that each year our grants went down to him and he kept writing back, support, support. This is why this meeting here with Dr. Defries and Dr. Young was so very important, because if we had not had Defries on our side, there was an excellent chance the grant request would have been vetoed four to two, and we wouldn't have gotten it. I'm convinced now if we had not received it I wouldn't have hung around here very long, and I'm sure Humphry would have left sooner. Nothing at all would have started here."

When Dr. Hoffer and Dr. Osmond received their grant, they constituted the Saskatchewan Committee of Schizophrenia Research.[3] Research people for several years gathered periodically from all parts of the province to present their data, report progress or failure, and decide on a future course of action. At the first meeting, early in 1952, thanks to their preliminary work and the help of others, the two were able to outline the bare bones of what has been known as the adrenochrome hypothesis of schizophrenia.

The body can be compared to a factory where hormones are made, destroyed, or changed into other hormones in a constant orderly fashion, with split-second timing. These hormones are important to the functioning of that great body computer, the brain, which sends out messages and interprets messages which come in.

Any hormone that so much as stubs its toe can cause a serious upset in this procedure, so that messages may come to the brain after one another instead of before one another.

One of the hormones which is important to emotions is adrenalin. The adrenal gland is a little triangular-shaped organ weighing only one ounce, which sits on top of each kidney. It produces a hormone called noradrenalin in its central area, the medulla, and from this comes adrenalin. Adrenalin flows from the medulla through the outer part of the adrenal gland, the cortex, and into the blood stream. In an emergency situation, the adrenalin enters the blood stream in increased quantity to help mobilize the body's biological resources for "fight or flight," and to act as coordinator of the many mechanisms required for the gigantic tasks ahead. It also plays a role in smaller quantities.

It was known that adrenalin solutions become red on standing and that discolored adrenalin could produce mental changes in normal subjects who inhaled it. Little else was known about the products of the adrenal gland. They wondered what was in the discolored adrenalin to produce these changes.

By the time they had their first research meeting, Dr. Hoffer had already discovered, from a search of the literature, that most of the hallucinogens then known were indole, but he had not heard of adrenochrome. At this meeting they called upon Professor Duncan Hutcheon, then professor of pharmacology at the University of Saskatchewan in Saskatoon, Professor D. MacArthur> and Dr. V. Woodford of the University Medical School, and asked for their help. When Dr. Hoffer showed the indole structure to Dr. Hutcheon, the latter pointed out that pink adrenalin was also an indole, called adrenochrome. At that time, very few other hallucinogenic substances were known, and these included ibogaine and harmine, which are found in South American plants as well as in LSD.

Dr. Hoffer and Dr. Osmond considered themselves fortunate to have found something in common in all these compounds and that the compounds were indoles capable of being produced in the body. If adrenochrome was found in the body, their theory would be proven valid. Mescaline, similar in structure to adrenalin, could theoretically form an indole in the body. The

3 This committee served well until it was ordered, dissolved, about 10 years later, by an irate Director of Psychiatric Services because he feared the few professors who were members constituted too much influence by a University on the committee.

change would be comparable to the oxidation of adrenalin to adrenochrome. There is no evidence that mescaline is converted into an indole in the body, but no search has been done to test this idea. Adrenochrome seemed to hold great promise.

They derived two guidelines from their adrenochrome hypothesis which sharply simplified the problem of isolating a substance from the body which was one of the causes of schizophrenia.

"We said to our biochemist colleagues, first, look in the body for an indole which is also an hallucinogen. It is obvious not every indole could be an hallucinogen, nor every hallucinogen an indole," Dr. Hoffer said. "But since very few indoles were known to be present in the body it became possible to test every known animal indole. Secondly, look for an indole derived from adrenalin. Adrenochrome turns into adrenolutin. Similar compounds come from 3, 4-dihydroxy-phenylalanine (dopa), dopamine, and noradrenalin, and are the only indoles, which satisfy both guidelines. This was the determining influence which has guided all our research into schizophrenia.

"We immediately began three major inquiries. First of all, we began a study of the chemical properties of adrenochrome and adrenolutin and the substances which come from them. We wanted to know what their properties are, and, in particular, their effect on the body. This was essential to the main question, was adrenochrome in the body? When we first proposed our hypothesis, some people predicted we would never find it because, they said, it wasn't there. But if it was in the body, was it there in higher concentrations or quantities in the person suffering from schizophrenia? These studies have been reported in a large number of reports by our biochemical group under the direction of Dr. R. A. Heacock.

"Secondly, we began studying the psychological changes induced in animals and man by adrenochrome and adrenolutin and the chemicals derived from them. We showed that adrenochrome and adrenolutin were active psychochemicals in changing behavior and response of every animal tested.

"Thirdly, we started a treatment study of chemicals which could decrease the production of adrenalin and adrenochrome. Our basic biochemical equation for schizophrenia was noradrenalin -> adrenalin -» adrenochrome.

"If the hypothesis was correct, then chemicals which could slow down these reactions, or reverse them, could be treatments for schizophrenia, and our hypothesis would be strengthened. If these were not successful, it would make it very difficult for us to go on with our adrenochrome hypothesis. It was, of course, possible the drugs would work even if the hypothesis was not correct."

The chemical examination of blood and urine was started by Dr. Hoffer with the help of Dr. Roland Fischer. Miss Marg Callbeck, who was then Charge Nurse at the Wing, later joined the research as research nurse, taking quite a reduction in salary.

The offices allotted to research, in the basement of the Munroe Wing, were bleak and barely furnished. Looking through the one small window in Dr. Hoffer's office, one saw only cement walks. All along the ceiling steam pipes hissed and sizzled. But morale among the research staff was high. They had a feeling of optimism and the excitement that comes from the hunt.

"Humphry played a very vital and interesting role," Dr. Hoffer says today. "It is difficult to define exactly what our roles were since we worked together as a unit. It was my job to direct the research, provide funds, keep it going, and maintain the even direction of the program. Humphry was doing the same at Weyburn. He acted as a useful stimulant and sparked many interesting areas of research. Throughout the program, our ideas were freely shared and we were not concerned about priorities as to who first thought of the idea."

For some of their experiments they needed human volunteers. Dr. Hoffer

was the first to take adrenochrome. He took a few micrograms because it was believed it might be as potent as LSD. When it was certain he had not reacted, he gave Dr. Osmond twice as much. Dr. Osmond's experience lasted a couple of days and he had no insight into the reason for his strange feelings.

Ten minutes after taking it he noticed that the ceiling had changed color and that the lighting had become brighter. He closed his eyes and saw a brightly colored pattern of dots which gradually formed fish-like shapes. He felt he was at the bottom of the sea or in an aquarium with a shoal of brilliant fishes. He later found the familiar corridors and buildings sharp, unfamiliar, sinister, and unfriendly. He had no feelings for human beings and "had to curb myself from making unpleasant personal remarks about them." He could not relate distance and time. Later, his observers wrote, "The change in HO marked by strong preoccupation with inanimate objects, by a marked refusal to communicate with us, and by strong resistance to our requests, was in striking contrast with HO's normal social behavior."

Later Dr. Hoffer took 10 mg of adrenochrome intravenously with a bit of sodium amytal. There appeared to be a marked decrease in insight.

Dr. Hoffer's behavior, after taking the drugs, seemed strange to his wife and friends, but he himself saw nothing wrong with it. After taking the amytal he was quite sleepy "and staggering around a bit, and yet I was determined to carry over a tray containing some valuable syringes and chemicals back to the Munroe Wing from the Regina General Hospital. Normally when I am a bit unsteady because of alcohol I do have enough insight not to attempt the impossible. This time I didn't. I was very active for the next eight hours until midnight, talking much more quickly, and was more aggressive, so much so that I was able to enlist four or five new volunteers for the LSD project.

"The next day all these volunteers declined to participate. That evening I attended a show by Ken Locheed in Regina College and bought one of his paintings for $60 although I was not financially able to do so. It was a very lovely picture. The next morning I very quickly cancelled the order. My close friends and my wife said that they had never seen me in this condition and although they said I appeared to be euphoric, I was not."

I. J. Kahan, research social worker, followed Dr. Osmond as a volunteer, this time with adrenolutin. Mr. Kahan was normally cheerful, relaxed, and friendly. His first reaction to adrenolutin was a disappointment to Dr. Hoffer and Dr. Osmond. Several hours after he took it Dr. Hoffer phoned him at home to ask him how he felt. He said they had given him colored water. Dr. Hoffer reported that Mrs. Kahan had noticed, he was reading the newspaper upside down and was reading only one spot. He said he was an individualist and could read the paper upside down better than anyone else he knew. Besides, it was an interesting spot.

Dr. Hoffer and Dr. Osmond began to think that perhaps adrenolutin and adrenochrome were not all that they had thought they were. They asked Mr. Kahan if he would be willing to take adrenolutin again, and exactly a week later they gave him a second and larger dose. Still he claimed there was no reaction. His skin seemed more taut, and his jaws were clenched. There was a closed, glazed look about his eyes. He seemed under control and very quiet. But soon changes began to be noted around his home.

He roared at the family, something he had never done before. When he was asked to explain himself, he gave long involved explanations which were unclear to the rest. Sometimes after an outburst he would deny having said anything at all. He was very irritable and critical of those around him. The only one who remained calm in his presence was his 18-month-old son who avoided his father like the plague, making wide

circles around him, and blandly pretending he didn't exist. Dr. Hoffer was delighted that Mr. Kahan had finally become schizophrenic. It restored his faith m adrenolutin.

Mr. Kahan remained schizophrenic about a week. What the researchers learned from his experience was the accumulative effect of adrenolutin. The second dose combined with the first to produce a prolonged reaction. His insight was no better than that of Dr. Hoffer's or Dr. Osmond's because he kept maintaining that everyone was peculiar but himself. He made jokes as usual, but he didn't look or act like he was joking.

The Munroe Wing staff soon learned that it was not unusual for research staff members to be out of character occasionally because of the experiments with LSD and other drugs.

Both adrenochrome and adrenolutin are mood-changing for man, but their properties differ to a degree. Adrenochrome produces more severe psychological changes, but for shorter periods of time. Adrenolutin produces less marked changes, but these last much longer and so it is more dangerous. One of the most dangerous changes is loss of insight so that the subject does not realize that depression, change in personality, and so on, are due to adrenolutin. They were finding out that both drugs, like LSD, produced changes in perception, thought, and mood resembling the changes found in schizophrenics.

In February, 1953, Dr. Osmond had an idea that was to have far-reaching effects on mental hospitals in the United States and Canada. It occurred to him that the ability of adrenochrome to reduce insight could be put to good use. He outlined his idea in a letter to Dr. Hoffer.

"I have an interesting experiment which I hope to carry out before long. When we have the doses of adrenochrome checked, I think it would be a good idea for someone to take a large dose of it and spend the day on a ward or wards. We would then get a very clear idea of the impingement of ward life and surroundings on the sick person. We have often heard it said that the grievously mentally ill are not aware of, or do not worry about, their surroundings. All the evidence we have *is* exactly to the contrary and yet we repeatedly subject them to conditions which are aesthetically unsatisfactory for well and hale people. The advantage of seeing psychiatric wards through psychotic eyes lies in having a description by a known observer whose capacity for observation can be checked, and (any skeptic) can go and see for himself (plus 10 to 25 milligrams of adrenochrome, of course)."

This was never followed up with adrenochrome, but later LSD was used for this purpose when Dr. Osmond and K. Izumi, a Regina architect, began architectural and psychological studies of mental hospitals (Kahan, 1965). Their findings are incorporated in many psychiatric centers.

During those years Dr. Hoffer had to spend a great deal of time traveling in search of more funds for research. In 1954, in addition to the support they got from the provincial government, they got a research grant from the Rockefeller Foundation.

At the same time, he and Dr. Osmond shared their ideas with interested people, hoping that someone would duplicate their work and either prove them right or wrong. No one did, but once in awhile they received a word of encouragement. One research scientist in the United States wrote, "The work of your group has been followed with considerable interest and enthusiasm as one of the few original and logical approaches to the problem of schizophrenia. It is heartening to know of original and bold approaches such as yours being introduced into this most perplexing of medical fields."

They had not found adrenochrome yet but were working on refining their chemical techniques, and given the time and money they were sure to find it. Meanwhile they were accumulating evidence that it was, indeed, in the body.

It was learned, for example, that

adrenochrome lowers the vitamin C level of the adrenal cortex of rats and lowers the blood cell count. They didn't know why this occurred, but it was known that schizophrenics need large doses of vitamin C.

The effect of adrenochrome on the body temperature of rats was confirmed, and Dr. Hutcheon believed that this was a central activity of the central nervous system which confirmed the belief that adrenochrome passes the blood brain barrier into the hypothalamic centers of the brain.

This was another interesting finding since schizophrenics have lowered temperatures, probably they reasoned due to the effect of adrenochrome. Since adrenochrome can pass the blood brain barrier, this made it more likely it could be a factor in schizophrenia.

They also learned that adrenochrome affects the brain waves of epileptics, another clue that adrenochrome has an effect on the brain similar to changes found in schizophrenia.

A subject involved in this finding was a girl suspected of having epilepsy who was sent for EEC investigation. At that time they were testing adrenochrome in epileptics to see what it would do to the EEC. No epileptic activity was seen, and she was therefore given 50 mg adrenochrome by vein. Epileptic activity appeared on the EEC and in half an hour the subject complained she felt unreal and that faces were different. Later that day she went home. In a few days she became psychotic and was admitted to another hospital where she was diagnosed as schizophrenic. After a few weeks on no treatment her psychosis cleared and she was re-diagnosed epileptic. Since then she has shown no evidence of schizophrenia, is well and happily married. After this, they stopped giving adrenochrome to epileptics.

These findings could perhaps be ignored by some people who had no real concern for their patients, but not by the research group.

In 1952, they came, by chance, upon an important difference between schizophrenics and non-schizophrenics. They were studying the effect of histamine injections as a treatment and discovered that chronic schizophrenic patients can tolerate remarkable quantities of histamine before the blood pressure goes down.

Dr. John Lucy, a research colleague, was following the procedure of giving increased quantities of histamine until the blood pressure went down to a given degree. But when they began their studies they found that so much histamine was needed to lower blood pressure they quickly used up all their research supply. They asked a drug firm to make them solutions of histamine 10 times as concentrated as before. The request was so unusual the firm was reluctant to do so unless they received a special release, since they had not previously known these large quantities could be given to subjects.

As they learned more about adrenochrome and schizophrenia, they found there was even more to be learned. They wanted to know, for example, how adrenochrome related to the physical immaturity of many schizophrenics. Did adrenochrome or something like it prevent premature aging? They had a schizophrenic patient, a 45-year-old woman, who looked 10 or 15 years younger than her age. Was this common?

Those who were opposed to the research, and their numbers began to grow, recruited by word of mouth, criticized Dr. Hoffer and his chemists for not having been able to pick adrenochrome out of the body and show it to them.

Dr. Hoffer and Dr. Osmond were not bothered by the criticism because they did not consider it intelligent or rational.

"The first indication the research was going to run into rough water was the reaction of the other psychiatrists working at the Munroe Wing who resented having their patients tested and researched," Dr. Hoffer said. "This is going on in every research unit in the country unless the top man in the institution is the research director.

"This is natural between researchers and clinicians because the latter often don't understand what research is all about, nor do they like people tampering, as they see it, with their patients. An additional factor is that the psychiatrists in the Munroe Wing appeared to feel threatened by our work. To illustrate the horror our work generated there, I'll tell you about how a psychiatrist, who had succumbed to Freud, attacked me in what he considered to be a most devastating way. In a discussion with me he said, 'I suppose you think one can take a sample of blood from a patient's arm through a screen, so that the patient cannot be seen, and diagnose the schizophrenia.' This idea really horrified him, because it went directly against his idea that schizophrenia was due entirely to life stresses."

The next thing that happened in Saskatchewan was that the research began to get "too much" publicity, beginning with an article which Sidney Katz had written in **Maclean's,** a national Canadian magazine, in 1964 (Katz, 1964).

Mr. Katz appeared in Weyburn without notice to do a story on mental hospitals, heard about LSD, got to know Dr. Osmond, and volunteered to take the drug. Since at that time research people were looking for volunteers, they were quite happy. Christian student movements sent volunteers into the mental hospital for the summer, and rnany of these volunteered for LSD as well. Then Mr. Katz got his photographer down and they did some drawings and pictures. The issue carrying that story had a very lurid cover. This was the first popular magazine in the world to run a big story on LSD.

When the story of Mr. Katz's colorful LSD experience came out, there was a mixed reaction. The first cry of disapproval came from the College of Physicians and Surgeons in Saskatchewan which sent a strong letter to Dr. McKerracher asking him to appear before their council to explain why this was reported in the lay press before having appeared in the medical journals.

"Griff came to talk to me about it and I told him we had by that time published several papers on our LSD work in the medical literature, which the College didn't know about," Dr. Hoffer said. "I gave him a list of all the papers which had been published, and when the College discovered that their basis for their criticism was wrong, their whole action collapsed.

"Then I began to hear rumors—false ones—that the top professors in Canada like Professor Stokes had been extremely annoyed by this LSD article and were going to see to it that no one in Saskatchewan ever got any more research money. I found this very amusing and very false because that year I had been put on a research subcommittee for the federal Department of Health and Welfare. These rumors were only an indication of what was happening.

"Apparently there were three kinds of reactions:

1. The psychiatrists objected.
2. The general physicians were interested, perhaps, but mostly indifferent.
3. The public loved it.

"Maclean's kept a record of the letters which came in and most were highly supportive of the kind of story which was written. At that time the patients in Weyburn had a form of self-government, and at the meeting following the appearance of this article they moved a vote of thanks to **Maclean's** for having shown the people in Canada for the first time what mental hospitals were really like. The magazine published their letter. This was symptomatic of the things which were going to happen. We could see, in fact it is quite obvious by now, that the public was going to accept our research much more easily, quickly, and enthusiastically than the professionals."

The criticisms, Dr. Hoffer maintains, have no validity because they were highly contradictory.

"I can list dozens of things that are said, and I am sure they will continue to be said 20 years from now. First of all they said we were publishing too much. Then they said we were publishing too little. It seems we can't please anyone. Then they said we were publishing

prematurely although nothing was ever published until it was carefully researched.

"They have said our work has not been corroborated. Corroboration can and often does mean that no one has ever tried, or they haven't tried the right way, or that they have in fact tried to do it properly and haven't been able to produce the same results. So far, only a few people have tried to duplicate our work properly and have produced the same results we have."

For years, Dr. Hoffer said, professionals have been saying that the adreno-chrome work in Saskatchewan was proven to be invalid. They based this claim on a report at an American Psychiatric Association meeting that a group of workers at Boston, under M. Rinkel and R. W. Hyde, were unable to confirm their findings.

"As research workers we liked to have our published work either confirmed or refuted by other research workers because either way we get valuable information. We had certain confirmation of our work with adrenochrome on the EEC effect and some chemical studies."

The Saskatchewan research group thus sent the Boston group a prepublication report on the results of their research with adrenochrome and expected that, having tried to reproduce the work and failed, the group would have written back to ask the reason for the divergence in results. Instead, the Saskatchewan group heard only indirectly about the report but were not able to trace its origin until a few months later.

"At the time, Dr. Hyde kindly sent us a manuscript of his paper and there I discovered that they had not used adrenochrome at all in their experiments, but had used adrenochrome semicarbazide, an inert derivative of adrenochrome which has totally different properties, thinking that this was adrenochrome. Adrenochrome itself is completely unstable, whereas its derivative is stable. Adrenochrome markedly inhibits Warburg respiration, whereas the semi-carbazide has no effect. Adrenochrome has a marked effect on the pattern the spider spins, whereas its stable derivative has no effect. Finally, adrenochrome produces psychological changes whereas the semicarbazide does not. If it has any properties at all, they are antitension properties.

"I contacted Dr. Max Rinkel and pointed out to him that his statement regarding our work was inaccurate. He wrote back stating that they spotted their •error and were submitting a correction to the journal which had published their original paper. A few months later I ran across an article by Rinkel in the **Journal of Diseases of the Nervous System** (Rinkel et al., 1954), in which he again stated that they were unable to confirm our work, and they referred to our adrenochrome preparation disparagingly as home-made adrenochrome. This time I wrote to the editor of the **Journal,** who contacted Dr. Rinkel. The latter wrote me that he was submitting a further correct."

This illustrates how easily research can develop a bad reputation by an error made by a research center. It is much easier to publish this type of report than it is to have it corrected later on. No doubt there are professionals who still claim the adrenochrome work was never confirmed, without bothering to find out the facts. The error of the Boston group can be explained only by the fact that they were totally unaware of the significance of structural alteration of molecules. Yet for a long time the public was told that Saskatchewan research had not been confirmed.

By 1954, the research had survived two uneasy periods. The first one was created when Dr. McKerracher wanted Dr. Hoffer to study psychosomatic medicine for a year at another center. Dr. Osmond was adamant in opposing this.

"Thank God," says Dr. Hoffer, "I did not go."

Another crisis occurred when Dr. Osmond and Dr. Hoffer were both on the verge of resigning over an issue which involved a Superintendent who opposed

Dr. Osmond's efforts to bring the Weyburn hospital into the 20th century. Fortunately, this was resolved by the provincial government, which sent the Superintendent away on a year's leave of absence, with full pay.

At the end of 1953, Dr. Osmond, now Superintendent of the hospital, wrote Dr. Hoffer, "As I look back over our more than two years' association, I realize how much I am indebted to you, not only in the research in which you have been so much help, but in your support and encouragement in numerous ways. It has been good to work with you and I have greatly enjoyed it. Most of all I appreciated your decision in August not to go to England for a year. I know that this was a very hard one to make and that it imposed a heavy sacrifice. I believe that you will agree in the long run it is correct, but it doesn't make it any easier to do the right thing. The immediate gain at Saskatoon would clearly have been very attractive, but I believe that in this way the long-term gain will be much greater; but I do realize that I forced a decision in this matter in a way that most other people would have resented.

"I count myself.very lucky to have found such a partner as you who has a great similarity in outlook but a widely differing collection of assets. This makes our association much more productive than it would otherwise have been and relieves us of the necessity of overloading ourselves with surplus learning which one is best without.

"On the brink of our first major publication, it seems good to look around, because it may be years before we have a chance to do so again. There will be controversies, more papers, and probably years of research ahead to confirm or confute our observations of 14 months ago. My own belief is that we have made the first major dent in the armor of schizophrenia, and that this will be gradually enlarged until we know and can treat this illness with many new weapons of psychiatry generally ..."

Dr. Hoffer shared his optimistic mood. "Perhaps 1953 will mark the most productive year of our research project. I cannot imagine that we will even in one year open up as many research areas as we have, but none of this would have been possible without your leadership and assistance in shaping the research programs."

II. HISTORY-MAKING SCHIZOPHRENICS

Each year brought them closer to the answers they were looking for. Their psychological work with adrenochrome was not believed until years later when a group of psychiatrists in Prague, led by Dr. Vojeechovsky, repeated it using a double-blind controlled study and corroborated their results. Dr. Hoffer and Dr. Osmond also completed a double-blind controlled study of adrenolutin.

Studies on adrenochrome and adrenolutin were continued in Sweden, Russia, Czechoslovakia, Germany, Switzerland, Canada, and the United States. The drugs were given to spiders, mice, rats, cats, dogs, rabbits, and monkeys. Animal behavior was altered markedly in every study but one, where adrenochrome was used in too small quantities to produce any effect. It was found that there is an impairment in the quality of the webs spun by spiders which are fed adrenochrome, mescaline, and LSD, and that monkeys and other animals were unable to function normally. In 1957 it was reported that extract from schizophrenic urine produced a similar effect in spiders and that schizophrenic bile produced a form of disinterest and indifference in pigeons which has been called catatonia. These and other research trails sometimes impinged on problems seemingly unrelated to schizophrenia yet linked by the biochemical chain. Their main interest was schizophrenia, but their curiosity took them down many highways and byways in the biochemical factory of man. While some scientists came forward to support their work, the professionals in general increased their efforts to keep the research in a

diminutive, unimportant, and silent position.

As soon as Dr. Hoffer and Dr. Osmond had a theory, they began looking for a treatment. They felt there was not another moment to lose. Assuming they were right, they began looking for a treatment aimed at the biochemical process, but one which was safe, easy to administer, and cheap so that it would be available to everyone for as long as it was needed.

Their objective was to stop the harmful chain of reactions, and this could be done in two possible places. The first was between noradrenalin and adrenalin where they could slow down the production of adrenalin by interfering with the conversion process. To convert noradrenalin to adrenalin, the body must attach a methyl group—a carbon atom with three hydrogen atoms attached to it —to the nitrogen group on the side chain. But if methyl groups were used up before this happened, the production of adrenalin would be reduced and therefore so would its conversion to adrenochrome.

Very few substances were known to do this, and of these few, nicotinic acid and nicotinamide, both B vitamins, were best known. Each molecule in these vitamins can bind one methyl group, keeping it from attaching itself to anything else. Enough nicotinic acid could theoretically have an appreciable effect on the total production of adrenalin and therefore on adrenochrome.

Both nicotinic acid and nicotinamide are forms of vitamin B3. Nicotinamide is the amide form of nicotinic acid. To prevent confusion with nicotine, a toxic substance in tobacco, the vitamins were also given the names niacin and niacinamide.

In January, 1952, Dr. Osmond tried niacinamide on a young, very acute schizophrenic, giving him what he and Dr. Hoffer hoped was a large enough dose to deplete the methylating systems and a small enough dose not to be toxic. They tried him for three days on 500 milligrams a day and wondered why this did not have any special effect on him. They decided to pursue this idea further. Even if nicotinic acid and the amide were not acting as methyl acceptors, they speculated, there were other reasons for supposing they might be useful. (The evidence the vitamin does interfere with production of adrenalin from noradrenalin is very slight and they now consider this a minor activity of the nicotinic acid molecule.)

Nicotinic acid is a component of the pyridine nucleotides and is required by all living cells. Coenzyme one, or diphosphopyridine nucleotide (DPN), has been known since 1960 as nicotinamide adenine dinucleotide (NAD). Coenzyme one is synthesized in the body from niacin or niacinamide which cannot function in the body except as a precursor of NAD. In other words, the role of these vitamins is to allow the formation of NAD, an important component and essential link in the respiratory chain of enzymes.

The cells of the body have to take food, combine it with oxygen, and give off carbon dioxide and water. In doing this, the energy present in the molecule is converted into useful work, either for keeping the body warm or for movement and activity.

Dr. Hoffer explains the system by comparing it to a lump of coal which gives off heat when it burns in the furnace, giving back the energy that was put into that coal by the sun.

"You can't burn something in the body because you would destroy the tissues. So you have to take the energy off in small little chunks, so it doesn't burn itself up. The respiratory enzyme system is a system of perhaps two or three dozen enzymes, chemicals which are involved in a long chain like a bucket brigade-where you pass your bucket of water to the next man and he gets it up the hill. Thus each enzyme has a small role and as the products are degraded a little package of energy comes off. This is called a respiratory enzyme system, and NAD is one of its most important components."

At the first meeting of the Saskatchewan Committee on Schizophrenia Research, in 1952, Professor V. Woodford reminded Dr. Hoffer and Dr. Osmond-that if adrenochrome was really formed in the body, it could interfere with the flow of energy down the respiratory chain. It would follow that to restore normality, large quantities of a substance capable of producing NAD would be needed to compensate to some degree for any deficiency in NAD activity. Nicotinic acid and nicotinamide had this capacity.

Finally, nicotinic acid had other desirable qualities as a chemotherapeutic agent. It could be given by mouth, it was safer than nearly every chemical used for treatment in medicine, it had been studied in animals and man since 1935, and it had been used in doses of up to 1 gram a day for senile confusronal conditions, for pellagra, and for bromide psychosis.

Pellagra psychosis is so similar to schizophrenia that it is often impossible to distinguish between the two. It was not until vitamin B3 was added to bread in 1942 that it was virtually eliminated in parts of the United States. Both nicotinic acid and the amide prevent pellagra and as vitamins are used interchangeably in the body. They were used to treat this disease for a few years after they were proven to be antipellagra vitamins. To prevent pellagra, less than 100 milligrams per day is required. However, if pellagra has been present for a long time and has been very severe much higher doses are required.

Very often concepts in medicine which are well established blind doctors to other possibilities. Although it took 40 years to establish firmly the concept that vitamins were necessary to treat and to prevent certain deficiency diseases, once established it seemed ludicrous arid scientifically wrong to doctors to use doses which were higher than those required to treat or prevent deficiency. Vitamins were also very expensive at first so there was some economic justification for this view.

Although Dr. Hoffer and Dr. Osmond did not know it at the time, Dr. W. Kaufman (1943, 1949) had made the first breakthrough in this dosage constraint. In 1939 he began to use doses of nicotinamide which were much higher than required to treat pellagra/ and by 1949 he was using 4 to 5 grams a day for the treatment of certain forms of arthritis. Kaufman's publications did not stir much interest because the concept of using more than vitamin doses was unacceptable, especially for diseases known not to be due to a deficiency of the vitamin. In addition the steroid hormones were announced about that time as wonder drugs and have since been firmly linked to arthritis in fancy if not in fact. Dr. Kaufman had committed the crime of introducing two new concepts which were unacceptable. He not only recommended a very high or megavitamin dose, but also used it for arthritis, a condition "known" to be unrelated to pellagra.

The next breech in the maximum dose range came from Dr. Hoffer's and Dr. Osmond's work with schizophrenia. The vitamin B3 was soon joined in the treatment plan by another vitamin.

A second place where the psychiatrists could alter the chain of reactions was between adrenalin and adrenochrome. This process occurs by oxidation and therefore an appropriate substance could cut down the amount of adrenalin which could be converted into adrenochrome. Since large quantities would be needed their attention was drawn to vitamin C which is known chemically as ascorbic acid. They knew they could safely use up to 10 grams of vitamin C a day, and this became the second vitamin they intended to study.

Two weeks after the failure of their first treatment experiment, they decided that if nicotinic acid was to be used at all it must be given in massive doses of at least 5 grams a day. Confident that it was a very safe therapeutic tool and that there was no danger even up to 10 or 15 grams a day if indicated, they waited for their first opportunity. It came shortly after.

H. M. came to the Weyburn hospital the usual way, by ambulance, via the Munroe Wing in Regina.

The Wing, a 39-bed ward, admitted patients likely to respond to short-term therapy and therefore with a fairly good prognosis and a high natural remission rate. The Weyburn hospital drew the more disturbed and chronic patients with a poorer prognosis and a lower natural improvement rate. Thus the Munroe Wing often acted as the gateway to the Weyburn hospital.

H. M. was admitted to the Wing late in 1951 for a peculiar organic psychosis. He had been given a careful evaluation which included neurological examinations, air studies for lesions of the brain, and an electroencephalogram. It was concluded that he was suffering from an unusual form of early senility known as Alzheimer's Disease. This was and is considered to be an irreversible brain change, and so he was committed to Weyburn to become another statistic in the growing list of chronic patients.

On February 10, 1952, H. M. was standing naked in a small room off a main corridor. He had been very talkative about his delusions and bizarre ideas, and objects about him looked different and rather strange. He was heavily sedated with the rather ineffective drugs available then, but he had oscillated between being stuporous and confused, and overly active and restless. This day he suddenly attacked a psychiatric nurse who was walking by. This led to a review of his diagnosis, and it was concluded by the hospital staff that he suffered from catatonic schizophrenia, a severe form of the disease.

Four days later he was given 1 gram of nicotinamide a day. Two days later he was much improved, and after several weeks of medication he was discharged, well.

A few weeks later, a young farm boy was committed to the hospital with schizophrenia. Tranquilizers were not known in those days, and he was given in turn the only treatments known to have some value. He was first treated with a series of insulin comas, then the best treatment known and still used effectively in a few hospitals. After about 25 comas he was so much worse that this treatment had to be stopped. He was then given a series of ECT, but before these were completed he developed severe Bell's palsy, and these had to be stopped.

He continued to sink into a catatonic stupor and eventually became incapable of feeding himself and lay confined to his bed where he refused to take care of himself. He was unable to talk and unable to use the bathroom. His physical condition deteriorated so much that he was placed on a terminal care list because it was felt he would die, and his family was informed.

That afternoon Dr. Hoffer was in Weyburn for a research meeting, and he and Dr. Osmond were notified that J. B. was apparently dying from his schizophrenia. They decided to give him massive doses of both nicotinic acid and ascorbic acid since there was nothing to lose and perhaps a great deal to gain. Since he was in a coma, he was given 10 grams of nicotinic acid and 5 grams of ascorbic acid by stomach tube in divided doses.

It is not hard to imagine their feelings when, the second day, J. B. was out of the coma and was able to take the medication himself in a glass of water. Two weeks later the boy they thought would die was normal. His Rorschach then showed a certain amount of inner tension, but no more than is often found in adolescents. He remained well, and after four weeks they stopped the medication but kept him in hospital another month as it was expected he would relapse.

At that time his parents came on a routine visit to see him and found him so well they discharged him and took him home. When Dr. Hoffer interviewed him in Saskatoon in 1964, J. B. remembered only vaguely being at Weyburn and had no recollection of what had gone on in the hospital. He is now married, the owner of a prosperous contracting

construction firm, and an active member of his community. He is a past president of a local social club. In December, 1966, he was seen again and found to be normal.

The next case, Mrs. T., presented mixed manic and schizophrenic features during her several admissions to the hospital. She responded temporarily to shock treatment, then slipped back into her psychosis. She felt that everyone was listening to her, that radio broadcasts were being made about her, and began trying to tear up registers and plug pipes. In short, she became a very difficult nursing problem. She was put on 5 grams of vitamin B3 and vitamin C and became a different person. She became quiet, subdued, and sensible, with no paranoid ideas and no overactivity. She was by no means well because she still maintained her delusion, and though she relapsed, she was still better than at the beginning of treatment.

Dr. Osmond noted that it took about 10 days or so for the medication to act. He said this period seemed to be a common factor in other treatments, such as lobotomy, deep insulin and histamine, and ECT. He interpreted this as indicating that there must be a period of time over which the treatment is accumulated before anything happens, which strongly suggests that some toxic factor is being eliminated or dealt with in some other way. He therefore thought it was important to look into a 24-hour treatment. The histamine treatment, for example, lasted only about an hour and ECT only a few seconds, although the latter had certain other effects as well. It was decided they would need studies on the proper dosage of vitamin B3 and vitamin C for schizophrenics to insure that a continuous treatment was maintained. These early cases were encouraging because, as Dr. Osmond put it, an illness that can be influenced for the better by the haphazard methods they were using was clearly likely to respond well to a concerted massive attack with a more effective treatment method. After these preliminary trials, two schizophrenics were treated in Regina. One was a single woman of 45 who had first been struck with schizophrenia at the age of 17. This was marked by a rapid change in her personality together with depression. After three to six months she recovered, but she remained shy and unmarried.

During an office Christmas party in 1950, Miss. L. suddenly became aware that her employer was in love with her and planned to marry her. This disturbed her very much and she felt sorry for his wife. This delusion gradually expanded to include other workers in the office who were making fun of her, talking about her, and condemning her.

In April, 1951, she was admitted to the Wing for treatment for schizophrenia. She was given nine ECT and was so much improved that she was able to return to work.

The following December, at the office party, she became delusional again and was once more admitted, in 1952. On that day she tried twice to kill herself and was immediately started on another series of eight ECT and psychotherapy of a dynamic kind, three hours a week. Again she was improved and again discharged, but her schizophrenia returned so quickly that she was admitted for the third time in April, 1952. This time she was started on 3 grams of nicotinic acid a day. After one month she was well enough to be discharged.

Miss L. was maintained on the vitamin for three months after discharge. She remained well for another month, and then her paranoid delusions returned. Her employer was fed up with her behavior and considered discharging her, but he was persuaded not to. She was again started on nicotinic acid, and her sister promised to supervise her medication.

She continued regularly on her medication until 1956. During this interval a question arose about the effect of nicotinic acid on sugar levels in the blood. A routine sugar-tolerance curve showed her blood sugar was elevated when she drank 100 grams of sugar while

taking nicotinic acid. However, she did not have diabetes and required no treatment. As time went on, her personality changed, she became more outgoing and friendlier, and performed her job as head stenographer of a very large firm more efficiently. She moved into an apartment of her own whereas before she had been dependent on her family. She took nicotinic acid only four years and has remained well thereafter.

Miss. L. was one of the cases of schizophrenics who, it is safe to say, were cured.

The second patient treated in Regina was Mr. P. F., age 39, who was ill at least three months before being admitted to the Munroe Wing early in 1952. He was a veteran who had fought in Europe for four years, had been wounded when caught in a severe shell blast, but had remained normal. After discharge in 1944 he continued to farm in Saskatchewan, married and began to raise a family. He remained normal until 1952 when he slowly became schizophrenic. He developed a paranoid delusion to explain an episode which had occurred in Germany. He and two friends were searching for parachute silk and wandered too close to the German lines. They were discovered and while running back the patient was wounded in one heel, but his two friends were killed.

Late in 1951 P. F. began to brood and worry about this episode. He could not understand why he had not been killed. Later on he concluded that the whole episode had been staged by the Canadian army to test him for some unknown reason. This relieved his anxiety to some degree because he knew his two friends were still alive somewhere.

This version consoled him until he received a copy of his regimental history. There he saw that his two friends were listed as killed in action, and his panic returned until he realized that, if the army could stage the whole event, it did not require much skill to print a special copy of the history for him. The plot, he decided, was merely being developed further.

He was also very paranoid about his wife and his father and believed that they were helping other people in the community conspire against him. He was started on 1 gram of nicotinic acid a day, and 10 days later suddenly left the hospital and returned home. His father reported he seemed better, and he was allowed to remain at home for the weekend. On the following Monday he returned and the nicotinic acid dose was increased to 2 grams a day.

P. F. reported on his return that he had felt impelled to go home because of his certainty that there was a community plot against him which he had to investigate. When Dr. Hoffer asked him whether he had found evidence of such a plot, he sheepishly replied that he had not. Four weeks after admission he was discharged. He was much less certain about his paranoid delusions, and his mind was still a bit foggy.

He continued to take the vitamin, 1 gram a day for three months, and continued his recovery at home. He has remained well, up until the time he was last seen in December, 1966.

It is instructive that in this one case there was no relationship between *stress* and the patient's schizophrenia, for after he recovered he ran into a series of misfortunes for which he was not responsible. There was a succession of crop failures, and his wife became very ill and required surgery. But he was able to cope adequately and did not have a relapse.

Dr. Hoffer, for his files, divides his history into four periods as follows:

"While in the army, P. F. was under great stress but was well. From 1944 until 1950 he was under normal stress and was still well. From 1950 until 1951 he was under stress created by his own paranoid ideas and was schizophrenic. From 1951 until 1966 he remained normal in spite of a strong stress period in 1955, and during the normal stress period from then until 1966."

These cases were included in the first treatment trials with nicotinic acid. At the second meeting of the Saskatchewan

Committee on Schizophrenia Research, June 30, 1952, Dr. Osmond reported that he had given nicotinic acid as a pilot trial to six schizophrenics. Present at the meeting were Professor C. MacArthur, professor of biochemistry, Professor D. E. Hutcheon, professor of pharmacology, and Professor V. Woodford, department of biochemistry, all of the University of Saskatchewan, Dr. John Lucy, and Dr. Hoffer. Five of his patients, Dr. Osmond reported, recovered and were discharged and one was improved. Out of the total of eight schizophrenics treated with massive doses of nicotinic acid, the response was rapid and enduring in seven, and these were discharged. The eighth patient was better, but not well enough to be discharged.

This pilot study convinced the two research psychiatrists that, first of all, nicotinic acid in doses of 3 to 10 grams a day was safe when given up to several months. They have since found that it is just as safe given over 12 years. Between the years 1952 to 1968 Dr. Hoffer had given vitamin B3 to 1,000 patients. Less than 5 percent had to stop for side effects which were unpleasant, but not dangerous. This makes it one of the safest medications known.

Secondly they found that nicotinic acid can be safely combined with every other psychiatric therapy and in fact worked better when this was done. Finally, they learned that patients did not object to the nicotinic acid flush as they adapted to it very easily.

Dr. Hoffer and Dr. Osmond can still recall their great interest and excitement over these early reports and were a little surprised to find that none of the other psychiatrists, either in the Weyburn hospital or in the Munroe Wing, were particularly interested. On the contrary, psychiatrists with many years of experience believed that other factors were responsible for schizophrenia, even though every other treatment had failed. They could not really accept the novel concept that massive doses of nicotinic acid could help a condition which they "knew" was not caused by a deficiency of nicotinic acid.

Physicians who came fresh into psychiatry were caught up in the so-called dynamic psychiatry of the 1950's—a wonderful name, Dr. Hoffer remarked, for a half-baked form of psychoanalysis —and became intensely angry even to think that a drug which was not a drug like barbiturates could do what they had not been able to do with dynamic psychotherapy. So the battle lines were drawn and still rage.

After the pilot studies, they began a series of double-blind controlled studies, the first group in psychiatry to do so. Supporting them, in addition to their early successes, were their findings that niacin stops many of the LSD psychological changes in subjects and rapidly reverses the EEC changes induced by adrenochrome in epileptics. At the same time, a study was already underway at the hospitals at Weyburn and North Battleford to test yeast nucleotides as a therapy for schizophrenia.

Nucleotides are a body-building substance, like proteins and carbohydrates. Seguin discovered that the cerebral spinal fluid in schizophrenics was higher in nucleoprotein content than that of normals. He was aware of the Swedish work that there was some defect in nucleoprotein metabolism in schizophrenics.

The Department of Health and Welfare in Ottawa became interested in seeing whether nucleoproteins have any real value, and Dr. Roberts invited the Saskatchewan Psychiatric Research unit to undertake this trial because no other hospital in Canada was interested. It was agreed to test 80 acute schizophrenics in the North Battleford hospital, 80 acute schizophrenics at the Weyburn hospital, and 40 chronic schizophrenics at Weyburn. Yeast nucleotides were to be tested as a treatment, using other groups of schizophrenics as controls. This became the first double-blind experiment in the history of psychiatry in which the treatment given was coded so that neither patient nor therapist knew what

the patient was getting.

Since very few well-controlled clinical trials had ever been undertaken by mental hospitals, the research group felt that this series of clinical trials would serve as a model for others to follow. The patients were chosen only after thorough physiological and psychological examinations, and at this point the question arose of a method of assessment for the chronic population which was rapid, easily reproducible, and statistically valid from psychiatrist to psychiatrist.

The Weyburn chronic project was completed April 30, 1953, and the third assessment made by Dr. Lucy, Dr. Osmond, and Dr. Smythies. The clinical impression was that there was no improvement. Dr. J. Handforth, director of research in the North Battleford hospital, reported that 22 percent of the 40 patients were improved and *V* percent were discharged, an improvement which is about what one would expect with a similar group of schizophrenics who had been given placebo. For this reason the North Battleford project was discontinued, with the approval of Ottawa, and the acute schizophrenic study in Weyburn was not begun.

As a result of this project, the Weyburn group, notably their psychologist, Ben Stefaniuk, had developed a new assessment form for evaluation of chronic schizophrenia.

If Dr. Hoffer were to do the research over again he would not choose the double-blind technique.

"I favor the comparison method," he says today, "the kind used by Sir James Lind and many of the other early physicians. With the kind of controlled experiment where the control group is supposed to be more or less comparable to the group receiving the new treatment, it is hoped that other variables are equally influential on both groups. Doctors, nurses, and patients are not supposed to know which patients are getting the new and which the standard treatment, or none. This is supposed to eliminate the effect of patient's expectations and observer bias. However, it has so many hidden errors that it is extremely doubtful it can be helpful, even when run completely blind. Most double-blind studies are in a way fictitious since the treatment code is usually broken by alert nurses and doctors.

"Contrary to the opinion of many psychologists, psychiatrists, and mathematicians, not every disease requires a concurrent control group. If it is found that the natural remission or cure rate has been constant for a long time and that nonspecific factors such as psychotherapy, hospital treatment, and sedatives play little role, one can logically assume that the same recovery rate will operate on the group of patients receiving the new treatment.

"There is a general bizarre idea in psychiatry that simply operating a research trial will suddenly mobilize a host of factors which suddenly produce cures, even though a determined attempt to take advantage of exactly the same factors yields only the expected recovery rate. Chance is given the status of a new therapeutic variable and is invoked at every opportunity to explain results one finds unacceptable. But in 1952 we were not aware of the inherent defects in the double blind."

Dr. Hoffer's and Dr. Osmond's chief objective was to find convincing mathematical proof, in the most objective way possible, that nicotinic acid was or was not useful as a treatment for schizophrenia. They believed the double blind to be a good method.

At the same time, the statistical method is required by governments and societies in preventive health programs. It seems important to know that from one million people a certain proportion are ill. But governments, insurance companies, and others are less interested in whether a particular John Doe will or will not respond to a treatment, while a physician is interested in a particular patient and much less in knowing that 60 percent of a group of patients do well.

Research physicians and professors take the numerical point of view. This is

often the basis for conflict between researcher and clinician. Today researchers tend to believe that the only valid controlled experiments are double blind and ignore the large number of factors which negate the double blind. There is still not a single treatment, except for the megavitamin treatment, introduced or perfected in psychiatry as the result of the double blind.

Dr. Hoffer and Dr. Osmond were in the position of being research psychiatrists and also doctors who were interested in their patients as individuals. They naively believed that facts derived from scientific studies would overcome professional resistance and change the complexion of psychiatry for the benefit of the patient. They didn't know how adept some psychiatrists are at sweeping scientific proof under the rug. They didn't know that facts are often feeble weapons against prejudice and belief, and in defense of other psychiatrists it can be said that this is common to most medical discoveries. Furthermore they didn't know that the word "cure" was to become a vile word in psychiatry and does not appear in any of the standard psychiatric dictionaries.

One of the first things they had to do was to find a reliable method of deciding who was schizophrenic and who was not. They tried to do this chemically, by examining blood and urine differences, and psychologically. This was important because they did not want their groups contaminated by non-schizophrenics. One of the things they learned was that schizophrenia is much more prevalent than was previously suspected. Another was that several patients diagnosed neurotic actually had schizophrenic characteristics. On a follow up of the same patients in the same psychiatric center, it was found that 20 percent of those diagnosed neurotic were later re-diagnosed schizophrenic by other doctors. As a rule, 50 percent of the patients diagnosed as having depressions are in 20 years clearly schizophrenic, and the diagnosis is changed accordingly. As a result they had to lay down strict standards of diagnosis.

In schizophrenia, the spontaneous or natural remission rate is roughly about 30 percent. Any treatment, if it is any good, must do better than that. It was hoped the experiments would yield an answer to the question, *do* the vitamins shorten the length of illness, or alleviate suffering even if it does not cure, or yield a higher cure rate than one would expect from the natural recovery rate only? In other words, a group of patients given the treatment must fare better than an untreated group.

Every patient diagnosed schizophrenic by his psychiatrist, on admission to the Munroe Wing, was eligible for the first double-blind study. All patients were given the most up-to-date therapy available, prescribed by their own therapists, except that insulin coma was not used. The treatments included electroconvulsive therapy, barbiturates, and three 50-minute hours of psychotherapy of a dynamic sort a week.

Before a patient was accepted for the study, Dr. Hoffer examined him to make sure he was typically schizophrenic. In the first study only one or two were rejected. They were also given an extensive series of laboratory tests.

The original design called for 30 schizophrenic patients who were to be divided by random choice into three groups. One group was given 1 gram of nicotinic acid three times a day, another was given identical tablets of nicotinamide at the same dose schedule a day, and the third was given placebo, an inert substance like cellulose or sugar which can have no therapeutic effect. The placebo tablets were in the same dose schedule as the vitamins.

The reason for giving the amide was that niacin produces a marked flush which would soon give the code away, whereas the amide produces no such reaction. No one at the hospital, including I. J. Kahan, research social worker, knew that nicotinamide was included, and so it was assumed that all patients who did not flush would be on placebo.

After 33 days of medication, the patients were re-evaluated in the same way as before treatment began. After all 30 patients had been treated, the code was broken and the relationship between treatment and response studied.

It is important to emphasize that, except for the addition of the niacin, the amide, or the placebo, all of the research patients received equal treatment by their own psychiatrists. Those who remained well were not given any medication after discharge. If a patient showed a relapse during the follow-up period, this was brought to the attention of the therapist who placed some of these on nicotinic acid as outpatient treatment. In this case, those patients who relapsed while on placebo were considered a failure for placebo, but if they improved on nicotinic acid, they were considered a success for nicotinic acid.

Before the code was broken, it was reported by their own doctors that only four of the 10 placebo patients were improved on discharge. Thus, 40 percent of the placebo patients were improved by standard therapy plus placebo. Since this is not much better than the natural recovery rate, it was obvious that standard therapy in 1952 did no better than one would expect from no treatment whatever.

The 40 percent improvement rate showed that the 30 patients tested did not have a better chance of getting well than any other schizophrenic patients. On first treatment they did less well than one would have expected.

Dr. M. Pritchard (1967) on the basis of a comparison of outcome between 1948 and 1956, concluded "the introduction of pharmacotherapy, although producing an improvement in short-term outcome, has had no effect on the longer term prognosis." Vitamin B3 was not used. The readmission rate of the 1956 group treated with tranquilizers was higher than the 1952 group in the Saskatchewan study.

The improvement rates of the nicotinic acid and amide patients were identical.

The fact that both are forms of the same vitamin immediately ruled out the flush itself as a factor. Out of 11 schizophrenics given nicotinamide, nine were improved, and out of nine given nicotinic acid, eight were improved.

Since the division into three groups was by random chance, 11 were placed into a nicotinamide group. In the same way, a coin tossed 20 times may frequently come up 11 heads and nine tails. In other words, 17 out of 20 vitamin B3 patients were improved, a rate of 85 percent. This is much higher than the control recovery rate and couldn't have happened by chance (see Table 1).

TABLE 1

		Number Improved at Months Shown				
Treatment	**Number**	**3**	**6**	**9**	**12**	**15**
Placebo	**10**	**4**	**3**	**3**	**3**	**3**
Nicotinamide	**11**	**9**	**9**	**9**	**9**	**7**
Nicotinic Acid	**9**	**8'**	**8:**	**8**	**7**	**7**

Since the argument of chance was a favorite one of opposing psychiatrists, this was checked out. An analysis of these differences, by statistical techniques, showed that the probability this could be due to chance is less than one in a 100. After this study it was decided to follow up the patients, because discharge evaluations are often unreliable. Then, too, in schizophrenia, there is a high relapse rate. So Mr. Kahan was given the job of seeing these patients at intervals of 3, 6, 9,12,15, and 18 months. They were evaluated with respect to their work record, their relationship to their families, and the presence of schizophrenic symptoms.

Few psychiatrists, even today, know what is going on inside the schizophrenic patient. Mr. Kahan was soon to find out a great deal of these patients' problems through his study.

"There was no problem getting schizophrenics to cooperate," he recalls. "If you ask them, 'Do you hear voices?' they will tell you whether they do or not. Few psychiatrists ask them about their

visual or auditory disturbances and I believe there is a reason for this.

"The reason is that if the psychiatrist wishes to follow a treatment program which he likes, he must give the diagnosis appropriate to the treatment, rather than the other way around. It is possible psychiatrists do not want to hear about voices and visions since this would force them to diagnose schizophrenia, and once this diagnosis is made they immediately assume that nothing more can be done for the patient. This is the cult of incurability which has psychiatric and allied professions in its grip. Since psychiatrists are moral men, and want to give psychotherapy, they prefer not to know that the patient really has schizophrenia. This is why they are afraid to ask the proper questions."

As an example of this, in 1952 a Dr. M. in the Munroe Wing gave a woman patient psychotherapy for three months with no response, but he was determined. Dr. Hoffer then spoke to the patient and discovered that she was disturbed by what her sister, sitting on the wall of her room, was telling her. Her sister, even if she could sit on a wall, was in Edmonton. When he told the doctor that his patient heard voices coming from visions, he was shocked. The next day he committed the woman to the Weyburn hospital.

"We believed that schizophrenics, like anyone else, will cooperate when given a good reason," Mr. Kahan explained. "We explained, to begin with, that they were on a treatment research program and that their cooperation would be very valuable to themselves, other patients, and the research team. I believe, also, that they appreciated the kind of objective interest we were showing in them."

The follow-up study was a difficult job because there were no examples for this type of study. It seemed at that time that no one considered such a study either feasible or warranted. Therefore, to meet the special needs of their study they were on their own.

"We had to start by realizing that what we wanted was a measure of improvement," says Mr. Kahan. "The measurement had to be accurate, sensitive, and simple, and had to be short enough so that it did not take up much time. It was decided to set up brief questionnaires together with rating scales. The questionnaires were to tell us only what we needed to know regarding the treatment; we were not interested in the personal lives of our patients except for what we needed specifically to answer the questions on our study. We were not interested in going into the sociological, psychological, or Freudian concepts of the patients' intimate lives."

To determine whether the patient was better, the group devised a questionnaire to include four areas — personal health, work adjustments, relationship with family and friends, and social participation .

The questionnaires could be completed by interview or, when this was not feasible, by mail. A low score indicated difficulty in adjustment and the necessity for outpatient treatment or further hospitalization.

Saskatchewan has many widely separated communities. Some of the patients were as far as 200 miles from the Wing and often were isolated in winter when roads became impassable. It surprised the group, and it surprised most people as well, to find that the mailed questionnaires were quite effective and the percentage of replies was extremely high — well over 90 percent.

"We found the questionnaires and rating scales to be accurate and sensitive instruments," said Mr. Kahan. "Generally, we could predict with considerable accuracy when a patient required re-hospitalization. Only one patient who had a very low score did not require hospitalization. He was a farmer and trapper in an isolated area and often did not see his neighbors for several months. He was very uneasy in the city and very uneasy with people whom he saw as wandering animals. The houses in the city looked like herds of cattle to him. He was able to stay out of hospital because he could hallucinate quite freely in his

isolated state. He only sought help when his illness became intolerable to him, and he then became very anxious and frightened. When this happened, he would find the city and the people the lesser of the evils, and he would ask for help. Thus, although his rating showed less than 18, he was able to stay out of hospital.

"I think that the success we had with the questionnaires was due to their brevity and directness. The long interview can be detrimental, especially to schizophrenics, and as a result patients may resist answering many questions and give the wrong information. Because the questionnaires were brief and simple, patients had no trouble completing them and did not regard them as burdensome. It is well known that schizophrenics find interviews and communication with others difficult, and the briefer and the more direct the interview, the easier it is to cope with them. For some, the mailed questionnaire was a way of giving information without having to deal with a much-feared interview."

Another feature of the short questionnaire was that it reduced the chance of the group being accused of contaminating the study (they were later accused of it anyway).

Long and frequent interviews establish a relationship—which may be a good or a bad one—but which nevertheless may be considered by some people to be a part of the treatment because attention and interest is shown in the patient.

"Our patients seemed to like coming to see us, and many came to me for help in finding a job, or in smoothing relations with their employers. I did not do social case work, but where an explanation was in order to an employer, or where a job was required by the patient, I did what I could to help," Mr. Kahan said. "If a patient wanted to come in just to chat, that was fine with me. I sometimes had to encourage them to stay on their prescribed medication, which was understandable. Schizophrenia is an all-encompassing illness. It attacks the human being where he is most vulnerable, and without encouragement and support of the right kind, he is often completely helpless. It was important to the study that patients cooperate fully by taking the medication regularly, whether it was the vitamin or the placebo."

After 15 months, 14 of the B3 patients out of 20 were improved compared with three out of 10 placebo patients. This was determined from the information received from the questionnaires, combined with other factors such as the number of readmissions, the time spent in hospital, the number of suicides, and so on.

Patients rated improved were by normal psychiatric criteria nearly normal. Patients **rated unimproved were** ill and ready for readmission to hospital, or already in hospital when evaluated.

One of the placebo patients was so ill on discharge that he was started on nicotinic acid and recovered within three months. Thereafter he remained improved. Another placebo patient, unimproved at 12 months, was started on nicotinic acid, and by the 15-month period was improved. These two were not counted in the follow up since their severe illness required a change of procedure. Not one of the 10 on placebo improved spontaneously after discharge.

At the end of the 15-month period, no follow up was available on four of the 11 patients on nicotinamide. The other seven remained improved. At the same period, no follow up was available on one of the nine nicotinic acid patients. Seven remained improved.

Another study compared patients who were treated with nicotinic acid and sedatives with patients treated with nicotinic acid, ECT, and sedatives. One of the advantages of this simple comparison experiment was that it allowed an analysis of the combination of nicotinic acid with other treatments:

In 1952, ECT was much more effective than sedatives or psychotherapy and was considered by many to be the treatment of choice. Dr. Hoffer and Dr. Osmond observed very early that nicotinic acid did not interfere with ECT and very

greatly decreased the confusion and memory loss so often found as a transient but disturbing consequence of ECT.

Seventeen schizophrenic patients were given nicotinic acid only, plus other treatments, while 12 were given ECT, nicotinic acid, plus other treatments. The ECT. was given, or not given, according to instructions by the patient's therapist who was not a member of the research staff. These patients as a rule did not get nicotinic acid in the community. Now Dr. Hoffer insists that his patients stay on nicotinic acid for at least five years.

At 15 months, six of the nicotinic acid patients were improved, compared with three of the nicotinic acid plus ECT patients (Table 2).

TABLE 2

Treatment	Number	Response to Treatment, Improved			
		Discharge	3 Months	9 Months	15 Months
Nicotinic Acid	17	16	14	13	6
Percent of group followed who were improved					
	94		82	93	100
Nicotinic acid and ECT	12	8	7	5	3
Percent followed					
		67	58	83	100
Total on NAC	29	24	21	18	9
Percent followed					
		82	72	90	100

The results suggest that the patients given nicotinic acid plus ECT did not do as well as those taking nicotinic acid alone. But since only the most seriously ill schizophrenics were given ECT at this hospital, one could, conclude that the group given ECT would not have responded quickly enough to nicotinic acid alone.

The reaction of the Munroe Wing staff, when they first heard of the results of the double-blind study, was comparable to the effect of someone stamping his foot in a water puddle and splashing everyone around him.

In planning for the first double-blind study, the research group had several meetings of all the psychiatric staff.

"I remember one meeting," said Dr. Hoffer, "when I presented to the staff the plan I was going to follow. This was in the fall of 1952.

"At the first meeting all the staff felt that they had to advise me on how to do the research although none of them had had any research experience. I got annoyed and told them I wasn't asking for their advice but was only telling them how we were going to do it. Then the studies got started and many of the staff were very disturbed to think a specific chemical might work. After the first double blind was evaluated, a clinical research conference was held where a report of the findings was given to the psychiatric and nursing staff. For the first time they were told about the nicotinamide control comparison group. This is what we call the hidden control. They thought there were just two groups and that everyone who flushed would be a nicotinic acid patient, and everyone who didn't would be placebo when in fact half of the non-flushers were getting nicotinamide.

"Their reaction was unexpected. We expected, rather naively, that there would be great interest which would be followed up by either further testing or by a general use of this simple, apparently effective therapy. But instead there was a series of critical questions aimed, not at eliciting information, but at demonstrating that it could not have been the megavitamin therapy. All the clichés of psychiatry were invoked, including our personalities (but they were not our patients), the great god

Chance, to account for any unacceptable response.

"A senior psychiatrist, trained in the vague holism of Adolf Meyer that everything in the history of the patient is important to the illness, but who nevertheless was friendly to the research, remarked that if the results were true we would get the Nobel prize. I did not understand the meaning of that remark at that time, but I do now. It was a very unfortunate statement because it established a philosophy that only recognition by the Nobel committee would establish nicotinic acid therapy. Since the odds one can win a Nobel prize are very slim indeed, it practically doomed general acceptance of the nicotinic acid therapy in this hospital."

Once the research headquarters moved to University Hospital in Saskatoon, nicotinic acid therapy was discontinued in the Regina psychiatric center which relies heavily on tranquilizers and social workers. With the advent of community psychiatry, a new technique has been added—very ill patients are refused admittance because, they are told, they are not sick.

Another study started in 1952 was a 10-year follow-up study. The study included 16 schizophrenics who were given 3 grams of nicotinic acid a day for at least 33 days, as well as standard treatments. The rest of the schizophrenics admitted in 1952 had not been given nicotinic acid. To enlarge the control comparison group, the research included all schizophrenics treated at the same hospital in the first six months of 1953 without nicotinic acid. A comparison of the two groups is shown in Table 3.

TABLE 3

Treatment	Number	Mean Age	Female	Number Hospital	Mean Days in Acute	Number ECT	Number on
Nicotinic Acid	16	32.4	8	82	8	7	
Other treatment	27	32.0	19	54	14	11	

The two groups were comparable with respect to mean age, number of females, proportion from each group receiving ECT, and proportion from each group who were acute. The nicotinic acid group were treated in hospital longer, but this is understandable.

The two groups were not all involved in the double-blind study and so were not assigned to the groups by random choice. There was a powerful bias exerted by the staff against the vitamin, and in a proportion of cases patients who were considered good candidates for psychotherapy were not allowed to receive nicotinic acid. This may explain why a large proportion of the other group were female. The psychiatrists at this time were all male, and it has been shown that male psychiatrists are more apt to give female schizophrenics psychotherapy. The nicotinic acid group were sicker and had failed previous therapy.

Eight from this group had been admitted previously once, for a mean of 700 days in hospital. When one of the group who had been in a mental hospital 14 years is excluded, the mean for the remaining seven decreased to 82 days. From the comparison group of 27, five had had altogether seven admissions for a mean of 54 days.

The nicotinic acid group averaged 82 days each because one young catatonic schizophrenic was so interesting to her psychiatrist he kept her in 365 days. Over a period of five years, no other patients stayed so long on this ward.

Ten years later the admission and discharge data for all of these patients was collected up to January 31, 1963. Since 1952, the psychiatric units in the province kept the research group informed on all admissions and discharges of all research patients.

The number of patients in hospital each year from 1953 to 1962 can be seen in Table 4. The differences in these two groups cannot be accounted for by the possibility that in some way the nicotinic acid group had a better prognosis. Even today there is no reliable way of selecting patients who will do well or not, *so* it is hardly likely that this could be done in 1952. The one chronic schizophrenic in the study was in fact in the nicotinic group, and the nicotinic acid patients were, if anything, sicker than those who did not get this treatment. Since psychiatrists wanted to treat their patients with psychotherapy, they kept the better patients for themselves.

TABLE 4

Number of Patients in Hospital Each Year 1953 to 1962

Group	N	1953	1954	1955	1956	1957	1958	1959	1960	1961	1962
Nicotinic acid group	16	1	1	0	0	1	0	0	0	0	0
Comparison group	27	10	9	11	9	8	7	6	5	3	4

Even if faith were as important to the recovery of the nicotinic acid patients as some professionals have suggested, it could have played little part in this study. Most of the psychiatrists involved had no faith whatever in nicotinic acid because they did not believe that biochemical factors played any part in schizophrenia.

One of the doctors who was directly involved in this particular study had some faith in it, but that was not very strong. In any case, Dr. Hoffer and Dr. Osmond only treated four of the nicotinic acid group. The other 12 were treated by psychiatrists who were indifferent, skeptical, or openly hostile to the whole idea. Indeed on several occasions a quick response to the vitamin resulted in a change of diagnosis.

The case of Don F. is an example of this diagnostic switch. Dr. R. had convinced him that he had a personality disorder. Later Dr. Hoffer told him that he had schizophrenia.

During the spring of 1952, when he was only 20, Mr. F. became quite depressed and irritable and began to avoid his friends and neglect his work on the farm. He became very angry with his father several times a day, but did not argue with him.

On July 24, 1952, he was referred to an outpatient mental health clinic and placed on the waiting list of the Munroe Wing. Meanwhile he decided to end it all and tried to kill himself by carbon monoxide poisoning. He was admitted to the Wing on September 9, 1952. There were no perceptual changes, but he had thought disorder, inappropriate hostility, overall anxiety, and was deeply depressed. His psychiatrist diagnosed him as being schizophrenic, paranoid form, and referred him to the first double-blind study. Mr. F. was given 3 grams of nicotinic acid a day and deep psychotherapy. Three weeks later he was so much improved that Dr. R. re-diagnosed him as an anxiety neurosis. Dr. R. could not believe that a schizophrenic could recover so quickly and therefore assumed that his original diagnosis was wrong.

As a result of the change in diagnosis, Mr. F. was taken off nicotinic acid and given outpatient psychotherapy. He remained well until October, 1953, a month after he began his university studies. His anxiety slowly began to return and by the end of the year he was again very ill. For much of the time during November and December he was

mentally confused. In January, 1954, he saw his family physician who treated him in a general hospital for two weeks. But as his paranoia became more severe and aggressive, he was readmitted to the Munroe Wing in February, 1954, again clearly psychotic, with well-marked changes in perception, affect, and thought.

Mr. F. was started on nicotinic acid, 6 grams a day, and given five ECT. He was discharged much improved. On May 13, 1954, he reported that he was well and that he had had only a few bad spells. However, he did not wish to continue taking the niacin. He had had too many psychiatrists who had given conflicting diagnoses, and therefore would not cooperate with the treatment. To illustrate how deep his resentment was, a few years after he was married his wife discovered several bottles of nicotinic acid which were still unopened. When she asked him what they, were he refused to answer and threw them all down a gopher hole on his farm.

In a discussion of these studies, Dr. Hoffer pointed out that seven of the patients on the 10-year study receiving nicotinic acid also had ECT during their admission (Table 3). These seven had five of the six readmissions during the 10-year follow-up with a mean of 49 days per admission, while there was one re-admission for 59 days from the nine who had nicotinic acid only.

"This might suggest that ECT did not help and might have harmed patients," he said, "but this is not so. We believe that the patients who needed ECT were sicker than those who did not get it, and this may account for their readmissions later. ECT was used for those patients who were very aggressive, excited, paranoid, or depressed. Many of them would probably have refused their medicine without this additional treatment, and tranquilizers were not in general use in 1952. We also have data which show that a large proportion of schizophrenics will not respond to the megavitamin therapy alone and therefore require the addition of ECT. We still consider that ECT has a place in treating schizophrenics, combined of course with nicotinic acid.

"One of the disadvantages of niacin, and this is inherent in all medication, is that control of the schizophrenic process occurs gradually and slowly. Thus, with certain agitated and disturbed patients, it should be combined with a more quick-acting treatment to permit it some time to exert control. It is most useful in the early stages of schizophrenia, is effective in adolescent schizophrenia, and is indicated ' for pseudoneurotic schizophrenia."

III. SECOND AND THIRD DOUBLE-BLIND STUDIES

The results of the first double-blind were so encouraging that the research group designed a second and larger one to process 120 patients.

Once the barriers were broken, discoveries poured out in a flood. Trying to follow the research trails was like trying to watch a 10- or 12-ring circus. It soon became apparent that nicotinic acid is an amazing vitamin and may well prove to be the most important therapeutic agent known to man.

One day, in 1954, Dr. Hoffer told his mother, "Here, take these pills. They'll make you younger."

About this time he had begun to believe that nicotinic acid can prevent senility (Hoffer, 1962). The brain, he said, should be able to last longer than any other tissue. William Kaufman (1955) was one of the first to report that nicotinamide in large doses is useful in reversing old age changes.

Dr. Hoffer thought his mother had aged quite rapidly and was tense and anxious, perhaps due to the serious illness of his father. And besides, being an incorrigible researcher, he was happily enlisting his family as guinea pigs.

Shortly after this, Dr. and Mrs. Hoffer and their son, Bill, left for a three-month tour of Europe, visiting research

centers in England, Scotland, France, Italy, Switzerland, Germany, and Denmark, on a Rockefeller Foundation travel grant, In Italy he met Dr. Cerletti, discoverer of electroconvulsive therapy (ECT).

While in Europe, they received a long letter from Dr. Hoffer's mother. It was the first time in nearly a year, she wrote, that she was able to hold a pen to write a letter. The swelling on her hands had gone down, the nodules on the joints of her fingers seemed to be disappearing, the pain was much less, and she was able, to her surprise, to hold cups without dropping them and do dishes and other housework without difficulty. She couldn't understand why she was better, but she was overjoyed as at times the pain had been almost unbearable.

For those doctors who claim niacin is not safe in massive doses and even predict that it will cause liver damage, here was a woman who took it in large doses for over 20 years without damage.

On their return home, Dr. Hoffer drove the 120 miles from Regina to see the remarkable change in his mother for himself. This was his first discovery of the use of nicotinic acid as a treatment for arthritis. He has since prescribed it for other arthritic patients with equally good results.

In August, 1957, after a paper was published on the use of nicotinic acid in schizophrenia, he received a letter from Dr. Kaufman. In 1959 he published a paper which reviewed Dr. Kaufman's work.

When.Dr. Hoffer's first arthritis article appeared in the **Canadian Medical Association Journal** (Hoffer, 1959) the Dean of Medicine at the University of Saskatchewan was severely criticized by rheumatologists from the east for permitting him to publish it. When the Dean spoke to Dr. Hoffer about it, the latter told him it was none of his business and that he would publish whatever he liked.

"Luckily," said Dr. Hoffer, "I did not work for him."

Nicotinic acid as a treatment for arthritis has not been accepted any better than as a treatment for schizophrenia. One of the arguments for "not believing" is that there are many forms of arthritis and therefore niacin cannot be a cure. There are indeed many forms of this condition, but since no one knows what its causes are it is possible, says Dr. Hoffer, that very few basic forms are present. But the vitamin B3 helps the most common forms like rheumatoid arthritis and osteoarthritis if started before irreversible bone changes occur. It does not help gouty arthritis.

Dr. Kaufman reported on his work on 663 patients in 1955. Without exception, he said, those patients who took adequate amounts of niacinamide continuously enjoyed clinically significant and measurable improvement. There were additional benefits, such as an increase in muscle strength and working capacity, a decrease in fatigue, relief from depression, and others. This was not accepted by the medical profession. In the early years, too, Dr. Hoffer and Dr. Osmond found niacin to be effective in terminating delirium tremens in alcoholism—a toxic condition which comes about after a long period of hard, steady drinking. The alcoholic with the DTs has frightening hallucinations, is confused and very ill.

They later learned that about one-third of a very severe group of alcoholics admitted to hospital had the biochemical abnormality which is the basis of schizophrenia and that niacin helped them as well.

Dr. Hoffer and Dr. Osmond knew niacin was therapeutic for schizophrenia but worked best for early cases. They knew that it was therapeutic for epilepsy in that it enables one to cut in half the dosage of sedatives and thus provides adequate control without the drowsiness of sedation. They knew it had some value in the therapy of some biochemical mental defectives, that it prevented and cured sea sickness whether induced by land, air, or sea, and that it reversed most of the LSD phenomena and cured pellagra psychosis. They had found that it reversed the action of adrenochrome

on the EEG, that it cured bleeding gums, and later that it helped relieve pain and symptoms of severe senile osteoarthritis. They did not believe that it was a cure-all, but they did believe that it produced some very dramatic results. Then they learned something which they found very interesting, that it decreased the blood cholesterol of rabbits.

One day when Dr. Hoffer was visiting the late Dr. R. Altschul, professor of anatomy at the University of Saskatchewan in Saskatoon, the latter told him he was doing some work with cholesterol. When he exposed animals to ultraviolet radiation, their blood .cholesterol went down. The fact that it did so with animals didn't prove that it would do the same thing with humans.

Dr. Altschul complained that he could find only one or two doctors who would cooperate by allowing him to give ultraviolet radiation to their patients and this was not enough. So he asked Dr. Hoffer whether he and Dr. Osmond would allow him to work with some of their patients in the mental hospitals.

The mental hospitals were so bad and the patients so neglected, reasoned Dr. Hoffer, that anyone running around the wards doing something must have some benefit to the patients. He knew Dr. Altschul couldn't do them any harm. He invited him to come to Regina and offered to drive him from there to Weyburn to see Dr. Osmond and some of his staff. He was sure they would cooperate.

Meanwhile Dr. Hoffer wrote to Dr. Osmond who replied that he would be very happy to help out in this work. Several weeks later Rudolf Altschul came down by train to Regina. On the way to Weyburn Dr. Hoffer kept telling him about the use of nicotinic acid for treating schizophrenia and the results of the first research. Dr. Altschul in turn kept talking about his work with hardening of the arteries, arteriosclerosis.

He said that he thought that the main problem was that the inner lining of the blood vessels, called intima, was defective in certain people so that it couldn't take the wear and tear of many years of work.

This started Dr. Hoffer thinking about wear and tear and repair. He remembered that many months before he had had a problem with his gums. They were bleeding very badly, and no matter what the dentist did, they kept on bleeding. Dr. Hoffer gave up and decided he would have to put up with it as long as he could and eventually have his teeth taken out.

About this time he was giving his patients large quantities of nicotinic acid and was curious about this vitamin! He decided he would take it himself to see what it was like. He also thought that, if some harm should come to some of his patients, although he was sure it would not, and if by chance he should be sued, he would have a stronger case if he could tell the judge that he himself had been taking it for months or years at the same dose level.

One morning, about two weeks later, he realized with a start that, while brushing his teeth, his toothbrush was clean —not a drop of blood on it. A few days later he went to see the dentist who examined his gums very carefully and said, to his surprise, that they had all healed.

While talking to Dr. Altschul, it occurred to Dr. Hoffer that the reason the gums had started bleeding was that the rate of repair of the gum tissues was not keeping up with the rate of destruction. He had what is called malocclusion—where the teeth don't hit evenly and so, every time he bit down, he tore the ligaments along the side. As long as the tissues were repairing themselves rapidly they didn't bleed. It seemed logical, therefore, to believe that the nicotinic acid had increased the rate of repair of the gum tissues, stopping the bleeding.

Dr. Hoffer told Dr. Altschul that if. it's just a matter of the intima being in a good state of repair, then nicotinic acid might be worth considering, and asked if he would like to try it out on the rabbit experiments to see if it would prevent them from getting hardening of the

arteries.

Dr. Altschul agreed to try it, and Dr. Hoffer sent him a pound of nicotinic acid. He didn't hear anymore from him until several months later. One day he phoned in great excitement, and began shouting into the telephone, "It works! It works!"
"What works?" asked Dr. Hoffer.

"The nicotinic acid lowers cholesterol levels!"

Dr. Hoffer hadn't been thinking about that, but Dr. Altschul had, so when he heard about the work with nicotinic acid and knew the vitamin in large doses was safe, he got the idea it might have some effect on cholesterol.

He fed his rabbits baked egg yolk cake to give them high concentrations of cholesterol and then gave them nicotinic acid. He found to his great surprise that the cholesterol levels immediately went down to very normal ranges. He now wanted to try it on people.

Dr. Hoffer went down to see Dr. J. Stephen, the pathologist at the Regina General Hospital. Dr. Hoffer was his consultant in biochemistry. Dr. Hoffer told him the whole story and said, "Let's try it out on some cases in the wards. Do you think you can Help me?"

"Luckily for us," says Dr. Hoffer today, "the Regina General Hospital was so disorganized that most doctors didn't know what was happening to their patients. So within two days Dr. Stephen was able to find 70 patients on whom he did cholesterol levels. We put these patients on nicotinic acid and measured the levels again. This was a very fast study. The results were very exciting because the human cholesterol levels went down very fast, within 24 hours. I sent the data to Altschul and we published our first paper in the **Archives of Biochemistry and Biophysics** early in 1955 (Altschul et al., 1955), where we made our first claim that nicotinic acid lowered cholesterol levels. We had also found by this time that nicotinamide did not. This was the first idea that led to the general use of nicotinic acid in preventing hardening of the arteries and preventing coronary disease."

In 1968 it was reported that Dr. Edwin Boyle and his colleagues at the Miami Heart Institute had used niacin on about 1,000 cases of elevated blood fats and cholesterol, all of them coronary patients. Of 160 whom Dr. Boyle kept on niacin and under special observation during a 10-year period, only six died against a statistical expectation of 62 with conventional after-care.

How can one explain the ability of nicotinic acid to help the human being in so many ways?

"I favor the hypothesis that niacin restores normal permeability of the cell membranes and restores to normal aerobic respiration in the body cells. This hypothesis explains every action it has in the body in cholesterol, pellagra, schizophrenia, and all the rest," Dr. Hoffer said. "In my opinion Dr. Altschul has contributed more toward the study of arteriosclerosis than any other person. We felt honored to have him as a respected colleague, distinguished critic and collaborator. He also assisted us in our toxicity studies of schizophrenic blood serum. This, together with his studies on cholesterol, our own studies on arthritis, retardation, and alcoholism, and our chemical investigations, went on simultaneously with our larger treatment studies on schizophrenia."

The larger research double blind was begun in 1953. The results of the first study were convincing as far as one can be convinced with a small series of cases. But with a disease as variable as schizophrenia, larger studies are preferable. The finding that megavitamin B3 improved the cure rate so much was sufficiently important for a second and more detailed study. The first half of the second double blind was completed at the Munroe Wing, and when the headquarters of the research moved to University Hospital in Saskatoon, the project was continued there.

The group planned to test 120 subjects and so called it the 120 study. However, it became more and more difficult to obtain schizophrenic patients at University

Hospital, and as a result it was terminated when 82 had been treated. The study ended December, 1958, after it had been operating for six years. This is probably the longest serial double-blind study ever conducted in psychiatry.

Simple studies, Dr. Hoffer explained, are more accurate than complicated ones. Since both nicotinic acid and nicotinamide seemed equally effective, they ran this study using only nicotinic acid and placebo.

If the results corroborated those of the first double blind, one could assume that nicotinamide would have produced the same results as before. The only reason for selecting nicotinic acid was that it cost less, and with small research budgets this was an important consideration. They supplied the patients with the medication for several years.

The design of the second study was similar to the one used in the first. Patients were diagnosed first by their own psychiatrists who then referred them to the study.

"It was rather curious," Dr. Hoffer remarked drily, "that for one of those years schizophrenia suddenly became very scarce. Psychiatrists not associated with research were reluctant to have their patients on the study and began calling them depressions and everything but what they were. To prevent this flight from diagnosis one should run studies simultaneously on schizophrenics and depressions. While there was a dearth one year, however, there was a compensating surplus the next year as the same patients came back re-diagnosed schizophrenic. When the staff changed somewhat, more schizophrenics were again diagnosed schizophrenic.

"All patients referred to us were evaluated for one week, given several psychological and physiological tests, and started on treatment tablets. We simply referred to the nicotinic acid and placebo as treatment tablets."

The clinical staff was not informed that nicotinamide would not be used. They were told the design was exactly the same as in the first study and would thus assume that half the non-flushing patients were on placebo and half on nicotinamide as before.

Once the pretreatment investigation was completed, patients were placed on the treatment decided upon by the psychiatrist in charge, plus placebo or nicotinic acid. The standard treatment included barbiturates and ECT before 1956, and tranquilizers or ECT after 1956. Psychotherapy was also given according to indications peculiar to the therapist.

Patients were kept on medication for 33 days, using 3 grams a day of vitamin B3 or placebo. Other treatment doses were controlled by the doctor in charge. After treatment was completed, the patients were again evaluated for any treatment response.

Since the patients were given either nicotinic acid or placebo by random choice, the two groups should theoretically have been similar. They were, in fact, not too different from one another as shown in Table 5. Both groups had spent nearly the same number of days in hospital and had nearly the same average age. Nearly half the placebo group was given ECT while less than half of the nicotinic acid group was given ECT.

TABLE 5 Comparison of Placebo and Nicotinic Acid Groups

Group	Number	Mean Age	Number Female	N umber Given ECT	N umber Days in Hospital
Placebo	43	32	14	21	74
Nicotinic acid	39	30.3	17	15	72

The researchers measured the results of this study in a variety of ways to make sure the findings were firmly based. If there was a chance they were wrong about their treatment, they wanted to be the first to know it. They measured them first by the patient's condition on discharge. Each patient was evaluated clinically by his therapist and this was recorded. Since the therapist could not know whether nicotinic acid, nicotinamide, or placebo was used, his bias for or against this therapy was minimized.

Therapists provided another measure of recovery by the number of requests they made to decode. If at the end of 33 days the patient was found to be no better, or if he had shown some improvement but not enough, the therapist could ask for the code to be opened. This was done to give the patient a chance to get on nicotinic acid therapy if he had been on placebo.

The number of requests to decode and the ratings after the 33 days of treatment are shown in Table 6.

TABLE 6

Response to Placebo and Nicotinic Acid

Group	Number Improved	Number Not Improved	Request to Decode
Placebo	18	25	18
Nicotinic acid	31	8	1

There were 18 requests to decode in the placebo group. Eighteen of the 43 patients in this group were classed by their therapists as improved and 25 as unimproved. There was only one request to decode in the nicotinic acid group. The difference is highly significant. Of this group of 39 patients, 31 improved and eight did not improve.

"It is clear," said Dr. Hoffer, "that the therapists who knew their own patients gave their best ratings to those who had received nicotinic acid, and they further expressed their conviction by asking, in 18 cases out of 43, whether their patients had received placebo. These results could have occurred by chance in only one out of a thousand similar experiments. Most scientists will accept a 5 percent probability and are delighted with a 1 percent probability that the results could be due to chance."

The second measurement of treatment results was the condition of patients after discharge.

"We were concerned, not only with the improvement of patients on the vitamin while in hospital, but also whether or not patients needed mega-vitamin B3 for maintenance after discharge," said Dr. Hoffer. "There are some diseases which require lifetime medication if the patient is to remain well. Some examples are Addison's disease, diabetes mellitus in young people, and so on. It would be considered malpractice to bring a patient with diabetes into the hospital for a month, control his diet, determine the best dose and form of insulin and other drugs, and then discharge him well but with no follow up on insulin and other treatment. As long as the diabetic patient watches his diet, his program of activity, and his dosage of insulin, he is well and has a normal life expectancy. He can never be considered cured, but can be considered well.

"At the other extreme of serious diseases are acute infections like pneumonia, where antibiotics are given for a few days and can cure a patient. After that no more drugs are needed, and it would be considered a form of malpractice to keep a patient on 1 gram of penicillin a day in order to prevent pneumonia from recurring in 10 years.

"These are two extremes, but they do illustrate the importance of knowing the natural history of the illness in determining how long the medication must be taken.

"Schizophrenia is a disease which covers the entire range from the acute single attack which may last one week and never return, to the illness which never relents and permanently cripples the person. This is well known to any psychiatrist with any experience with schizophrenia, and was well known for many years, but I am sure that some of the younger ones who are being badly trained are unaware of this."

Some schizophrenic patients may need megavitamin B3 for only one month, as in the case of J. B., the catatonic boy who recovered in 1952 in Weyburn hospital and is still normal.

"He is cured," said Dr. Hoffer, "and represents an example of the first type. If his schizophrenia returns it will not mean, as many will assert, that his treatment of 1952 had been a failure, but that he has been struck a second blow. Others may need it for their lifetime to remain well.

"We needed information on the distribution of schizophrenia between two types. For this reason, on discharge patients were given either nicotinic acid or placebo in a new randomization. We therefore finally had four groups."

The first group included those who had received nicotinic acid in hospital and continued oh the nicotinic acid oh discharge for as long as they would take it. This group was called the nicotinic acid-nicotinic acid group (NAC-NAC).

The second group was comprised of those who received nicotinic acid in hospital and went on placebo on discharge. Those were in the group called the nicotinic acid-placebo group (NAC-P).

The third group received placebo in hospital and nicotinic acid after discharge. This was the placebo-nicotinic acid group (P-NAC).

The fourth group was the placebo-placebo group who received placebo while in hospital and after discharge (P-P).

At the end of 1959, Dr. Hoffer made a final evaluation of every patient. He contacted everyone by letter or telephone and was able to have a personal interview with most of them. At the time of the interviews he did not know what medication was received in hospital and after discharge since the code had not been opened. This was true for all patients except for those who, at any time during the follow-up period, relapsed. They were then classed as a treatment failure and their participation in the study was over.

Some of them, however, remained on as research patients when their therapists indicated they wanted no more of them. Research workers also continued to observe others who were put on niacin after relapse.

The question is often asked, which comes first, the chicken or the egg? Some people, in defense of their antiquated notions, are clinging to the slim hope that environmental difficulties can. produce a biochemical upset in the body, resulting in schizophrenia.

"We don't care which comes first as long as we can treat our patients successfully," says Dr. Hoffer. "So far there is very little evidence that environment plays a role, and a fantastic amount of evidence that it is biochemical.

"One of our patients demonstrated, as many have before and since, that once recovered she could stand great stress at home. She lived with her three children and a chronic psychotic father and was divorcing her husband. These difficulties were so great that she was overwhelmed and came to the hospital. It was found that she had been on placebo and was treated with niacin. She then went back into the same community, to exactly the same problems, but obtained a job and was able to support her children and her father. She came in to see me in 1956 and told me with amazement that she could not understand why she was gaining more confidence in herself and was able to carry on so well, in spite of the fact

that there had been no change in the situation at home. In fact, the situation materially improved just because she was so well."

After Dr. Hoffer's evaluation was recorded, the treatment given was decoded.

"In this study," he says, "we believed we were treating our patients ethically since they had also received the optimum therapy known for schizophrenia. The only difference was that some had gotten nicotinic acid as well and some placebo. We felt that a failure on placebo should be given a chance on nicotinic acid if his therapist was so inclined.

"Since it can be difficult to evaluate improvement if the patient does not recover, we used many measures. Of these, the most important one is clinical, that is, the judgment of the doctor. Most objective tests are merely attempts to constrain clinical judgment into narrower ranges, and they are seldom as good as clinical judgment by an experienced clinician, and* never have they been better. In spite of serious efforts to develop so-called objective tests., we are not convinced there is anything better, excluding the Hoffer-Osmond Test or the Experiential World Inventory test. The Rorschach, MMPI, and other tests are much less helpful. When good diagnostic tests like the HOD are developed, clinical judgments must yield. I am continually surprised at patients who deny perceptual changes until they do the HOD. But we didn't have the HOD test then, and therefore we used very rigid and tough criteria for judging improvement." The judgments were:

Well: The patient was normal whether or not drugs were required to keep him well. A patient was normal when he had no symptoms or complaints and on psychiatric examination showed no evidence of schizophrenic thinking or behavior; he or she was fully employed at a job, at school, or in the home as a housewife; and in addition he or she was getting on well with the family and the community.

Much Improved: He or she had a full-time useful job, got on well with the family and community, but still had a few complaints and symptoms. In most cases this meant that she or he was probably as well as she or he had been for several years before the illness finally struck him or her hard.

Improved: The patient functioned well in only two out of three areas, that is, in his job and in his relations with the family and community, but still had symptoms of schizophrenia. Thus, a patient who was able to do her housework well but still suffered from fatigue and paranoid delusions which made life difficult for her husband, but which did not interfere with her relationships with her neighbors, would be classed improved.

Unimproved: This meant that the patient was able to remain in the community only because of the tolerance, forbearance, and understanding of his or her family.

Most schizophrenics today, treated by tranquilizers alone, would be classed unimproved by these criteria since they are generally unable to work, have symptoms dampened by heavy doses of tranquilizers, and are kept in the community by the creation of mental hospital enclaves in the homes of their families or in the homes of people prepared to keep them on boarding-out programs.

This is community psychiatry as it is practiced today.

Any home with a sick schizophrenic in it is not a normal home because it has had to yield to the needs and demands of the patient. The normal members of the family are exhorted to live with the illness, presumably because it is all their fault, and are obliged to accept social workers or home-care workers coming into their home and telling them what they must do to help the patient readjust or be rehabilitated. In other words, the family becomes an auxiliary staff to the mental hospital which can't or won't *do* anything for the patient, but which gives

the family instructions and supervision on their way of life. This is a mental hospital enclave—the mental hospital has been brought into the home.

The placebo patients demonstrated statistically what is happening in community psychiatry today. Tables 7 and 8 show how the research patients on placebo and the standard treatment of the day compared with the nicotinic acid patients. If nicotinic acid really does improve the outcome of schizophrenia, the two groups showing the greatest difference should be the NAC-NAC group compared to the P-P group. This is, in fact, what happened.

TABLE 7 Clinical Condition of Patients, End of 1959

Treatment	Total	Well	Much Improved	Improved	Unimproved	In Hosp
NAC-NAC	25	10	5	3	7	5
NAC-P	29	7	5	4	13	13
P-NAC	8	5	1	0	2	0
P-P	20	3	2	2	13	11
ALL NAC	62	22	11	7	22	18

TABLE 8 Clinical Condition of Patients, End of 1959, Percent

Treatment	Well	Much Improved	Improved	Unimproved	In Hosp
NAC-NAC	40	20	12	28	20
NAC-P	24	17	14	45	45
P-NAC	63	12	0	25	0
P-P	15	10	10	65	55
ALL NAC	35.5	18	11	35.5	29

The P-NAC group did best because they were the smallest group and probably were better to begin with. A group of eight can be atypical. Sixty percent of the NAC-NAC group were well or much improved, 28 percent were unimproved, and 20 percent were in hospital. From the P-P group who were deprived of nicotinic acid therapy, only 25 percent were well and much improved, 65 percent were unimproved, and 55 percent were in hospital.

"The outcome of the latter group is the standard outcome of schizophrenic patients treated everywhere from 1850 to 1960, including most patients in the province of Saskatchewan," commented Dr. Hoffer. "There is no need to list the numerous papers written on this subject because they are so uniformly consistent in their statistics. With any group of patients treated by any standard treatment including tranquilizers, one-third will recover, one-third will be in and out

of hospital, and one-third will not recover at all. The present popular treatments are therefore no better than no treatment.

"The NAC-P did-not fare as well as the NAC-NAC group. This showed conclusively that the majority of patients required nicotinic acid more than just 33 days, but we did not know how long treatment should be continued. However, even the group which got nicotinic acid in hospital only did better than the placebo group."

Similar clinical evaluations were made every year after discharge. Since patients could be well one year after discharge, much improved two years after discharge, and ill one year, the final and single rating at the end of a follow-up period gives only a partial account of the patient's progress. The research group therefore used an index which they called community years per patient. A patient in the community for five years will have five community-year units. This evaluation is shown in Table 9.

TABLE 9 Clinical Condition of Patients in the Community

Treatment	Total Community Years	Well	Much Improved	Improved	Unimproved
NAC-NAC	101	35	19	29	7
NAC-P	109	23	13	23	4
P-NAC	36	15	7	7	0
P-P	56	9	4	11	4
ALLNAC	246	73	39	59	11

Seventy-three patients in the NAC-NAC, NAC-P, and P-NAC groups were well, 39 were much improved, 59 were improved, and 11 were unimproved for a total of 246 community years, compared with nine patients in the P-P group who were well, four much improved, 11 improved, and four unimproved for a total of 56 community years.

This data is very similar to the previous data. The total number of community years for the P-P group *is* only half of the total possible because this group contained the largest number of patients who refused to come in for an interview, or refused to respond to mail or telephone calls. The best follow-up success was with the NAC-NAC group.

Another measure of improvement in response to therapy is the number of patients who, while in hospital, had not responded enough for discharge, or who had deteriorated enough in the community to warrant readmission unless the illness was checked. One way of doing this was to decode, and if the patient had been on placebo, to medicate him with nicotinic acid. This was done for six out of 20 patients from the P-P group, and for eight out of 29 in the NAC-P group. In general there was then an improvement in their clinical condition. This is shown in Table 10.

It also follows that patients on nicotinic acid should, during follow up, generally become better since chronic illnesses do improve with time when given specific medication. In the same way, patients with hypothyroidism slowly improve on thyroid hormone. Conversely, patients on placebo would, as do schizophrenics everywhere, continue to deteriorate (Table 11). At the end of five follow-up years, all patients in

TABLE 10

Effect of Adding Nicotinic Acid to Therapy of Patients Who Had Failed on Placebo

	Condition Before Beginning Nicotinic Acid Number	Condition After Treatment With Nicotinic Acid
Well	**1**	**4**
Much Improved	**1**	**4**
Improved	**4**	**6**
Unimproved	**8**	**0**

TABLE 11 Number of Community Years Well for Follow-up Years Shown

Treatment	Follow up Year				
	1	**2**	**3**	**4**	**5**
NAC-NAC	28	33	34	40	60
NAC-P	21	20	22	31	25
P-NAC	25	38	38	43	80
P-P	20	15	10	10	17
All Follow-up onNAC	53	71	72	83	140

the nicotinic acid groups were well 140 community years, while the P-P patients were well 17 community years.

Thus, the predictions were supported by the follow-up data. Each year up to five years, the number of well community-years on nicotinic acid increased. Five years after follow up there were 140 well units compared with 53 after the first year. The same improvement was seen in the P-NAC group, but there was no improvement in the NAC-P group, and the P-P group deteriorated.

In addition to all the other evidence of the value of nicotinic acid as a treatment, it was found that the NAC-NAC group produced the greatest number of patients who had reached five-year cure rates. Many of this group had not yet reached five years of niacin therapy, because not all subjects were started at the same time. In order to get a real five-year cure rate one has to follow patients up about eight years to make sure that every patient at the beginning of treatment has been able to go through a five-year period. From the 25 patients on NAC-NAC, eight or 32 percent were considered five-year cures, from the 29 on NAC-P, six or 20 percent, from the eight in the P-NAC group, five or 63 percent, and from the 20 in the P-P group, 3 or 15 percent.

With longer follow ups, the five-year cure rates improved substantially. Furthermore, the NAC-NAC group had fewer readmissions.

Psychiatric patients do not go back to

hospital unless they, their family, and their physician all agree that they are ill and require further treatment in hospital. Readmission statistics are therefore the best criteria for measuring the patient's clinical state. They are much stronger than discharge data, since discharge is determined primarily by the doctor who may have many reasons for discharging, of which the actual clinical condition of the patient is only one factor. The number of readmissions is shown in Table 12, which also shows the medication being taken the year of readmission. Seven out of *25* NAC-NAC patients were readmitted 11 times; 15 out of 29 NAC-P patients were readmitted 28 times; two out of eight P-NAC patients were readmitted seven times; and seven out of 20 P-P patients were readmitted 21 times.

TABLE 12*

Treatment	Total Number	Number Patients Readmitted	Number Readmissions	Medication Year Readmitted	
				NAC	Placebo
NAC-NAC	25	7	11	4 out of 77	7 out of 22
NAC-P	29	15	28	0 out of 14	28 out of 95
P-NAC	8	2	7	2 out of 21	5 out of 15
P-P	20	7	21	1 out of 6	20 out of 50
			TOTAL	7 out of 118	60 out of 182

***With more experience and use of higher doses, results improve greatly. Dr. Hoffer points out that the earlier the patient is seen, the better the results. If he can see a patient in the acute or subacute stage where he or she has been ill only a year, and if the patient is prepared to cooperate with treatment for at least two years, he can get over 95 percent recoveries.**

This data corroborates the clinical evaluations previously described. Patients taking nicotinic acid relapsed only seven out of 118 patient years, while those on placebo had frequent relapses, 60 out of 182 patient years.

"The chances are less than one in a million that similar results could have occurred by chance," Dr. Hoffer emphasized. "Many of those who had relapsed had stopped taking their medication. It may be argued that patients stop medication because they begin to relapse, but this runs counter to all our experiences with schizophrenic patients. We have observed schizophrenics in the community since 1952, and it is not the habit of patients to discontinue medication unless they believe there is a good reason for it."

There are at least three reasons, he said, why patients will stop medication. The first is that they are well and have been for a long time.

"Many will then stop on a trial basis after consulting with us. Many years ago, before we had this kind of firm data, we would allow them to stop at their request. But now we advise them to continue for many years after they are well. We point out to them the possible disastrous consequences of a relapse. However, if they still wish to do so, we advise them to go ahead, but to resume medication at the first indication that the illness is returning. The best early warning symptoms are unusual fatigue, irritability, and/or depression."

Another reason is that they are neither well nor improving and rightfully conclude the medication is not helping them.

"But these patients should not give up

until they have tried it for a long period. They require continuing support from the doctor for with nicotinic acid therapy there may be no improvement for several months, followed by a dramatic improvement in a few weeks. Some of the nicotinic acid patients did not get this support and in fact were encouraged to stop treatment by psychiatrists, surgeons, or general practitioners who did not understand their illness or their treatment."

Finally, some patients will stop medication because they cannot tolerate the side effects, just as they will discontinue tranquilizers because they cannot tolerate the sluggishness and sedation which prevents them from doing their job, or they are frightened of the side effects.

"We are convinced that patients who know they have schizophrenia, who have been educated and are knowledgeable about it, will not discontinue medication except for these reasons alone. We began telling our patients in 1960 that they had schizophrenia, and they became more cooperative after this. The high relapse rate on placebo medication is therefore a real phenomenon. It proves that the act of taking inert tablets does not prevent relapses. This is not surprising for, in spite of protestations from psychologists and psychiatrists that faith (confidence) in pills can prevent relapse, they have not presented data to support their position. There are no published data showing that placebo has ever cured more than one-third of any group of schizophrenics. This is the natural recovery rate."

The conclusion, said Dr. Hoffer, is inescapable that nicotinic acid therapy markedly reduces relapse rates.

"Those who maintain that schizophrenia is a disease of personality, a maladaptation, rightly expect that only a personality transformation can lead to a cure, and they consider that every relapse after chemical treatment supports their contention. Nicotinic acids ability to cut down relapses supports the view that schizophrenia is a metabolic disorder which can be controlled by biochemical treatments. It also appears to be a metabolic disorder which comes on slowly for the relapse rate does not begin to reach the level of those who have not had this vitamin until several years after it has been discontinued."

The reduction in relapse rate is shown again in the number of patients from each group who had to be readmitted during the five-year follow-up period (Table 13).

TABLE 13

Readmission Percent

	Follow-up Years				
Treatment	**1**	**2**	**3**	**4**	**5**
NAC-NAC	8	12	4	6	20
NAC-P	36	24	17	13	41
P-NAC	13	25	25	30	0
P-P	40	21	40	55	50

At the end of five years of follow up, 20 percent of the NAC-NAC patients, 41 percent of the NAC-P patients, 50 percent of the P-P patients, and none of the P-NAC patients were readmitted. The readmission rate of NAC-NAC patients encouraged Dr. Hoffer and Dr. Osmond to work harder since one day in the future there would be no need for readmissions.

In addition, where re-hospitalization was required by NAC-NAC patients, it was for a shorter period of time than for other groups. This provided another measure of efficacy of treatment. A measure of the serious degree of a patient's illness was the length of time he must be in hospital. In general, patients who required long treatment in hospital were sicker than those who didn't. There were exceptions, of course, especially when psychotherapy was considered the main therapy, for in these cases patients judged good candidates for psychotherapy could be kept *in* hospital for a long time, while sicker patients not judged good candidates were given drug therapy and so recovered more quickly. But in Saskatchewan no unit used psychotherapy as the main treatment variable. The length of treatment in hospital is shown in Table 14.

TABLE 14

Duration of Treatment in Hospital

Treatment	Number	Total Days In Hospital	Total Years In Hospital	Mean Days Per Patient	Range Days In Hospital
NAC-NAC	25	925	2.5	103	23-184
NAC-P	29	2875	7.9	120	7-344
P-NAC	8	326	0.9	54	31-123
P-P	20	3318	9.1	207	7-1584

Thus, the 25 patients who received nicotinic acid in hospital and after discharge fared best,. In the follow-up period, from 1953 to the end of 1959, they needed 2.5 years of treatment in hospital, or six days per patient per year. The worst off were the placebo-placebo group who each required *27* days per year of hospital treatment, four and a half times as many, totalling 9.1 years.

If daily hospital costs are estimated at $20, the mean of psychiatric ward and mental hospital costs, each NAC-NAC patient required hospital care which cost $730 over a follow up of six years while each P-P patient required about $3,300 in care. The niacin given the patients thus saved taxpayers thousands of dollars. Getting schizophrenics well would save each province or state millions of dollars every year.

When the range of days in hospital was considered, the NAC-NAC group again proved to be superior. Dr. Hoffer compared this with other medical illnesses.

"There is a general rule in medicine that the less specific our remedies the more variation there is in treatment and in number of days in hospital, because more depends upon the art of medicine and less upon its science. When we had no specific therapy for pneumonia such as penicillin, patients were kept in bed, either in hospital or at home, anywhere from one week to several months depending upon the orientation of his physician. A series of pneumonia cases would therefore yield a wide range of days in bed or in hospital. But today with penicillin, very few cases need be in bed more than seven days, and some are treatable at home out of bed. There is a sharp decrease invariation in duration of therapy between patients.

"The same situation prevailed with tuberculosis where the range of variation was great before antibiotics were introduced, but is much less today. Similarly with syphilis of the brain. Patients were once kept in hospital up to many years until they died, whereas today syphilis is

hard to find and is treatable very simply. The only diseases today where one finds a similar wide variation of days in hospital are those where we have no generally accepted specific remedies such as in the cases of arthritis, multiple sclerosis, and others." It is quite obvious, he concluded, that nicotinic acid is quite specific for schizophrenia since it has sharply reduced the variation of days in hospital.

In 1957 Hoffer et al. reported results of nicotinic therapy on 74 patients and on 97 controls who had not received the vitamin B3 treatment. The control group received the best psychiatric care available. The data from the 1957 study was added to those reported in the second double-blind comparison study. The results are shown in Table 15. Table 16 shows it is possible to compare the four groups by the criteria described.

TABLE 15

Treatment	Number	Number Patients Readmitted	Number Readmissions	Total Years	Mean Days Per Admission
NAC-NAC (1957)	24	7	10	5	193
(Present)	25	5	9	2.5	103
Total	49	12	19	7.5	147
NAC-P (1957)	36	8	14	7	39
(Present)	29	13	24	7.9	120
Total	65	21	38	14.9	155
P-NAC (1957)	14	3	4	0.3	31
(Present)	8	2	6	0.9	54
Total	22	5	10	1.2	45
P-P (1957)	97	29	65	38	210
(Present)	20	7	16	9.1	207
Total	117	36	81	47.1	209
ALL NAC (1957)	74	18	28	12.5	165
(Present)	62	20	39	11.3	106
Total	136	38	67	23.8	139

TABLE 16

Treatment Response

Criterion	1 Best	2	3	4 Worst
Clinical-Well and Much Improved	P-NAC	NAC-NAC	NAC-P	P-P
No Readmitted	NAC-NAC	P-NAC	NAC-P	P-P
No. Readmissions	NAC-NAC	P-NAC	NAC-P	P-P
Five-Year Cures	P-NAC	NAC-NAC	NAC-P	P-P
No. in Hospital	P-NAC	NAC-NAC	NAC-P	P-P
Consensus	NAC-NAC	P-NAC	NAC-P	P-P

The various indices of improvement showed that the best treatment for schizophrenia is to give the patient nicotinic acid while in hospital and for a long time after discharge. Continuous treatment after discharge *is* better than treatment in hospital only, and the worst therapy is every standard psychiatric therapy in use today, plus placebo.

The third double blind was done by a psychiatrist in a Saskatchewan mental hospital who, late in the 1950's, expressed great doubt that nicotinic acid was of any value in treatment of schizophrenia. He came to Dr. Hoffer and suggested he would like to do a controlled double-blind study to prove the vitamin had no value. He was encouraged to go ahead as it was felt that performance of a study, and not its motivation, was important in research.

As subjects for this trial, Dr. Ray Denson (1962) chose male schizophrenics entering the mental hospital at North Battleford as new admissions or readmissions. A few were certified patients returning from trial leave. Only those requiring ECT were selected because of the relative certainty of the diagnosis. Voluntary and committed patients were included, but cases complicated by mental defect, alcoholism, personality disorder, physical illness, or special legal considerations were rejected. It was thus hoped to eliminate borderline cases and to reduce the number of patients whose stay in the hospital might be determined by factors other than response to treatment. The trial started May, 1959, and ended April, 1961.

The study included 36 patients who represented about one-third of the total number of male schizophrenic patients who entered the hospital during the period of selection. Nicotinamide was chosen instead of nicotinic acid because it was felt the flushing would give the latter away.

The placebo and the nicotinamide were made up in two lots of large white tablets identical in appearance and flavor. Neither the staff nor the patients knew which patients received the vitamin B3 or the inert tablets. ECT began within two weeks of admission, and the tablets were started about the same time. Both the vitamin B3 and the control groups took three tablets twice each day for a period of five weeks. Any patient who left the hospital at this time was given the required number of tablets to take home. Meanwhile the patients were given the therapy prescribed by their own psychiatrists, and on all subsequent admissions only standard treatment was given.

Of the 17 patients treated with ECT and nicotinamide, only one was still in hospital after two months. Of nine who had received ECT and placebo, eight were still in hospital two months after the study began. An assessment 12 months after the trial began did not show any significant difference in the two groups. Eight months after that, it was found that the nicotinamide group had done markedly better than the placebo group.

The nicotinamide group spent a total of 1,810 days in hospital during this period, giving an arithmetical mean of 106.4 days per patient. The placebo group had spent 3,373 days in hospital, or 177.5 days per patient. The difference was just over 10 weeks per patient. In other words the patient who received placebo spent, on the average, 25 weeks in the hospital during the year whereas the nicotinamide patient stayed only 15 weeks.

This study took into consideration the fact that one patient who had responded promptly to treatment returned to hospital in the third quarter with a broken leg which presented complications in healing. A large portion of the time he spent in hospital was due to his surgical condition and not to his schizophrenic illness. Nevertheless, the time he spent in hospital was included as his total stay.

Another patient made an unauthorized departure from the hospital during the third quarter, and with the help of his family began to establish himself in the community. Fifty-nine days later he was

discharged by the Superintendent without having returned to hospital. His total hospitalization excluded these 59 days.

"Any unauthorized separation which is successful," Dr. Denson explains, "implies some ability to live in the community and intimates that a therapeutic goal has been reached."

Only one patient had received treatment elsewhere. This, too, was taken into consideration. Dr. Denson therefore concluded that "the results suggest that nicotinamide therapy can shorten the length of stay in hospital for schizophrenics, and support the hypothesis that nicotinamide is of value in the treatment of schizophrenia."

A fourth study was undertaken in the Weyburn hospital by Herjanic et al. (1967).

"Our findings support the previous reports; the outpatients treated with nicotinic acid show a better clinical improvement, fewer hospital admissions, and as a whole, less time spent in the hospital during the study period," they reported.

Since these experiments were completed, the research findings have been confirmed clinically in many parts of the world.

Judged in a variety of ways, whether by the ability of the individual to perform normally at home and in the community, the number of days in hospital, the rate of readmissions, the number of community years in the community, nicotinic acid and its sister vitamin proved to be the best components of treatment known for schizophrenia.

IV. HOW IMPORTANT IS FAITH OR BIAS?

Dr. Hoffer and Dr. Osmond were long puzzled that, as Dr. Osmond put it, "a remedy so safe, cheap, simple, and elegant had not commended itself to psychiatrists who have been zealous enough in using treatments which were none of these, and were ineffective besides except for a short time."

There were many examples of the unnecessary problems and hardships created by the refusal of these psychiatrists to accept the research findings. One schizophrenic consumed $60,000 in hospitalization costs for over a period of 10 years. This patient could have been started on the new treatment in 1954 when he first became .ill.

They were forced to conclude that their colleagues felt it would be undignified to approach schizophrenia, the greatest of madnesses, with such a feeble weapon as a well-known vitamin which can be bought at any pharmacy when far more drastic methods have failed.

Psychiatrists gave many bizarre reasons for refusing to try the treatment: It is no better than aspirin; it may cause liver damage (or diabetes); this is all in the research stage and nothing has been proven; schizophrenia is not a disease and has nothing to do with vitamins; schizophrenia is hopeless. The most common ones were that niacin patients recovered either by chance or because of Dr. Hoffer's faith in the treatment or the patients' faith in him.

Therefore when Dr. Hoffer and Dr. Osmond realized that some psychiatrists were using nicotinic acid, either because they were interested in it, or in spite of the fact that they were lukewarm about it, they decided to study the results. Surely these psychiatrists, unsullied by bias, untainted by niacin enthusiasm, and respectable because they had no objection to the usual ineffective treatments, could not be accused of the grave crime of willfully getting their patients well.

Although it was very improbable, Dr. Hoffer and Dr. Osmond thought it was possible, as many said, that the results of the double blinds were due to factors within the research which were unknown to them. Perhaps Dr. Hoffer did indeed have extraordinary powers of suggestion which brought about recovery even on those patients who had long before forgotten what it was to be well.

It was impossible, they knew, that a patient's confidence in his doctor, or a

doctor's confidence in his therapy, played any role since the three double-blind experiments yielded similar results. However, there was no doubt that the doctor's approach to the patient is extremely important and could determine the response to a degree. This kind of information would not be available from double-blind studies.

A doctor who treated a diabetic patient with insulin but failed to tell him he had diabetes or to advise him on diet or warn him of the undesirable changes diabetes might produce would not get as good results as a doctor who treated the diabetic competently. Dr. Hoffer and Dr. Osmond believed that exactly the same considerations applied to schizophrenia. Competent treatment of schizophrenia included telling the patient his diagnosis, explaining what schizophrenia is and how he or she would be treated, and guiding him as he recovers (Hoffer and Osmond, 1966).

A large number of patients were treated by psychiatrists who did not use this approach. Their results could illustrate the efficacy of nicotinic acid alone, unsupported by this approach. Neither did these psychiatrists routinely follow up patients after discharge with nicotinic acid. Nor was the climate exactly warm to the treatment.

"I presented a report on niacin and early schizophrenia to our University staff last night," Dr. Hoffer wrote Dr. Osmond January 14, 1959. "I realized clearly for the first time we were discoursing in different fields.

"I tried to demonstrate by scientific logic and demonstration how useful it is. I even referred to patients treated here over the past three years by Dr. McKerracher. Using his patients alone, 90 percent of the ECT and niacin patients were not readmitted, 60 percent of the ECT-only patients were not readmitted, and 56 percent of the control patients were not readmitted.

"However, the clinicians kept looking searchingly for loopholes and referred to non-measurable variables. I suggested I would like the same standard of criticism used in evaluating all treatments; chemical and psychological. This method, I said, would satisfy most critics^ but no one had yet produced a paper on psychological therapy which would satisfy the scientists. I told them I was not interested in persuading them to use niacin. I was convinced it should be used and they could treat their patients any way they saw fit. Frank Coburn supported my point of view. He reported he routinely uses niacin on his patients since it will do them no harm and may do them a lot of good."

Even without the enthusiasm attributed to Dr. Hoffer and Dr. Osmond as a treatment factor, and without the kind of support they gave their patients, nicotinic acid proved to be efficient as a treatment.

The psychiatric ward, University Hospital, began to treat patients with nicotinic acid in the fall of 1955. The research staff searched the records and selected all the schizophrenic patients who were under the care of Dr. McKerracher and Dr. Coburn. The 78 patients were divided into three groups: those who did not receive either ECT or nicotinic acid, those who received ECT but not nicotinic acid, and those who received ECT and nicotinic acid, or nicotinic acid alone. In addition, all patients received -psychotherapy and either barbiturates or tranquilizers as indicated. The reasons for giving or not giving nicotinic acid were unknown, but may have been due to factors which were specific to time or patient. ECT in this ward is often given to disturbed or severely ill schizophrenic patients. The less severe or more acute patients might not receive ECT.

After treatment the patients were either discharged in the community or transferred to a mental hospital for prolonged treatment. During the latter part of 1959, the whereabouts and mental state of each patient was ascertained by referral to the clinical hospital records or by discussion with their therapist. If they remained in the community and there was no record of

further psychiatric treatment or hospitalization, they were said to be well. If they had been readmitted to University Hospital or to a mental hospital, or transferred from University Hospital to a mental hospital, this was indicated.

There were *22* patients who received neither ECT nor nicotinic acid. Their mean age was 37 and they were in hospital only an average of 26 days. This group therefore cannot be compared with the other two groups who were in hospital an average of nearly 66 days. This difference is probably due to ECT being given for a series of about 12 treatments which usually means about 35 days in hospital all told. On discharge, one was rated as recovered or much improved (according to the clinical charts) and 13 required readmission. Only two were well in the community, six were ill, and one committed suicide.

Those who received ECT only were the same age, but stayed about two months in hospital. On discharge, five out of 26 were recovered or much improved and 13 were subsequently readmitted. However, 10 remained well in the community. There was one suicide. Nearly 40 percent were well in the community compared to only 10 percent of those who did not receive ECT. Apparently ECT increases the chances of long-lasting improvement in schizophrenia.

The third group consisted of 30 patients who received a combination of ECT and nicotinic acid and four who received only nicotinic acid. This group was somewhat younger than the other two groups. Age, however, appears not to play a major role in recovery. Several authors hold that the earlier the onset of schizophrenia, the worse the prognosis; others don't think this is so. Of all these 30, seven were rated as recovered or much improved. This does not differ significantly from those who only had ECT. But out of the nicotinic acid cases only six were readmitted compared with 13 in the ECT group. This difference is highly significant. (Chi square is greater than 4.0).

The greatest difference appeared in their progress in the community. Twenty-four of 30 on nicotinic acid were well at the end of 1959. Only 10 of 26 patients who received ECT were well. It is possible that the evaluation "well" is not as accurate an evaluation as a readmission. However, the same method of evaluating was applied to all three groups and one would expect the errors to cancel each other. Seven were still taking nicotinic acid in the community.

This suggested that the research group's bias was not responsible for the good therapeutic response to nicotinic acid when used as an adjunct to therapy.

There was another way of comparing the results of the nicotinic acid treatment with other treatments. The psychiatric ward in University Hospital became operative late in 1955. Until December 31, 1962, the schizophrenics that were treated were divided into three groups. Group 1 were under the care of a psychiatrist who routinely treated most of his patients with nicotinic acid as an adjunct. Group 2 patients were treated by another psychiatrist who allowed his resident freedom to decide whether or not it would be used. Group 3 patients were treated by a number of psychiatrists who routinely did not use nicotinic acid. The records of all these patients were examined for readmissions to any psychiatric facility in Saskatchewan.

A means of comparison was further provided by a large group of schizophrenic patients who did not receive any nicotinic acid because they were not treated at this hospital. Because of the few beds available for a city and environs of over 150,000 population, many patients were treated in the North Battleford hospital 100 miles away. Many were either committed, or sought voluntary, informal admission themselves.

Others, because of some emergency situation, were admitted first to the University Hospital and then transferred to the mental hospital in one to three days. These comprised a small portion of the total admissions per year. This group was the emergency group, and readmission data was also available for

them. Most of the readmissions were to the same hospital.

The differences were startling. Seventy-six schizophrenic patients who received nicotinic acid required 2,453 days (seven years) hospital treatment over a seven-year period, or about five days per patient per year, while 226 patients treated with the standard tranquilizers plus ECT plus psychotherapy but without nicotinic acid required 24,946 days (about 70 years) or about 16 days per patient per year. Seventy-six patients treated over a seven-year period required one hospital bed per year for after treatment, whereas the group of 226 patients consumed 10 beds per year. It therefore seems that the routine use of nicotinic acid will markedly reduce the number of beds needed for readmission.

The emergency patients were not treated at University Hospital, but were held there for one to three days until they were transferred and treated at a mental hospital. Out of 115 emergency patients, 39 were readmitted for 91 readmissions and a total of 18,311 days in hospital. There were 26 in hospital on March 31, 1963. One committed suicide in 1961.

A comparison of all patients, including research patients, with and without nicotinic acid, from 1956 to 1962, shows that 70 of the 169 nicotinic acid patients were readmitted for 137 readmissions, totalling 12,452 days in hospital. Six were in hospital March 31, 1963, and none had committed suicide. Of 349 comparison patients, 166 were readmitted for 380 readmissions and a total of 44,823 days in hospital. On March 31, 1963, 43 were in hospital. Five had committed suicide.

The group which received nicotinic acid, it was clear, had the best record which showed most clearly in the total days of rehospitalization, i.e., about 11 days per patient per year. The comparison group required about 19 days per patient per year. Had the entire 349 schizophrenics been given adequate treatment with nicotinic acid, they would have had 25,600 days of rehospitalization instead of 44,823 days.

In these *studies,* schizophrenics either got well or remained ill depending on the whim of their psychiatrists or resident doctors. To become well meant to become normal, productive, independent of the network of psychiatrists, psychologists, social workers, home care nurses, sheltered workshops, and rehabilitation centers forced upon society by the cult of incurability.

Dr. Osmond once described the illness as follows:

"Among the ills which afflict mankind today few are more formidable, more universal, more persistent, more damaging, more mysterious and more elusive than schizophrenia - the shattered mind. It is one of the gravest and one of the most tragic illnesses. Everything from lack of mother love to a specific inherited weakness of constitution, from the unkindness of an industrial society to invasion by yeast-like organisms has or has had eloquent and industrious advocates. Our work has been on a small scale and perhaps lacking in refinement. We have tried to do as Helmholtz once advised: To trust the inadequate and act on it and then it will become fact."

V. "DIGGING FOR GOLD

Medical history is marked by a universal reluctance of medical men to accept new techniques which later prove to be valuable.

Santorio Santorio (called Sanctorious) in 1602 published a small book describing a pulsilogium. It was a pendulum where the length of the string was altered until it best coincided with the pulse. By measuring the length of the string, physicians got an estimate of pulse rate.

In 1707 Sir John Floyer introduced the physicians' pulse watch which went exactly one minute. His invention was not widely adopted. Effective pulse watches did not come into general use until over 100 years later.

Sanctorious in 1612 published his work describing the thermometer.. Thirteen

years later he described how it was to be used to diagnose. Before 1800, only a very few physicians had used the thermometer for clinical purposes.

Sir William Aitken in 1802 made such a thermometer, but it was 10 inches long and was described by M. Allbutt as being like a short umbrella. This instrument was clumsy and required 20 minutes to register. From 1848 on, Prof. Carl Wunderlich began keeping temperature records in most of his cases. In 1868 he published his book, translated in 1871, "on the temperature in diseases, a manual of medical thermometry." But few physicians were patient enough. In 1867 Allbutt made a short thermometer six inches long which took a temperature reading in five minutes. Shortly thereafter he made one three inches long.

The stethoscope, although harmless like the other diagnostic devices, was not used for 100 years after it was invented.

All of these instruments have changed the course of medical history, facilitating diagnosis and saving numerous lives. In the few cases where tests were useful for psychiatry, the condition for which they were used left psychiatry and joined other branches of medicine. Thus, serological tests for syphilis, followed by specific antibiotic therapy, took from psychiatry general paresis of the insane— a disease which at one time was more troublesome and deadly than schizophrenia. Similarly, blood and urine assays for nicotinic acid were soon followed by enrichment of all American flour in 1942 and took from psychiatrists the psychoses associated with pellagra.

This leaves schizophrenia, the third member of the great psychiatric illnesses, and it is still with people as a chronic problem.

Freud and Meyer retarded the development of perceptual tests for schizophrenia by establishing a scapegoat. Instead of keeping the scapegoat purely objective, as bacteria or chemical changes became in other diseases, they placed it on a moral level, implying shame and moral responsibilities.

Later, in 1911, E. Bleuler considered that there were no perceptual changes in schizophrenia, and this was accepted at its imposing face value for no reference to perceptual anomalies appears in psychiatric case histories. Psychiatry became blindfolded by an unfounded belief that the "primary symptom in schizophrenia" is thinking disorders. The American Psychiatric Association in its manual completely overlooked the perceptual world in its definition of schizophrenic reaction.

The tragic result is that psychiatrists, by and large, do not bother to find out what their patients are experiencing.

An example of this is a young man who came into University Hospital in Saskatoon in 1958. The resident and staff members concluded he was probably a young psychopath in the making and accepted his story about his family quite glibly. Had they probed his world more carefully they would have discovered, as Dr. Hoffer did, that there had been a marked personality change in this boy. His story about his parents, and the real story about his parents, were incongruous. He had been seeing faces on the ceiling when lying down at night since he was eight years old and these faces had begun to be the face of a devil with a scar on it. He had a similar scar on his own face due to an accident at the age of two. Dr. Hoffer began treating him with nicotinic acid and vitamin C, and his only comment on the case was that it was the American ideal to study every known factor and come up with irrelevant conclusions.

The lack of precision in psychiatric diagnosis led to what Dr. Hoffer and Dr. Osmond considered to be one of the most unpleasant and continuing dissatisfactions in the practice of psychiatry —the diagnostic battles which characterized most clinical conferences. When they started their work it soon became apparent that for many psychiatrists, diagnosis was determined by their own special interests and had little relevance to the clinical state. The principle of diagnosis by consensus appeared and the method of diagnosis became democra-

tized, with all the faults and none of the virtues of the democratic system. After each acrimonious discussion, a vote was taken and often the majority vote determined the diagnosis. Untrained physicians just out of medical school were given equal voting power with specialist psychiatrists with many years of experience. As with most democratic meetings, certain people are more influential than others, and chiefs of staff usually carried the field.

The fact that this kind of diagnostic conference was so common is the best proof there is that the art of psychiatric diagnosis was not very well developed. In no other branch of medicine would this kind of conference be allowed.

In 1959 Dr. Hoffer hit upon what he thought was the major reason why diagnosis is difficult in psychiatry.

"It is due to a logical error in thinking. It is said that the cause of schizophrenia is not known. Then it is immediately said that schizophrenia cannot be caused by LSD or mescaline or syphilis. If the first statement is correct, the second cannot be. Most psychiatrists believe both to be true and use cause to exclude certain syndromes from the schizophrenia field.

"Classically, diagnosis follows three logical procedures in sequence: The patient tells the doctor about his symptoms and their development; from this a picture or a pattern emerges; then laboratory or other tests are used, such as EEC, chemical tests, physiological tests for blood pressure, or psychological tests for IQ. However, the third step is possible only if such procedures are known. When not known, diagnosis must stop at the second step where the clinician forms an idea of the disease from the pattern which emerges.

"If a factor is found which may produce a mental picture similar to schizophrenia, then the final diagnosis would be 'schizophrenia associated with bromide,' as the case may be. This scheme would markedly sharpen diagnosis and remove much disagreement. "For example, in one of our conferences one of the staff diagnosed a patient as being schizophrenic. Later he was told she was partially deaf. He immediately changed his diagnosis since he believed her mental picture could have been due to her deafness. According to the scheme I suggest, she would have been diagnosed schizophrenic associated with deafness. This idea has the main merit of being honest and consistent. It states bluntly we do not know and refuses to hide under the subterfuge of a psychosis due to a function of something (a functional psychosis)."

It was obvious to Dr. Hoffer and Dr. Osmond that psychiatrists who are also physicians are as keen as any other physicians to diagnose accurately. The problem, they believed, was not the motivation but the lack of objective evidence.

While this evidence was being sought in Saskatchewan, a newer psychoanalytic movement developed which made a virtue out of necessity and set psychiatric progress back another 40 years. Ten years after Saskatchewan research studies began, leaders of American psychiatry like Dr. Karl Menninger began to teach that diagnosis was no longer relevant to psychiatry since what was required was a thorough knowledge of the individual. Later Dr. Menninger publicly blasted any psychiatrist who diagnosed schizophrenia and who made the gross error of informing his schizophrenic patient what his illness was. This latest development did not help the patients, but did help psychiatrists. It removed guilt from many of them who now felt no necessity to diagnose.

Psychiatrists now saw diagnoses as labels only, a matter of convenience. Had it not been for the Dominion Bureau of Statistics in Canada which demanded diagnostic cards with the diagnoses and numbers, many patients would not have been diagnosed. Very often it has been recorded that "we see no point in diagnosing but for purposes of the Dominion Bureau of Statistics we will call it personality disorder (or anxiety neurosis or depression)."

Diagnostic imprecision combined with a cavalier approach to diagnosis created another problem.

When Dr. Hoffer ran the first double-blind vitamin B3 experiment in 1953, it was agreed that every schizophrenic admitted to the Munroe Wing would be used. The diagnosis was made by the treating psychiatrist and Dr. Hoffer felt he had the right to exclude any patient if he did not agree.

As with most psychiatric centers, the diagnosis of schizophrenia was always made reluctantly and as a last resort, since no treatment was available which did any better than chance. As a rule, diagnosis of schizophrenia was made only after the appearance of hallucinations, severe paranoid delusions, or thought disorders so gross that patients could not even speak coherently.

Since Dr. Hoffer and Dr. Osmond were looking for biochemical factors which would differentiate between schizophrenia and other illnesses, and thus lead them to the biochemical error in schizophrenia, it became absolutely essential that diagnosis was accurate. They wanted to be sure that the schizophrenic patients they were studying were, in fact, schizophrenic.

The difficulties resulting from diagnostic fumbling could, they saw, be enormous. A measure which would differentiate between the various psychiatric classifications must be extraordinarily powerful, they concluded, since minor factors would never differentiate the groups. Until refinements in diagnosis purified the diagnostic groups, biochemists had little chance of being of much value. The diagnosis had to be clear and unequivocal.

Optimistic that efficient and simple psychological tests could be found, Dr. Hoffer brought a large psychological research group into the unit in order to define schizophrenia more carefully and to develop better diagnostic tools. Under Dr. Neil Agnew an intensive psychological survey was made of the literature. Of all the tests published, a battery of tests developed by Dr. J. Cattell seemed more appropriate.

The Rorschach, a strong favorite then, was intricate, difficult, time consuming, and did not lend itself to research control. The Minnesota Multiphasic Personality Inventory was better, but it too was cumbersome and required a lot of work in order to gain a little information. The research group therefore ran a detailed investigation of several of Cattell's batteries of tests on over 100 patients for over three years. After this study was completed, they found that the Cattell tests did not differentiate schizophrenics from non-schizophrenics at better than chance expectancy.

It is now clear to Dr. Hoffer and Dr. Osmond why the Cattell battery could not work. The Cattell tests were designed to measure certain aspects of personality. At that time it was commonly assumed that personality had much to do with the development of schizophrenia. This was one of the myths of psychiatry. In fact, personality has little to do with causing schizophrenia although it is a very powerful force in shaping the content of this illness. The research with Cattell's battery of tests they now recognize as one of the major errors in their research. It cost them nearly $50,000 to discover that measurements of personality have no value in the diagnosis of schizophrenia. By 1960 Dr. Hoffer and Dr. Osmond were generally unhappy with their psychologists. The latter were skilled in developing reliable valid scales or instruments, or at using those already in existence, but these precise instruments did not seem to measure anything of value to clinical psychiatry.

Their psychologists were unhappy because they had not been able to discover diagnostic tests which worked and because they were, in this area, making very little contribution.

One day Dr. Hoffer engaged in a long debate with the head psychologist who maintained that the real fault lay with psychiatry. Psychiatrists, said the psychologist, could not even agree with each other about diagnosis. Therefore,

why should they expect to find agreement with psychologists?

This was, of course, true. Dr. Hoffer replied, but psychiatrists could in fact agree very readily if only they were taught in a consistent way what the main diagnostic variables were, and if they agreed to share the same diagnostic criteria.

Also the psychiatric disagreement was grossly exaggerated by Kraepelinian nosology. Kraepelin divided schizophrenia into subcategories. Given the problem of diagnosing schizophrenia, most psychiatrists with experience would agree, but they might debate fiercely whether it was hebephrenic or simple schizophrenia. If one ignored these rather useless subcategories, agreement was much better.

This debate had one useful outcome. It raised the question of how diagnosis is made. Diagnosis is determined by symptoms and signs. Symptoms are complaints offered by the patient, and signs are things seen by the doctor, such as lumps, blisters, rashes, and so on. Dr. Hoffer and Dr. Osmond concluded that the art of diagnosis consists in knowing which questions to ask as well as in evaluating the significance of the answers.

Symptoms in schizophrenia can be divided into two categories, true and false. Patients can be asked, "Do you see visions? Do you have a pain? Do you hear voices? Do you have enemies?" One could therefore write these questions on cards and have the patient answer them by placing them into true or false categories. In this way, one could examine the patient's mental state in great detail.

The original idea was similar to the MMPI, to design diagnostic questions so that the greater the number of true cards, the greater the likelihood schizophrenia was present.

Dr. Hoffer and Dr. Osmond had a rich background of knowledge to draw from. They had studied schizophrenia at close quarters for a decade or more. They had examined its manifestations in hundreds of sick people, clinically, chemically, physiologically, psychologically, socially, and administratively. They had read more than 20 book-length autobiographies of schizophrenic people, as well as many shorter ones. They had a strong interest in the hallucinogens (Hoffer and Osmond, 1967), and were aware that the experiential world of the schizophrenic is quite different from his world when he is well. They had scrutinized accounts written by more than 200 volunteers who had taken a variety of psychotomimetic chemical substances such as mescaline, LSD, harmine, psilocybin, lysergic acid morpholide, adrenochrome, and adrenolutin. They had read many accounts of naturally occurring psychotomimetics like peyote, ayhuesca, ololiuqui, hasish, and the fungus psylocybe Mexicana heim, which is probably the same as the Aztec sacred mushroom teonanacatle. They had taken most of these substances themselves and found that they had access to many experiences which closely resemble those reported by people sick with schizophrenia.

They had read the classic papers of Dr. Nolan D.C. Lewis and of the early pioneers in psychiatry who had had some experience with schizophrenia. They had seen the success of the questionnaires designed by Mr. Kahan for the* early follow-up studies. From this fund of experience, they selected a number of questions which they aimed at the main components in perception—vision, hearing, taste, touch, smell, body image, and weight. They aimed other questions at thought processes, both process and content. Finally they aimed several at depression and its accompanying symptoms of fatigue and anxiety.

As the questions began to accumulate, the test was tried on patients in the Weyburn hospital. Satisfaction grew as it became apparent that the cards were doing what they were designed to do.

In April, 1960, Dr. Osmond commented: "The new perception test has many possibilities and I agree with you that we should be able to refine it so that

it picks up schizophrenia and excludes most other psychiatric ills. It picked up the psychotic experiences of a woman at a time when her social front was in excellent shape. I suspect, many psychiatrists would be very unwilling to use the label schizophrenia for someone looking generally so wholesome and well preserved, yet the cards show this up with startling clarity. They are better than personal interviews because, as we know, schizophrenics have difficulties in social relationships. It is therefore likely that the more impersonal the relationship, the easier the schizophrenic will cope. The cards ask direct and unambiguous questions which is all that a schizophrenic person can handle. They are a far better sample of schizophrenic experience translated into simple language than one could possibly get anywhere."

June 20, 1960, from Dr. Osmond: "I am toying with the idea of calling it the H.P.D. (Hoffer Perceptual Detector) but this seems a bit vain. I had considered S.P.D. test (Saskatchewan Perceptual Detector) but this is not correct. It would focus more attention on Saskatchewan and I suppose one could consider it a gift to Saskatchewan."

Later, "I have just seen the SSD of a quiet, mildly retarded depressed looking schizophrenic who had been here since 1947 diagnosed as hebephrenia. One might be inclined to call him burnt out, I suppose. He is loaded with perceptual anomalies. He is clearly a gravely and actively ill man. Thanks to wrong concepts, we have got hold of the wrong end of the stick. The illness does not lessen and stabilize as has been suggested, usually by implication. It simply becomes more crippling and prevents them from communicating. It is very exciting. Think of the years and hundreds of thousands of dollars which have been thrown away on the Rorschach."

June, 1960, from Dr. Osmond: "I have been *over* one patient's 65 true responses and it is remarkable what a vivid and coherent picture they give of his world. This is a quiet man who hardly speaks spontaneously. It would take hours and possibly weeks to learn this about him and even then one might not succeed for he might very well become anxious and distressed. The world which he inhabits is highly changeable. It pulsates, and not only do the direct cards pick this up but he will pick up two cards which say opposite things, 'Sometimes the world seems very dim as I look at it, sometimes the world seems very bright as I look at it.' This makes excellent sense to anyone who has taken LSD but less sense to those who have never done so."

July 5, 1960, Dr. Hoffer informed Dr. Osmond that "the perceptual test is producing some interesting results. It makes me both happy and sad at the same time. I am depressed by the ease with which psychiatrists overlook all perceptual changes and by the ease with which the cards show it. One of our recent patients complained chiefly of perceptual visual - changes and immediately was referred to the otolaryngologist because they thought it might be the inner ear. The report came back negative. The next diagnosis will be hysteria. Another man scored very high for schizophrenia on the test but as he fell several years ago and cracked his head, he is said to have an organic brain syndrome, whatever that is. The neurologist finds nothing wrong and suggested to the psychiatrist that he consider schizophrenia as a diagnosis. He will finally be diagnosed as depression or posttraumatic neurosis."

That month the SSD became the HOD test, the Hoffer-Osmond Diagnostic Test.

"The card-sorting test," wrote Dr. Hoffer, "provides objective evidence of the sort dearly loved by psychologists. But we have considered schizophrenia a disorder of perception for many years and have so described it. Clinicians can elicit it very easily if they will take time to question patients about it. But they have been so preoccupied with deep dynamics that they no longer test perceptual areas.

"It is clear that psychiatrists have considered only one visual perceptual

change, i.e., a visual hallucination. Since this is rare they concluded perceptual changes were rare. I think the whole basis for the feelings of unreality are perceptual changes—chronic patients probably cannot adapt because the fluctuations are unpredictable. Normals can adapt to a new but stable environment. Thus with upside down glasses one can adapt. But I doubt anyone can adapt to instability unless it is by hiding in some dark corner as free as possible of external stimuli."

An intelligent recovered schizophrenic took the test and said she wished it had been given to her when she was ill in the Munroe Wing in 1950. Dr. Osmond asked her why and she said it would have been reassuring.

"What she meant was," explained Dr. Osmond, "that when you get questions it makes it clear that someone else knows about the symptoms which you are having and which you had previously supposed no one else ever had. . . This woman's experience for about a month must have very closely resembled a prolonged LSD experience."

Another recovered patient gave Dr. Hoffer an excellent written account of the return of color in her life about three years after she started on nicotinic acid and how striking and good the world now seemed.

"I asked why she had not told me this sooner because I had questioned her before. She reported that I had asked her whether the world seemed normal to her. It did; being in a grey world for 10 years, she had forgotten that colors existed, and this was normal to her."

September 28, 1960, Robert Hall, research nurse at the Weyburn hospital, reported a startling discovery:

"I was surprised at the large number of cards scored as true by this group of patients. It would not have been so surprising if the patients in this sample had been acutely ill schizophrenics; however, the patients used are all long-stay, chronic—what we often refer to as burned-out schizophrenics. All of the patients used either work in hospital industries or take part in the occupational and recreational therapy group program. Most of these patients haven't mentioned any symptoms for years and show no signs of being bothered by hallucinations, delusions, and so on. Apparently they still have these, but have learned to live with them and ignore them. Because all of the patients were well enough and cooperative enough to do the test voluntarily, I did not expect to see so many of the cards put in the 'true' box.

"A few of the more communicative patients mentioned that some of the cards that are false now were true at one time. In particular some of the cards referring to taste, smell, and the feeling of rays of energy and electricity were said to be false now but are true when the patient has a relapse."

Dr. Hoffer and Dr. Osmond finally had 145 cards, and in 1961 they began their first clinical studies with the HOD test, when a random sample of 20 patients at University Hospital were tested. After this sample, it was clear that the test was accomplishing its purpose. It divided patients into two main groups—schizophrenic and non-schizophrenic. Normal subjects comprised a third group, with very low scores.

The first paper appeared in the **Journal of Neuropsychiatry,** August, 1961. In this paper Dr. Hoffer and Dr. Osmond described the cards and the method and scoring system used. A HOD manual, by Kelm, Hoffer, and Osmond, is now available, explaining how to score (Kelm etal., 1967).

The findings with the HOD and the chemical testing which proceeded simultaneously were so exciting that Dr. Osmond wrote to Dr. Hoffer, September 19,1963, "It is almost as if we are two old prospectors who have been saying for years, 'There's gold in them thar hills,' and of course everyone knows there isn't any gold. Real scientific geologists have made a real survey of the hills and have shown that there can't possibly be any gold there. Year after year you and I come down from them thar hills carrying

our little bag of gold nuggets. However, it is obvious that we couldn't have found them in them thar hills. What people have overlooked is the nuggets. Anyhow others are venturing towards them thar hills and rather dazedly they are finding gold there just as we said. But everyone knows we are mistaken. It is all very puzzling."

The gold they found with the HOD was the relationship of perception to youth, learning, schizophrenia, and the chemical mauve factor test. The HOD test showed up many errors in clinical diagnosis and punctured many psychiatric beliefs. One of these myths is that there are no perceptual disturbances in schizophrenia and another is that insight is needed for a good prognosis.

Clinical testing with the HOD began when it was administered to a group of 174 patients at University Hospital in Saskatoon by psychiatric nurses, usually a few days after admission and before vigorous treatment such as ECT or large doses of tranquilizers was given. The nursing staff had been instructed to test all admissions. Not all were tested, for various reasons, including too many, admissions bunched over a few days, emergency treatment with ECT before testing could be done, or lapses of memory. The group tested comprised about 60 to 70 percent of all admissions and was representative of the entire population admitted to the hospital over a period of several months. A number of patients repeated the test just before they were discharged.

Normal subjects, mainly doctors, nurses, and other hospital workers, were also tested. These did not exactly match the population from which the patients were drawn. There were very few perceptual changes, their thought processes were normal, and they usually classified objects according to their function rather than according to the way they looked.

It was found that while 85 percent of the diagnoses were believed by diagnosticians to be fairly good, their confidence in many cases was unjustified. In only 12 percent of the cases were the diagnoses considered doubtful.

Compared with the normal group, patients diagnosed as having neurotic depressions exhibited changes in visual perception somewhat more frequently. Auditory changes did not increase, but changes of touch and taste did. There were four times as many time changes, and olfactory disturbances were slightly up. There were three times as many thought difficulties. Objects were classified according to their uses rather than how they looked.

As one would expect, there was a marked increase in the proportion of cards marked true in the affect category.

Among the patients with involutional depressions, there were twice as many changes in visual perception compared with patients with other depressions, seven times as many auditory changes, three times as many changes in touch, and some taste and olfactory changes. Thought was altered twice as frequently. There was a marked shift toward visual classification. This diagnostic category, Dr. Hoffer and Dr. Osmond observed (1961), resembles schizophrenia far more closely than any other non-schizophrenic category, excluding toxic psychosis.

All patients diagnosed as anxiety states and personality disorders scored about the mean for non-schizophrenic patients. All non-schizophrenic patients, with the exception of the involutional depressions, have very similar scores.

In all categories except that of mood, the scores of schizophrenic subjects were several times greater than in the entire neurotic group. The patients with deliria and organic psychosis closely resembled chronic schizophrenia, and both resembled the LSD experience. This suggested that schizophrenia, deliria, and organic psychosis have an organic basis in common.

Karl Menninger defined schizophrenia as a long delirium. The elegance and accuracy of this definition, Dr. Hoffer and Dr. Osmond felt, was admirable, but it was curious that this very accurate observation should have led to so few

logical deductions. Dr. Hoffer and Dr. Osmond called it a long and slow delirium.

They concluded that the HOD is useful in diagnosis, particularly when one has little time and wants to exclude the possibility of schizophrenia. Patients, they learned, do not resent being given the test by a secretary or nurse. On the contrary, when they know that their doctors understand their mysterious illness more than they do, they are encouraged and relieved. Every time doctors demonstrate their knowledge, patients have further reason to be encouraged. The HOD put the psychiatrist in a position of being a medical man and not a philosopher.

Dr. Hoffer and Dr. Osmond were not surprised that a number of patients diagnosed neurotic scored high on the test. In one unit, a study of changes in diagnosis showed that, over a five-year period, one-fifth of the so-called neurotics were re-diagnosed schizophrenic.

The next group they tested was a large group of young people. They were only dimly aware of the striking perceptual differences between, adolescent youths and adults until they began to use the HOD test. Boys and girls, they suspected, live in a very different world from that of their parents. When they read, lines move up and down and words may be blurry. This, they say, may have something to do with "reading problems" in primary schools. In adolescence, these may still be present although the basic character of the young person is nearly formed.

During their testing of normal people, they gave the test to adolescents between the ages of 12 and 21 and were surprised to discover that a large number of these had scores which were in the schizophrenic range. Yet there was no doubt that they were not schizophrenic. One of these was an intelligent young man of 17 with no psychiatric problems of any sort. He completed the test very carefully and his perceptual score was high. He was questioned about each card and easily described the changes which he had indicated were present. They therefore tested a large number of normal young people in Saskatoon. Seven schools were sampled, using students aged 12 to 19.

The test was administered in groups to entire rooms selected at random by grade and by room. The cards were shown on a screen in random order and were also read aloud. Each student encircled his answer as yes or no after the appropriate number. Previous work had shown that results obtained this way were not significantly different from the individual tests.

One thing Dr. Hoffer learned was that "there is a beautiful simple relation between age and HOD scores. Normal children aged 13 had much higher scores than normal adults aged 19. This proved HOD is independent of IQ because IQ does not go down with age. But HOD probably determines performance."

About 1,000 students were tested. By the time 900 were completed, it became evident that slow learners had HOD scores nearly twice as high as other students.

Dr. Hoffer studied a group of 34 slow learners who could not meet the academic requirements and most of whom were two or three years behind. They were gathered from all over the city and taken to Technical Collegiate where they were given classes in mechanics, shop, sewing, and so on. They were a cooperative group. The results were as expected—they had more HOD disturbance.

When 15-year-olds were studied in one large sample, it was found that those who were in Grade 11 had much lower scores than those who were in Grade 9. In the same way, in the 16-year-old group, those who were in Grade 12 had much lower scores than those who were in Grade 9.

The present school system does not take into account these individual rates of learning. If some slow learners were given more time they might eventually reach the same final achievement level.

Intelligence level alone was not the reason for the poor showing of the older students in the younger grades, since intelligence ratings are independent of age. Perceptual scores decrease with age, but IQ does not.

Not only is perceptual instability common in adolescence, Dr. Hoffer concluded, but the ability to see and hear things in a stable way develops at different rates in different people. This explains why some adolescents have very low (adult) scores at the age of 14, whereas others have very high scores at the age of 18. Adolescents who mature more slowly than their mates are handicapped in modern schools. However, once matured there is no reason to suppose that they will be worse off than others their age who go through school with better records. In fact it is possible they will be more creative and productive, since some degree of perceptual instability seems to favor creativity. These findings have led to a different scoring system for patients under 21.

Similar results were obtained in the Weyburn hospital where Robert Hall, research psychiatric nurse, and Harold Kelm, research psychologist, tested psychiatric nurses with the HOD. When he examined the results, Dr. Hoffer concluded that the two student nurses achieving the highest HOD scores would probably fail the year.

The value of the HOD as a diagnostic tool became clearer when it was found to corroborate the mauve factor test. When Don Irvine, Hoffer, and M. Mahon (Hoffer and Mahon, 1961) found certain chemicals present in the urine of psychiatric patients, they found also that those who were positive on this test, whether they were diagnosed schizophrenic or not, had high perceptual scores on the HOD. Those who were negative on the biochemical test had low HOD scores.

For three years 317 patients were tested and compared with normal subjects. Patients with malvaria consistently scored higher on the HOD. It now seems reasonable to conclude that many psychiatric patients who suffer from disturbances in mood, thinking, and perception also excrete abnormal chemical substances in their urine.

It was inevitable that before long some psychiatrists would say the HOD test was no good. Most of them would confine their remarks to behind-the-back whispering. Two decided to make their claims in the scientific literature.

Dr. C. N. Stewart and Dr. M. Mahood (1963) reported that the HOD could not, as Dr. Hoffer and Dr. Osmond had claimed, differentiate between schizophrenics and other diagnostic groups. This marked discrepancy in the findings of two groups of investigators attracted the interest of Dr. F. Grunberg, then Superintendent of the Weyburn hospital, Dr. H. Kelm, and Robert Hall (1965). They re-examined the discriminative powers of the test with the aim of finding possible variables which might account for the discrepancies in these results and to determine whether certain adjustments or changes could be made.

They administered the test to 314 patients admitted to the male and female admission wards at the large hospital over a period of 16 months. All patients 60 years of age and under were tested within three days of admission except for those who refused to take the test or could not read English. Subjects aged 21 or under were excluded from the sample. Of the remaining 294 patients, 76 more were dropped from the study because they were alcoholics, mental defectives, suffered from organic or epileptic psychosis, had a mixed diagnosis, or were drug addicts under the influence of drugs.

The test was administered by a ward nurse using the procedure outlined by Dr. Hoffer and Dr. Osmond. At the end of the study the results were compared with the final diagnoses made by hospital psychiatrists.

Stewart and Mahood's sample had consisted only of female patients. In the Kelm et al. (1965) study it was found that non-schizophrenic females scored significantly higher than non-schizophrenic

males on all the HOD scores except the Paranoid Score. Male-female results in the other psychoses and psychoneuroses groups were compared and it was found that while the differences were not statistically significant, females tended to score higher.

Another difference was that while Stewart and Mahood had scored the DS which was added in 1962, they did not report it in their paper. If they had, it would have become clearer why their results were different.

In both studies non-schizophrenic groups scored higher on the Depression Score (DS) than schizophrenic groups. Therefore the DS score, as part of the Total Score (TS), lowered the discriminative powers of the test. Dr. Kelm, Dr. Grunberg, and Mr. Hall suggested that it would be advisable to remove the Depression Score from the Total Score. Although this change will not greatly increase the present discriminative power of the TS, they said, it can make a noticeable difference in borderline cases.

A further examination of Stewart and Mahood's data revealed that the correct scoring keys were used, but a number of errors were made. Thus using the same statistical test as employed by Stewart and Mahood, all HOD scores were found to be significant except the Depression Score. The study therefore confirmed Hoffer's and Osmond's findings.

Dr. Kelm then reviewed the published reports of the test, ranging over a period of six years and involving about 4,000 psychiatric and non-psychiatric subjects to whom it had been administered at various centers in Canada and the United States (see Hoffer et al., 1975).We found it to be reliable in distinguishing schizophrenics from non-schizophrenics, and psychiatric groups from non-psychiatric groups. Of the whole test, 17 items alone, he found, may be used by themselves as a short emergency scale when time does not permit the use of the whole test.

Dr. Kelm advised that different normal scores are required for patients 17 years and under, 18 to 21 years inclusive, and ages *22* and over, because of differences in perception. He warned that those students whose high scores do not go down as they get older, or whose scores even increase with age, should get special attention. If they are also having difficulty in school, this may be a sign of the development of schizophrenia which may then be further investigated.

Patients suffering from schizophrenia or from organic and toxic psychoses, such as patients who are drunk or suffering from delirium tremens, score very high.

Women score higher than men due to the influence of the menstrual cycle. In any group of women who have not reached the menopause, about 15 percent will be menstruating when they take the test. The HOD scores tend to be lowest at the halfway point in the cycle, during ovulation. For the next two weeks there is an increase in the secretion of progesterone which inhibits the secretion of estrogen.

But many women suffer from premenstrual tension, which is partly due to an inadequate production of progesterone. When this happens, HOD scores begin to rise and reach their maximum the week before and the week during menstruation. Thereafter scores begin to decrease.

It is well known that women generally are more irritable and anxious before menstruation and feel better afterwards. This must be taken into account when they are given the test. They will require two base lines of HOD scores: at ovulation, and just before or after menstruation has started.

The test, Drs. Kelm, Hoffer, and Osmond found, has many uses. As an aid to diagnosis it is reliable and valid. It will help determine when a toxic state is present, but will not determine which toxin is responsible.

If HOD scores begin to increase after admission, one should suspect the development of one of the complications of alcoholism, usually delirium tremens.

The HOD can be used as a monitor of therapy. An example of this is a young man of 22 who tried to commit suicide

when he was 16, while depressed. When he was 18 he tried to strangle himself. He was given group psychotherapy, but was not given any diagnosis nor told he was ill. A definite personality change had begun at 16.

In May, 1966, when he was 20, he again tried to kill himself and was admitted. He had feelings of unreality and often sensed Cod's presence. He was very paranoid and confused and deeply depressed. His total HOD score was 146.

He was placed on nicotinic acid and vitamin C, together with a tranquilizer, but remained very tense and depressed. He was readmitted and his total HOD score was 141. He decided to return to his parents' home for one month to convalesce.

On June 24, 1966, his score was 40 and he was definitely better. His thought processes were normal, and his depression was nearly gone. His insight had returned, and he was aware his paranoid ideas stemmed from his schizophrenia. In August, his score was 8.

He returned to complete his University and did very well, but in March, 1967, he reported he found it difficult to study. He was given a large dose of nicotinic acid to take a day, to accelerate his recovery, and started on a sugar-free high-protein diet.

Another young schizophrenic has learned how to monitor his own state of health. Mr. A. is happily married and active in Schizophrenics Anonymous. He completed his graduate degree in the sciences. In January, 1967, many years after having stopped taking his medication, he noticed a return of anxiety and tension. He was given the HOD test and found, to his surprise, that a large number of questions were true. This was very beneficial for it warned him he was more ill than he had supposed.

He was started on nicotinic acid, 6 grams a day, and one week later was normal. Thereafter he checked himself regularly with the HOD.

The test is helpful in determining the seriousness of symptoms. In schizophrenia, it is important to know how depressed the patients are because of the serious risk of suicide. Schizophrenics with very high depression scores should be watched very carefully and their families cautioned. It is not easy to kill oneself under the watchful eyes of nurses and other patients, yet many schizophrenics have done so. In the age group 16-44, in one year in University Hospital, suicide was the second cause of death. In the 45-64 group it was seventh. The Saskatchewan suicide rate is 100 for the province each year.

The usual rate of suicide per year in Canada is 10 per 100,000 population or about 100 per year in Saskatchewan. Dr. Hoffer and Dr. Osmond estimated that about one-quarter of these are schizophrenic. These figures are astounding.

If the HOD test shows certain symptoms such as paranoia, it can be expected that the patient will have difficulty in his relations with other people. Patients with very high paranoid scores may be very difficult.

The test can be used to encourage patients. Many improve so slowly that they are not as aware of the improvement as their therapist. Dr. Hoffer and Dr. Osmond have found it useful to show them their scores at each interview. They can see how their scores change, and when they see a marked decrease their recovery is often accelerated.

It is a useful guide to prognosis. If the test were given at regular intervals, Dr. Kelm reported, and plotted on a graph, it would be possible to see at a glance whether the patient is improving, remaining the same or getting worse. It can thus help the physician decide whether to increase or decrease medication, change the treatment, and evaluate its effects. Since patients who are not fully recovered are more apt to relapse, it is obvious that patients discharged with high HOD scores are more apt to relapse. The higher the scores on discharge, the greater the risk of relapse or return to hospital.

When HOD scores begin to rise, it is a sign the disease is beginning to return. The test can be given by follow-up

personnel or by mailed questionnaire. In fact, patients can take the test themselves. They are informed that when scores begin to go up it is important to take this as a warning that they need treatment quickly.

Some users of the test have expressed concern about a subject's faking the test. Dr. Hoffer and Dr. Osmond are not unduly concerned. Experience has shown that if a subject has faked the test there is usually a marked discrepancy between the test results and his clinical state. In addition, about 20 questions may be used to detect faking. Schizophrenics generally answer the questions truthfully, and the results of the HOD furthermore are confirmed by the mauve factor test.

During these investigations, other uses for the HOD occurred to Dr. Hoffer and Dr. Osmond.

"If 10 percent of the relatives of psychotic patients are themselves psychotic," said Dr. Osmond, "it means that when we discharge chronic patients we are exposing a very vulnerable group to stresses which may be beyond their limited tolerance and for which we make very inadequate allowances and preparation. The HOD test on patients and relatives can help us be more adept in our approach."

It occurred to Dr. Hoffer that the HOD could be used to test traffic offenders. He contacted the Saskatchewan Highway Traffic Board with this suggestion, but nothing ever came of it.

The HOD also helped them develop their perceptual hypothesis, which states that those areas of the brain which integrate, stabilize, and maintain constancy of perception are changed owing to a biochemical disorder. As a consequence, the patient's experience of the world is dramatically changed. When perception is altered, the person reacts to the new perceptions and therefore there is some change in personality and behavior. This explains the so-called queer or bizarre behavior of these patients. This, in a few words, is schizophrenia.

The HOD helped explode the favorite psychiatric myth that insight is important to prognosis. Insight is a commonly used word in psychiatry. It is employed in diagnosis and prognosis (psychotics are said not to have insight) and as a way of judging the results of treatment. It is used with different shades of meaning by different schools of psychiatry. It has been defined as a mental vision, a perception, discernment, a mental looking to or upon, while an early use of the word signified understanding or wisdom. For some psychiatrists, insight involves a perception of the part dynamics play in symptom formation. Others believe that insight is present when the patient understands that painful hallucinations are the result of disease. The presence or absence of insight is often held to be a measure of the quality of improvement in a particular patient, and it is widely believed and often taught that patients who have insight are more likely to get well than those who do not.

Dr. Hoffer and Dr. Osmond confined their study to the simplest form of insight—whether the patient believed he was ill or not. They wondered whether patients who believed that they were ill responded better to treatment than those who did not.

One of the HOD questions is, "I now am sick." If a patient placed this card in the true box it showed he believed he was ill and therefore had insight. The test was administered by nurses to nearly all patients admitted to a psychiatric ward for a two-year period. The proportion of patients who believed that they were ill varied from 50 to 70 percent for various diagnostic groups and did not differ significantly between groups.

Contrary to their expectations, derived from many textbooks of psychiatry, just as many schizophrenics know they are ill as neurotics. A large proportion of all these patients did not believe that they were ill, but nevertheless came into a psychiatric ward for treatment and most of them stayed there as long as they were required to.

Schizophrenics generally speaking have less favorable prognosis than

neurotic depressions or anxiety states which suggests that the presence or absence of this kind of insight has little bearing on the outcome of a particular illness. What is important is not so much what a patient believes but whether or not he is prepared to act upon the advice of his family and his physician, whatever his own views may be.

An offspring of the HOD is the Experiential World Inventory test, or EWI, developed in the New Jersey Bureau of Research in Neurology and Psychiatry, Princeton, by Dr. M. El-Meligi and Dr. Osmond. The EWI will no doubt be preferred by psychologists because it is longer and more complicated. It is a refined and more complex version of the HOD.

VI. THE MAUVE FACTOR TEST

The HOD test ploughed a new furrow in psychological testing. At a time when psychologists were obsessed with method and ignored what was clinically most important, the HOD test gave new direction. It examined time perception, self-perception, and the perception of others. It revealed to the therapist the kind of world the patient was experiencing.

The HOD showed that it was possible to acquire a wealth of valuable information in a short time and by a simple method. Psychologists like Dr. Harold Kelm in Saskatoon and Dr. M.EI-Meligi in Princeton, New Jersey, greeted it with delight and became interested in its possibilities. Dr. El-Meligi called it the "little beauty." Other psychologists were slightly less enchanted.

Strangely, the diagnostic test which aroused the greatest hostility was not the HOD, but a cold, impersonal and objective chemical test. Dr. Hoffer and Dr. Osmond called it the mauve factor test, and those who showed positive had, they said, malvaria.

Professional fear of the test is understandable. For over 70 years psychiatrists had said that mental illnesses, including schizophrenia, were conditions and not illnesses. To accept the reality of a chemical test by which schizophrenia could be diagnosed was to admit that the whole structure of psychiatry had to be changed.

The story of the mauve factor test, Dr. Hoffer said, goes back to 1952 when he and Dr. Osmond first began their work with LSD.

"We considered that the LSD experience modeled the schizophrenic experience. Therefore this would allow us to examine schizophrenia (its model) in detail in normal people who could transmit to us the essential nature of the schizophrenic world. In addition, we wanted to see the schizophrenic's world for ourselves, and this we were able to do through LSD.

"We also hoped to use it for developing tests and newer treatments and to establish more rational nursing techniques for dealing with schizophrenic behavior.

"We finally hoped to use the LSD experience as a biochemical model. Since I am a biochemist, it seemed likely that our biochemical work would move the fastest. But it did not. Our psychological, nursing, and clinical understanding of schizophrenia moved ahead very quickly, but biochemically we were still groping after the crudest of tests.

"Dr. R. Fischer wasted three years trying to make tadpoles diagnose schizophrenia by the effect on them of schizophrenic urine. Nothing came of this. But by 1957 I was able to lure in good biochemists who were given the task of examining the chemistry of adrenochrome.

"At that time adrenochrome was a brownish-red powder which was very reactive and deteriorated very quickly. Many internationally known chemists did not believe there was such a thing as a stable pure adrenochrome. This discouraged chemists from entering this very difficult field.

"When Dr. N. Payza came to work for me, I ordered him to do some work on

the chemistry of adrenochrome, but we could not solve the problem created by its instability. In 1957 I went to a conference on biochemistry and mental illness in Vancouver. During lunch I spoke to an expert organic chemist who told me that, in general, organic substances were unstable if they contained small quantities of impurities.

"Adrenochrome was made by oxidizing adrenalin with silver salts. It occurred to me that if we removed all the silver ions, we might have a pure stable form of adrenochrome. At that time chemistry had developed methods of purifying compounds by passing the chemicals in solution through adsorbing columns, which bound the impurities and allowed the chemical which was to be purified to pass through.

"I immediately sent my chemist an air mail letter asking him to follow this procedure with some impure adrenochrome which we had in the laboratory. Then I went on to Tulane to visit Dr. R. Heath and to see his taraxein work. From there I went to Boston to be first discussant after a paper read by Dr. Heath on taraxein. Many psychiatrists had expected me to be very critical of Dr. Heath's work. I disappointed them by supporting him.

"When I came home I rushed to the laboratory to see the pure adrenochrome and discovered that the experiment had not even been done. I was annoyed and half in jest told Dr. Payza that he would be fired if he did not have it done in a few days. The next day he came into my office to ask whether I would like to see the first pure crystalline adrenochrome. On a small glass plate I saw the first stable crystals. They were beautiful, sharp, needle-like crystals with a brilliant sheen. The method worked.

"A few years ago, Humphry told me an amusing story. At the American Chemical Society's meeting in Kalamazoo, in 1957, one authority stated that adrenochrome was inherently unstable and would never be synthesized. He demonstrated this by referring to its structural formula. At that time Humphry had been carrying 100 mg of pure crystalline adrenochrome in his pocket for some weeks and delighting chemists by letting them peek at it. He found this authority's certitude surprising."

Adrenochrome continued to suffer a stormy passage. In 1958 Dr. J. Axelrod and his group after reading a paper published by Dr. Payza on his method of measuring adrenochrome in human fluids reported that using a method they developed they could not find adrenochrome in the plasma of schizophrenics and normals. Saskatchewan chemists compared the Axelrod method with the Payza-Mahon method. No wonder the former got those results. "The fluorescence readings using the Szara, Axelrod, and Perl in method are so close to the blank readings one would readily agree with their conclusions," wrote Dr. Osmond and Dr. Hoffer (Osmond and Hoffer, 1959).

The method was at least five times less sensitive than the Payza-Mahon method. It was a dud method. But the report made the research critics happy. Since there were criticisms of the first method, Dr. Payza modified it and published a second method. Early in 1959 it was admitted at a public meeting in New York City, during a debate in which Dr. Hoffer appeared, that Dr. Axelrod had not obtained adrenochrome from Saskatchewan as reported in the paper but from a Washington scientist to whom Dr. Hoffer had sent it.

However, it was said that adrenochrome had no psychosis-mimicking properties, but this, too, was disproved. Indeed, Czech investigators have called it a "schizomimetic" substance. Next there have been those who consider that adrenochrome does not occur either in humans or animals. Opinions were very strongly divided about this. Lately a few were prepared to grant that adrenochrome did exist, was psychotomimetic, did occur in man and animals, but did not concede there was enough evidence to implicate it in schizophrenia.4

"Dr. R. Heacock then took over," Dr. Hoffer said. "Dr. Heacock is a brilliant

chemist who arrived about that time. He has done more to unravel the mysteries of adrenochrome and adrenolutin than any other chemist and is known internationally as the foremost expert on the chemistry of these compounds."

Dr. Payza continued to look for evidence of adrenochrome in blood and urine and succeeded in developing chemical techniques which would not destroy these sensitive substances. He and another chemist, M. Mahon, measured the distribution of what they believed was adrenochrome in both red cells and plasma (Payza and Mahon, 1960). According to them, adrenochrome was normally in the red cells and very little was in plasma. If LSD was given it came out of the red cells and the plasma levels rose. As the LSD effect waned the "adrenochrome" went back into the plasma. Now it became possible to examine the hypothesis that the LSD reaction resembles schizophrenia bio-chemically as well as psychologically.

"No chemist can find any chemical unless it has a unique property by which it can be traced," Dr. Hoffer explained. "To ask a chemist to find a schizophrenic chemical was asinine. He would not know how-to begin. So we laid down guidelines: (1) the substances were probably indoles; (2) they had to be treated gently or they would be destroyed; and (3) perhaps LSD would push these compounds into the urine.

"I selected an alcoholic, who was not schizophrenic, who was to receive LSD for treatment. We took a sample of morning urine and another three hours after he had been given 200 mcg LSD. Both samples were examined simul-taneously using a technique called paper chromatography, with solvents (solutions) which, we hoped, would not destroy the schizophrenic chemical. You can see for yourself how the method works when you drop ink on a blotter. If a big blob drops on the blotter, the ink begins to spread from the point where it was dropped in a radial direction. If you look closely, you can see that there is a clear margin of water which moves faster than the particles of pigment which make up the ink. Similarly, chemicals will travel more slowly than the solvent. How far they travel depends upon the structure of the molecules. Some are swept further from their origin than others and are called fast running or high Rf spots.

"Using this special technique, I hoped something would appear on the LSD chromatogram which was not present before. To our great pleasure, this happened. On the paper strip which was developed, a mauve spot appeared near the top which was not present in the first morning, pre-LSD, specimen. This became our number one target as the chemical which, if we were right, would be present more frequently in schizophrenic urine.

"However, certain additional tests had to be made first. We had to be sure it was not LSD or one of its degradation products; that it was not a tranquilizer or an artifact due to food, smoking, etc. These were examined and ruled out.

"A few weeks later I selected 12 subjects. Six were schizophrenic patients from the psychiatric ward of University Hospital and six were normal people from our laboratory staff. We collected urine samples, and to one of the normal urines I added some adrenochrome. The samples were then randomized and numbered from one to 12.

"By then, Don Irvine had joined our staff and had been given the job of perfecting the method for measuring mauve factor and for isolating it and identifying it. He was given the 12 samples.

"A few days later he came back and reported that six of the samples had mauve factor while one of the remainder was doubtful. When I decoded we found to our astonishment that all six schizo-phrenics had mauve factor while the one normal containing adrenochrome was doubtful. This kind of distribution was statistically already beyond the 1 percent

*** Prof. Mark Altschule of the Harvard Medical School has shown that the blood and urine of schizophrenics contains large quantities of amino chromes (substances resembling adrenochrome and adrenolutin).**

level of probability. It was a fluke.

"There is an interesting story to explain why so many scientists find evidence which supports their own hypotheses while other scientists are unable to do so. It seems that God is a scientist and among all men he loves scientists the most. However, men do not like to be scientists so they must be encouraged. Whenever any human develops a hypothesis and begins to test it, God sees to it that the data will support it. After several months that scientist is so excited and thrilled by having a hypothesis come true that he becomes hooked—a research addict. As soon as he has irrevocably set his path along research, God withdraws and allows nature to yield the real data. Thereupon most hypotheses are not supported because in fact they are not real and do not correctly explain nature.

"It is therefore very important for any scientist to keep doing his research until it is absolutely certain God has withdrawn from the scene. Then if the data still supports the idea, it must be true and other scientists will then also corroborate.

"Don Irvine was given one job—to identify the mauve factor. But I decided to outwait God by using the same test for many years until I was certain He was no longer interested. We therefore began to examine large numbers of patients of all diagnostic groups to see what proportion from each group had mauve factor.

"By 1961 we had sufficient data for our first series of papers. These were published in the **Journal of Neuropsychiatry,** August, 1.961. This was one of the few times one research group contributed every paper to one issue of a psychiatric journal. This, of course, created a tremendous amount of hostility. Other psychiatrists either did not read these papers, or read them and promptly forgot what was said. Anyway, we were met by a deafening silence. Whereas every other chemical paper purporting to find a chemical related to schizophrenia was examined quickly, and as quickly dis-proven, not a single report appeared on mauve factor. It seemed as if there was a worldwide conspiracy not to examine any claims put out by our group, even though this group had by then reported findings now considered very important (for example, the lowering of cholesterol by nicotinic acid). Several years before that, a pink factor found to be related to schizophrenia in some laboratories received vigorous examination in over a dozen laboratories and was not confirmed in most.

"But until 1965 the mauve factor remained lonely and uncorroborated. However, no one had disproven it either, suggesting that a few laboratories had corroborated us but were afraid to publish this, since this would make them our allies.

"By the end of 1965, the research had made great progress in various areas. That year the mauve was separated into nine components and was corroborated in Princeton, New Jersey, and Moose Jaw, Saskatchewan. The HOD and EWI were well established. We had made progress in our perceptual hypothesis of schizophrenia. The psychedelic therapy, with LSD, was well established and flourishing in Sheridan, Wyoming, Topeka, Kansas, Spring Grove, Princeton. The niacin therapy was well established and moving fast. We had influenced new principles and a new philosophy in architecture.

"Our adrenochrome hypothesis was enormously strengthened by the work of fellow scientists in the United States and Russia. Scientists could now mention adrenochrome in their literature without apologizing.

"Meanwhile we were giving a great deal of our attention to the mauve factor test. We examined several thousand subjects—patients and normal subjects -between 1961 and 1967."

One of the first findings was that the factor was more often present when patients were ill. Out of 57 urine assays made on patients who were ill or improving, 41 had the factor. Twenty-six tests were made on patients who were much improved or well. Of these, only five were positive.

Another finding was that schizophrenics who still had the factor present on discharge will have a poorer prognosis than those in whom it has disappeared.

One patient who was discharged as being "well" still had the factor, but he was readmitted twice in* the next two months. Another patient who also had the factor when discharged was placed on nicotinic acid as an outpatie'nt. Although he was an alcoholic, he stopped drinking and began showing a gradual improvement.

Thirteen patients tested positive for the factor when admitted. Nine were negative on discharge, and eight got along, fairly well in the community. One was readmitted a few months later and was again positive on readmission.

Four were positive on discharge. Of these, one had to be readmitted twice since discharge, and three improved while taking nicotinic acid.

Of a group of 13 patients who had the factor but were not diagnosed schizophrenic, one, a diagnosed hysteria, was admitted to a mental hospital a few days after discharge and improved after receiving ECT. Another, an alcoholic, was suspicious and difficult to get along with when drunk, and when sober had changes in perception, thought, and mood. A third, diagnosed as "adolescent turmoil," a fashionable diagnosis for young people, was considered psychotic by her uncle, a physician. Another, diagnosed anxiety neurosis, had changes in thinking, and her behavior was bizarre. Still another was considered to be schizophrenic by the referring psychiatrist. Most of these patients were hardly typical of the diagnoses attached to them.

On the basis of the massive data they acquired, Dr. Hoffer and Dr. Osmond came to the following conclusions:

The presence of mauve factor occurred more frequently among schizophrenics than among any other group. Normal subjects seldom had mauve factor. The frequency of mauve factor in the various diagnostic groups is as follows:

Schizophrenics — Acute — Those who had no previous treatment with tranquilizers and other types of treatment— 90 percent.

Acute, first attack and second attack— 75 percent.

Chronic schizophrenics—50 percent. **Chronic schizophrenics resident in mental hospitals over 20 years—**10 percent.

Schizophrenics recovered—all negative. However, not all schizophrenics who become negative recover. **Neurotics** — This diagnosis includes depressions, anxiety states, etc., and every other psychiatric condition excluding schizophrenics, personality disorders, retardation, and organic diseases. About 25 percent are positive.

Alcoholics — 35 percent positive. **Personality problems—**About 30 percent are positive over the entire age range, but a much larger proportion of 'teen age behavior problems are positive.

Retarded—At least 50 percent of any large group are positive. **Physically ill—**About 10 percent are positive.

Normal—About 5 percent are positive. **Families with one member schizophrenic** —A study of 40 families shows that if one member is schizophrenic, the incidence of mauve factor in the first order of relatives (parents, siblings, children) is 35 percent.

"In 1962 we decided the condition associated with the test had to have a name," Dr. Hoffer continued: "Writing from England, where he'd moved in 1961, Humphry said he liked 'malvuria' better than 'mauvaria,' which we named it at first. He thought malvuria was a little easier to say and clearer. Mauve derives from the color of mallow whose Latin name is 'malva.' In French 'mal' is bad, and since adrenolutin is being excreted, he thought this was an appropriate pun. From that I derived the word 'malvaria'. It is easier to say and still has the same reference to a factor in the urine. It has three implied meanings in it—its reference to the mauve factor, to the French word 'mal' or disease; and to 'var'—variation, meaning a disease characterized

by variability and the presence of a specific chemical in urine. We therefore had discovered a new disease called malvaria which we could define, with subtypes including those where the expression is schizophrenic, psychopathic, anxiety neurosis, and all the rest."

At that time they did not know what the mauve factor was, but in 1969 D. Irvine et al. reported in **Nature** that it is a pyrolle called 2, 3 dimethyl-3-ethyl pyrolle. It was still not known where the factor comes from.

It became obvious that the mauve factor cut across all diagnostic lines and was not a diagnostic test for schizophrenia as it is usually defined.

"This is not as serious an objection as might appear, since the diagnostic criteria for diagnosing schizophrenia are vague and even these vague standards are not used equally by different psychiatrists," Dr. Hoffer said. "This is why diagnostic psychiatric conferences usually split into three different factions which seldom convince each other. Furthermore, as with any disease which is not fully developed clinically, the early stages are not representative of the disease. Few psychiatrists associate depression or fatigue with beginning schizophrenia.

"This is why it is not unusual for early conditions to be mistaken for others. For example, the most common diagnostic error is t6 label early schizophrenics as being 'depression' in adults, and 'personality problems' in 'teen age patients.

"Many years ago Dr. Nolan D. C. Lewis reported that 50 percent of a large number of patients called 'depression' became classical cases of schizophrenia within a couple of decades. This was not due to a change in the nature of the illness but to an inadequate examination of the symptoms present when the patient first came to the doctor.

"In most cases schizophrenic symptoms were ignored in the diagnostic decision. Doctors tended to ignore or to overlook perceptual changes.

"In Saskatchewan we have seen many patients who for many years were labeled anxiety states or depression because their psychiatrists did not determine whether perceptual changes were present. As the disease developed perceptual changes became more clear. When visions and voices appeared, they were re-diagnosed.

"Diagnosis in psychiatry at present is something like the clothes we wear— they are determined by fashions. Over the past two decades age had been considered a main diagnostic variable. Thus schizophrenics under the age of 21 are very often considered to be adolescent reactions of one sort or another. Between the ages of 40 and 60, schizophrenia is often diagnosed as an involutional paranoid state or depression. Over 60 they are often misdiagnosed as senile states of one kind or another.

"With this degree of diagnostic confusion it would be most strange if even a perfect biochemical test showed perfect concordance with diagnostic groups. The latter are simply much too heterogeneous. This is not a new problem in medicine. Every illness goes through a similar phase until laboratory tests are developed. These eventually take on the main diagnostic burden."

An example of this, said Dr. Hoffer, is syphilis. Before the spirochete was discovered, syphilis was diagnosed by clinical impressions only. For many years it was taught that syphilis was the grand masquerader of medicine since it could mimic any other disease, including psychiatric diseases. Unless a specific skin lesion developed early, the disease was often overlooked. When it became possible to see the spirochete in the microscope, the diagnosis became very specific for whenever one saw these organisms one could be certain syphilis was present. Thus, the diagnosis no longer depended upon clinical symptoms but upon the absence or presence of these organisms; i.e., the main diagnostic factor switched from clinical impressions to a laboratory test—the microscope.

But the microscope test was difficult, requiring the utmost patience and skill,

and undoubtedly .many spirochetes were missed. To simplify diagnosis a serological test (Wassermann) was developed, which depended upon simple chemical reactions. Thus one could quickly examine blood or spinal fluid to see if the Wassermann test showed spirochetes were present somewhere in the body. This became, and is, one of the main diagnostic factors.

However, not even the serologic test is wholly accurate. It is stated, "In a very real sense all these tests are nonspecific. This fact presents no difficulties when it is employed to confirm a diagnosis of syphilis made by clinical examination or from the patient's history. The non-specificity becomes of the greatest importance, however, when a positive test represents the sole indication that a patient might have syphilis. For, in addition to syphilis, there are other states not necessarily infectious which give rise on occasion to a positive test. Such results are designated biologic false positive reactions. It has been credibly estimated that in certain highly selected populations in the U.S. the incidence (or false positives) may approach 50 percent (Ed., Cecil et al., 1955)".

The same transition has occurred in a few psychiatric illnesses, e.g., syphilis of the brain and pellagra. Many patients with brain syphilis are psychotic, and it was always difficult to distinguish them from schizophrenia of a chronic form. But when it was shown that a spirochete was present, and later that the Wassermann test was positive, they were re-diagnosed. A schizophrenic syndrome which later was found to be positive for syphilis was re-diagnosed as a case of syphilis of the brain, no matter what the clinical picture was.

This also happened with pellagra psychosis. Between 1940 and 1950 nicotinic acid came into general use as the specific treatment for pellagra. At that time, in some southern mental hospitals, as many as 10 percent of the admissions were pellagrins who clinically were schizophrenic. This is probably an underestimation. When nicotinic acid began to be used in doses up to 1 gram a day, a fair number of chronic schizophrenics began to recover. Since it was then believed schizophrenics could not recover, and since it was known patients with pellagra psychosis could, these cases were immediately re-diagnosed as pellagrins. This type of reasoning, said Dr. Hoffer, effectively prevented widespread examination of vitamin B3 as a specific therapy for schizophrenia.

"It therefore appeared possible that the mauve test might be for schizophrenia, in the long run, what the WR was for syphilis. However, as a preliminary step we decided to jump immediately from a clinical diagnosis to a laboratory diagnosis.

"In a recent paper, Lester S. King (1967) reviewed the three essential steps in making a diagnosis. These are (1) presence of an object as condition (disease) which must be classified; (2) knowledge of a class of things (diseases) which have certain characteristics, and most important of all (3) a decision that the particular object belongs to this class, or not. The last step, the decision, constitutes the diagnosis.

"Diagnosis allows us to use the large body of knowledge of a class of diseases in order to treat a particular member of the class. When we place a patient in a particular diagnostic group, we know a good deal about the illness, the best way to treat the patient, and the probable outcome.

"Diagnosis thus depends upon 'an exercise of recognition or intuition that a particular example does have features which characterize a particular class. 'The intuition,' according to the author, 'is an act of judgment. We can teach knowledge about a subject and our textbooks, monographs and journals are crammed with such knowledge. But can we teach judgment and intuition?' .

"It is because it is impossible to teach intuition that we must turn to laboratory tests. The history of medicine has been characterized by ever-increasing precision and refinement in diagnosing, but specific treatment is never far behind

accurate diagnosis.

"We decided to use the presence of the mauve factor as the chief diagnostic aid for a condition or state we called malvaria. A malvarian is any person who has mauve factor in his urine when the test is done by the method published in the **Journal of Neuropsychiatry,** August, 1961. By definition there is a perfect concordance between malvaria, a condition, and the presence of mauve factor in the urine.

"But it does not necessarily follow that this new state or condition is a disease. It could have happened that the presence or absence of mauve factor is completely irrelevant to the state of disease or ill health. This was quickly ruled out by the findings already reported that the most serious classes of psychiatric diseases contain the highest proportion of mauve factor, or of malvaria.

"In other words, we can say as a firm rule that the more serious the psychiatric disease, the larger is the proportion who have malvaria. The incidence of malvaria is greatest among schizophrenics, the most chronic and serious of all mental diseases, and is lowest among normal people. Even then it tends to occur in normals who are first-order (close) relatives of schizophrenics. The condition, malvaria, is therefore classifiable as a disease."

In 1960 Dr. Hoffer concluded that logically, there is no disease called schizophrenia. Writing to Dr. Osmond, he added, "nor is there any disease in medicine in the sense that there is a visible object. There are certain operations such as measuring blood sugar, or the presence of the mauve spot.

"The trouble with schizophrenia was that no one developed a generally accepted operational measurement. We can now define schizophrenia as that change in mental function which coexists *in* most cases with the presence of mauve factor in the urine. If this becomes generally accepted, then all other diagnostic tests are valueless and can be discarded. Clinical description would be useful to some degree in understanding the patient and his illness, in providing proper hospital and rehabilitative care, but not in treating him. After all, one can successfully set a broken leg without worrying too much about the personality of the patient."

The differences and similarities between schizophrenic malvarians and neurotic or retarded malvarians prompted a new study which took seven years. By October, 1961, Dr. Hoffer had tested 10 retarded children. Eight of these were found positive for the mauve factor. Two of the positive children were given nicotinamide, 1 gram a day, and were well several months later.

At the age of seven, one had poor motor coordination, short attention span, could not get by kindergarten, and could not relate to other children or adults. Psychiatric examination led to the diagnosis of mental retardation. In June she was started on 1 gram of amide a day. By October her coordination was good, she was much improved socially and was able to do Grade 1 without difficulty. When the same psychiatrist saw her again, he was not told of her medication, and reported his great surprise at the change in her.

The second case, a boy of 14, passed Grade 6 in the top half of his class, but could not get by Grade 7. A prominent psychologist tested him and found him retarded and lacking motivation. He was positive on the test. After two months on nicotinamide he was able to do Grade 8 without difficulty.

"I am convinced," said Dr. Hoffer, "that every child who shows any difficulty in learning or in emotional development should be given this test."

A month later Dr. Hoffer saw a 13-year-old girl who was one of the more difficult children in the John Do I an School for Retarded Children, in Saskatoon. By that time he was seeing one retarded child a week from this school. Mary appeared schizophrenic, not retarded. She was positive on the urine test. On checking her psychiatric history it was found that she was first seen by a psychiatrist in 1953 at the age of five

when her IQ tested about 70 and she was said to be a very difficult problem. At that time Dr. Hoffer asked the child psychiatrist to test the effect of nicotinic acid on some of his disturbed children, and she was started on the vitamin, 1/2 gram three times a day. Her mother was not properly prepared for the flush and ran to her pediatrician who told her to stop the nicotinic acid.

"This is one of our successful physicians with limited intelligence," Dr. Hoffer commented.

But the mother was made of sterner stuff and insisted on continuing. The girl was on nicotinic acid about *six* months. During this time she learned to talk and there was such a marked improvement that a psychiatrist, one of the opponents of cure in schizophrenia, recorded his astonishment in his notes. For reasons unknown, the nicotinic acid was stopped. Nevertheless, improvement continued another six months.

The question was raised of starting the child on the nicotinic acid again, but the psychiatrist stated she was making so much progress she should not resume the medication.

"This is such a bizarre form of reasoning I am at a complete loss to follow it," Dr. Hoffer said. "A few months later she had regressed to her pretreatment condition and nicotinic acid was started again which she took for an unknown time. Then she stopped. She became a young adult with severe emotional problems and apparently was retarded. Think of the wasted years and this girl's life shaped by schizophrenia when it could have been so markedly altered. I started her again on nicotinamide and kept her on it for several years."

Malvaria—the disease

More about malvaria is contained in a paper called "Malvaria: A New Psychiatric Disease," by Hoffer and Osmond, published in the **Acta psychiatric scandinavica** 39, 1963.

To determine the differences between malvarians and non-malvarians, the research group studied 104 patients with malvaria and compared them with 75 patients without it. The 104 consecutive patients were tested routinely over **a** two-year period and found to have mauve factor in their urine. The non-malvarians were every other patient tested who did not have mauve factor, but those who were positive on admission and became negative while in hospital were excluded and listed with the malvarians.

"If the mental status and HOD scores of malvarians who have become negative while in hospital is examined on discharge," Dr. Hoffer and Dr. Osmond stated in their article, "they are then found to resemble closely the broad classification of 'non-schizophrenics.' "

The clinical record of every patient was examined in detail for objective descriptive statements. If the psychiatric resident stated the patient had visual hallucinations, this was recorded as "yes" for visual perception. If no changes were reported it was entered as "no." Only visual and auditory changes were recorded.

If the patient was able to think coherently with no blocking or disorientation, he was listed as having normal thought process. If his thought process was normal but he had delusions, or ideas of any kind grossly at variance with his intelligence or environment, he was listed as having a disorder of thought content.

There were more females in the malvarian group, and more single than married people.

It was shown that about one-third of the malvarians have visual or auditory changes. Of this group 58 had no hallucinations, 19 had both, 16 had only visual changes, and 11 had only auditory changes—i.e., 46 patients or over 40 percent had either visual or auditory changes in perception. Fewer than 7 percent of non-malvarians complained of perceptual changes. Of this group 69 had no perceptual changes, two had both visual and auditory changes, three had

only visual changes, and one had only auditory changes.

Nearly two-thirds of the malvarians had pathological thought content and nearly half showed changes in the process of thinking. In contrast, non-malvarians showed changes in content in two-fifths of cases and only 4 percent showed changes in process. Half the malvarians had inappropriate affect compared to 10 percent for non-malvarians. In both groups about two-thirds were depressed. Malvarians had much more pathological behavioral activity and were more seclusive, more inappropriate, and more often overly active.

The HOD test results were then examined and it was found that the scores were significantly different for both groups for all but the depression score. These scores, therefore, reflect faithfully the differences recorded by residents in psychiatry in the case records of these patients.

Except for the 35 malvarians and 15 non-malvarians who were treated by research doctors, the treating doctors didn't know the difference between the two groups. Yet these doctors treated their malvarian patients differently. They gave them ECT and nicotinic acid much more often and LSD much less often.

There was, however, no difference in the amount of ECT given per patient. Both groups received about the same amount and variety of drugs—tranquilizers, antidepressants, or other medication, and both received the same quantity of psychotherapy and other therapies commonly given in modern psychiatric wards of university hospitals. These trends were maintained for repeated admissions. Both groups had similar readmission rates, but the malvarian group had 45 admissions before their first admission in this study, and the non-malvarians had only 17. Thus the malvarian group had a total of 2.25 admissions per patient, and the non-malvarians averaged 1.83 admissions per patient. Malvarians were kept in hospital longer, averaging nearly two weeks longer, and 16 percent of the malvarian group were admitted to a mental hospital during the follow-up period compared to 13 percent of the non-malvarians. At $30 a day the malvarians cost $360 more per admission—$65,000 for the entire malvarian group.

About 75 percent of the malvarians were schizophrenic and were treated as schizophrenics. The researchers therefore considered it logical to test the hypothesis that malvarians who were not schizophrenic would respond to the same treatment regime. They selected 14 adult patients and a group of retarded children for this project which lasted over two years. Six of the adults were alcoholics, five were primarily depressions or anxiety states, eight were mentally retarded, three were behavioral problems in children, and one was an immature personality.

Alcoholics

Before treatment for alcoholism began, it was considered important to know in advance whether the patients were schizophrenic or not, for schizophrenic alcoholics do not achieve a psychedelic experience as readily as ordinary alcoholics, and also require special precautions because they were either liable to have very slight reactions or to have prolonged reactions lasting many days (Hoffer and Osmond, 1968). The research group had been using LSD in an active treatment program for alcoholics for six or seven years.

One alcoholic, seen two weeks after receiving LSD, was very tense and depressed and complained that he had not come out of his LSD experience. His total HOD score was 122. He was started on nicotinic acid and recovered within a week. On retest four months later his total HOD score was 48.

Dr. Hoffer and Dr. Osmond began demonstrating how the mauve factor test should be used to separate the schizophrenic alcoholics from the non-schizophrenic alcoholics and to indicate whether nicotinic acid treatment should be used following an LSD experience.

Mr. D. S., age 31, was admitted in spring, 1960, complaining of anxiety and severe tension. He had been a heavy drinker since he was 16. He became fearful and easily frightened and could not get along with his father who had been treated successfully shortly before that for paranoid schizophrenia. For four years before admission he was employed as a mailman, but was in continuous turmoil over his relationship with prostitutes. He continued to drink heavily.

On admission he showed a few perceptual changes with visual and auditory hallucinations, was paranoid, complained of blocking, and was very anxious and tense. His urine test was positive. It was difficult to be certain whether his mental changes were due to schizophrenia or were the result of his drinking. But after his diagnosis was established by the mauve factor test he was treated for both alcoholism and schizophrenia.

He was given 300 mcg LSD by mouth for alcoholism. He abreacted much hostility toward his father, and the next day claimed he had some insight and was resolved to drink no longer. He was started on nicotinic acid, 3 grams a day, and this was continued on discharge.

He remained sober for about six months, then began to drink again. His father asked to have him readmitted, and he came into hospital once more, very restless and tense, over-talkative, and his speech slurred.

Three months after his first admission he had made a hasty marriage and his wife left him the following day and asked for a divorce. The nicotinic acid which he had taken steadily had not helped him very much.

He was therefore started on the next phase of treatment and was given five ECT and an increased dosage of nicotinic acid, 6 grams a day. *On* discharge he was improved. Since then he has been taking nicotinic acid regularly, has remained sober, has become reunited with his wife, and there was hope he would make a normal home.

The second case was that of a shy 39-year-old woman who had a five years' history of alcoholism. She was persuaded to come in for treatment by her husband. There were no changes in perception and no changes in thought processes, but she was paranoid and felt that people were watching her and talking about her. She was very tense and depressed and had considered suicide. An LSD treatment was planned for her, but the urine test was positive. She was therefore given LSD, but was started the following day on nicotinamide, 3 grams a day. At follow-up two months later she was well.

The next patient was not given LSD because he was mauve positive. He responded well to nicotinic acid alone.

Mr. M. M. had been a heavy drinker most of his life, but three years before admission he began to drink much more than usual. He had been a member of AA temporarily. On closer scrutiny it appeared that he was not, in fact, drinking more, but his tolerance for alcohol had lessened substantially. He was irritable, forgetful, had severe temper outbursts and blackouts, and threatened to shoot people. He had grandiose ideas about being immune from the law.

When he was admitted for treatment for alcoholism, he showed some mild perceptual changes and his thinking showed evidence of either senility or disorganization. He was garrulous, repetitive, and sometimes irrelevant. His memory was failing and his concentration was defective.

LSD treatment for his alcoholism was planned, but on running a routine urine test he was found to be positive and was therefore immediately started on nicotinic acid, 3 grams a day, and discharged.

He has continued to take nicotinic acid regularly and has remained abstinent. There has been a complete recovery of his mental condition and of his behavior. At no time was he given psychotherapy.

Alcoholics who are not schizophrenic by clinical criteria or who are negative on the mauve factor test do not stop drinking when they are given large doses of nicotinic acid. Of a group of six that

were studied, four are now sober and well. Two refused to take medication after discharge and remained ill.

Depressions

"Every psychiatrist must now and then be surprised when a patient who is severely depressed becomes markedly schizophrenic after either ECT or antidepressant drugs," Dr. Hoffer and Dr. Osmond remarked in their article. "In retrospect they are often labeled schizoaffective. The mauve factor test may help us to avoid some unpleasant surprises. There were five patients who were typically depressed; four were mauve positive to the surprise of the therapist, and the one who seemed most schizophrenic was negative."

Dr. Hoffer and Dr. Osmond cited three cases to illustrate the response of two positives who were treated for schizophrenia, and the one negative who was treated for a severe neurosis with LSD. All five patients in this group are now well.

Mr. H. H. had suffered from hypertension for many years for which he received Serpasil. He was well until one month before admission. About one week before admission there were no perceptual changes or thought disorder, but he was extremely tense and depressed and suffered an overall anxiety (pan anxiety).

On admission he denied having perceptual changes, but believed his family were dead and that he would be killed, was very suspicious, and showed thought blocking. He remained extremely anxious. The following day two urine tests were made, and they were both positive. Because of his severe hypertension and some myocardial damage, ECT was deferred for a few days in order to reduce the blood pressure.

The day after admission he was very delusional and showed great agitation and thought disorder. By June 1 he heard voices telling him that his psychiatrist was going to kill him and he became afraid to sleep at night. He was under close observation during this period. Nevertheless he made a serious suicide attempt, lost much blood, and required emergency surgical treatment with blood transfusion. After this his blood pressure became normal and stayed normal. Then he started receiving ECT and 6 grams a day of nicotinic acid. On June 10 his urine test was negative. On discharge he was markedly improved. He continued to take nicotinic acid for one year, but then stopped. He has remained well.

Miss G. M. had been a difficult behavioral problem since she was about 14 years old. At age 15 she became pregnant to defeat her parents and force them to allow her to marry a 21-year-old man whom she loved. After two months they began to quarrel.

For two weeks after her baby was born she was extremely anxious, tense, and restless. Then she seemed to recover. The marriage continued to deteriorate, however, and when she was 17 her husband left her and she moved into her parents' home with her son. Soon her severe anxiety and tension re-occurred, but she responded to simple reassurance and medication.

When she was admitted to hospital, she complained of perceptual disturbances. She seemed to float off her bed, and when she looked down the ground or floor seemed to move. There was no disorder of thought, and she was extremely tense, restless, and depressed. Clinically she appeared to be either an agitated depression, or a severe anxiety state.

Because her urine was positive for mauve factor she was started on 3 grams of nicotinamide a day and given six ECT. She responded quickly and was nearly normal on discharge. She was discharged somewhat early because she was a student at University.

Miss M. soon relapsed into a state of depression, anxiety, and apathy. She also became more seclusive. She failed her year at University although she was of superior intelligence. She was readmitted for 24 days for the next phase in the treatment program, which included nicotinamide, four ECT, and penicillamine. Again she was much improved

and remained improved for a few weeks when she quickly relapsed. Her complaints of severe tension became more marked. During the peak of tension she was stiff, her muscles would not operate properly, and her features were pale and tight. None of the major tranquilizers had ever helped her and, in fact, they made her worse. She was therefore readmitted for four days for LSD.

She was given 300 mcg LSD and had a very fruitful experience. She became aware of much of the dynamics of her problems and of her relationships to her mother and her young son. The following day she was well and remarkably free of tension, but within a few days after discharge her tension recurred in full force.

The morning after LSD her urine for the first time was mauve negative. Before that each of her seven tests had been positive.

Dr. Hoffer and Dr. Osmond had seen schizophrenics develop severe tension while recovering. It was as if feeling began to return after being numbed by the disease—as if the schizophrenia had tranquilized them. Because of this possibility she was started on Librium. With the first capsule there was a relief from tension, and until the time of writing there has been no relapse. She is still on nicotinamide, 3 grams a day.

Mrs. G. L., a Registered Nurse, was well until 1958 when she developed back pain and had a spinal fusion. She had also had hyperthyroidism, but a rather enthusiastic treatment with radioactive iodine had left her hypothyroid, requiring 60 mg desiccated thyroid daily. Two years later she developed infectious hepatitis and was left with numerous physical complaints. She became depressed and was hospitalized for five months and given ECT, medication, and psychotherapy.

After a brief period at home she was readmitted as. a day patient for four months. Late in 1961 she developed difficulty in eating and soon became unable to eat. She was kept in a mental hospital several months without improvement. She was discharged on condition she leave her husband who was a brutal and difficult alcoholic. She was placed on a 'plane and 2,000 miles later appeared at the Saskatoon psychiatric outpatient department, very ill and depressed.

No beds were free and she was referred to a physician skilled in hypnotherapy. She was admitted to a general hospital and received treatment several weeks with improvement, but after discharge she quickly relapsed. She was then admitted to the psychiatric ward.

On admission Mrs. G. L. was extremely agitated with pan anxiety. There were no perceptual changes and no changes in thought, but she was hostile, difficult, and irritable. Three weeks later there had been no improvement. Her remarkable resistance to all therapy given, including ECT, tranquilizers, psychotherapy, hypnotherapy, over four hospitalizations, raised the question whether she was not really schizophrenic (pseudo-neurotic). But several urine examinations indicated mauve factor was not present.

A new and more intensive treatment program was started which included three LSD experiences, conditioning therapy, and disregard of any complaints of symptoms. Any move toward normality was encouraged, but she received no psychotherapy. She was resentful, hostile, demanding, and difficult, but cooperated reasonably well.

She was discharged to day patient care for one month. She began to improve, conquered her fears, began to sleep well, and found a job in a local general hospital. When last seen, she was well.

Personality Problems

There were four patients in this group. The first three cases were malvarian, the fourth was not.

Z. K., a 15-year-old boy with an IQ of about 130, had been a problem for over a year. He was sullen and resentful, refused to obey his parents or teachers, and created turmoil at home and at school. He frequently truanted from school. His record in Grade 8 was very

erratic, but he passed with a B plus average in June, 1961. The following January his urine was positive and he started taking nicotinic acid, 3 grams a day. He could not understand why he had been admitted to hospital and was bewildered. His perception was normal, there was no disorder of thought, and he was cheerful, cooperative, and pleasant. The researchers intended to treat him with LSD for his behavioral problem. When tested after admission his urine was clear. On discharge he was negative for mauve factor.

He improved for about one month at home, but after that there was no further improvement. A urine test was negative, and his behavior remained bad. He was therefore readmitted in July, 1962, for two days for treatment with LSD. He was given 200 mcg, but did not have a good reaction. He appeared to be catatonic for about two hours at the height of his experience. His urine was mauve negative before he received LSD, but 24 hours later he was positive again.

He was nearly normal for two weeks after discharge, but then his behavior reverted to what it had been. During this period he continued to take nicotinamide regularly.

He was again admitted in August for four days for a second LSD experience. This time he was given 150 mcg and had a much more useful experience. Again his urine was free of mauve factor as before, but became positive 24 hours after the LSD. He gained some insight about the relationship of school to a future career. It was believed he would require several more treatments with LSD.

As a general rule, Dr. Hoffer and Dr. Osmond did not treat schizophrenics with LSD. In practice, however, they had seen several schizophrenics who were much improved after LSD and who maintained their improvement if they were then placed on nicotinic acid medication. It seemed that LSD allowed adrenochrome to escape from the blood red cells. This rapid excretion of adrenochrome could leave the patient feeling better. Some patients became mauve positive after the treatment, and although there was no evidence the mauve factor was related to adrenochrome, it did suggest to them that LSD can aid in detoxifying patients.

Miss E. R. had mild perceptual changes and was somewhat paranoid. Her HOD scores were high, but at that age this was not unusual. Her urine was strongly positive for mauve factor. She was started on nicotinamide, but her behavior remained unchanged. She continued to be a very grave problem.

On admission she presented the same picture of childish, immature, and irresponsible behavior. She would not conform to ward regulations. Her IQ was about 90. Because she had not responded to nicotinamide alone, she was given a series of 6 ECT and continued on nicotinamide. About six weeks later, in May, 1962, there was no improvement. She was therefore given another 6 ECT and penicillamine. Her behavior remained unchanged. She was given 300 mcg LSD, but she had a mild experience. Oh discharge she was slightly improved, but this was not sustained and other admissions appeared imminent. Her urine was tested five times and each time remained positive.

Mr. G. C, age 20, was of superior intelligence but was unable to complete his second year University. For one year there was gradual withdrawal of interest and toward the end of the year he spent most of the time at. home doing nothing.

On admission there were no perceptual changes and no changes in thought, and his mood was appropriate and normal. He seemed to be without goal or purpose. His withdrawal of interest suggested a slowly developing schizophrenic process, but there was no clinical evidence to support this. His urine did not contain mauve factor on several tests. He received LSD twice, but had remarkably unproductive experiences. It seemed likely he might be suffering from a prolonged atypical depression and he was, therefore, started on adrenalin methyl ether, an adrenaline-like mild stimulant.

Mentally Retarded Children

With the cooperation of the John Dolan School for Retarded Children in Saskatoon, 24 children were examined, one a week, for the presence of mauve factor in their urine. All children, whether positive or negative, were then started on nicotinamide, 1 gram per 50 pounds body weight. The parents were given the result of the test. They were then told that many children, whether positive or negative, responded well to this simple vitamin medication and the medication would be provided for them free as long as they felt their child was improving. Parents of retarded children are desperate for some cure for their children, and it was logical to expect them to follow the regime faithfully. Those who found the vitamin really helped would continue to ask for it.

After one year the records were examined to see how many from each group were still taking medication. Parents who stopped getting nicotinic acid did so in two ways. They either did not ask for it any more, or they would call and report no improvement. They were encouraged to continue a few more months, and if there was no further change the vitamin was stopped.

Out of 16 children who were mauve negative, five continued to take the vitamin and 11 discontinued. One of the negative who continued was an epileptic retarded child who was better controlled. Out of eight mauve-positive children none were discontinued and in all, the parents were optimistic and believed their children were better, that is, quieter, less aggressive, and starting to learn.

Dr. Hoffer and Dr. Osmond speculated that these malvarian children have a biochemical lesion similar to adult malvarians and should, therefore, respond to similar treatment. Unfortunately, these children are often first seen when they have been ill for years, and since the clinical picture is not that usually found in childhood schizophrenia, it is unlikely treatment would be given.

They recommended that every child be screened for mauve factor if he showed any significant deviation from normal in either physical or mental growth and development. "The earlier treatment is started the better the results are likely to be. Children cannot afford to lose vital months or years at so critical a period of their lives and if they do, are liable to be harmed permanently."

Dr. Hoffer and Dr. Osmond concluded that the few cases cited in their paper show that the mauve factor does, in fact, accomplish two objectives of diagnosis effectively. "The object of a diagnostic test is to indicate what treatments to use and some tests also tell one whether the treatment is working or not." The mauve factor test does both.

"Patients who have been treated as if malvaria can be equated with schizophrenia, even though they were diagnosed as alcoholics, depressions, or personality problems, have benefited substantially. These simple chemical treatments are not those usually given to all these diagnostic categories."

Relation of Malvaria to Prognosis

Patients who were positive on discharge had nearly three times as many admissions over a mean follow-up period of one year compared with those who were negative on discharge. Some of these patients who were positive became negative after later admissions and subsequently have shown much improvement.

Patients who remain mauve positive in spite of the most intensive treatments do not recover. But they can often remain out of hospital improved, or much improved, if they are maintained on continuous medication. The presence of malvaria which can be clearly shown to both patients and their relatives can be used to encourage the sick and their families to continue treatment.

Conclusion

By means of a simple chemical test, Dr. Hoffer and Dr. Osmond showed that a new psychiatric disease can be recognized which they call malvaria.

Malvaria is found in people who have in common a mauve-staining factor in their urine. They are found in various groups of mental illness. Generally speaking malvarians are much sicker than non-malvarians for they require more admissions to hospital, are in hospital longer, and receive more drastic treatments, including ECT. In addition, if malvaria persists they require more readmissions and each one of these needs about 12 days more treatment.

Patients who have malvaria resemble each other more than patients with similar diagnoses who do not have malvaria. A neurotic with malvaria, for example, would resemble a schizophrenic with malvaria more than he would a patient who was diagnosed neurotic and who did not have malvaria. As a group, the malvarian patients, regardless of diagnosis, have many things in common.

They believe that people are watching them more than they had in the past and in fact watch them all the time. They have visions of people when their eyes are closed. They feel unreal and see others as unreal. There is a mist or fog shutting them away from the world. Many times objects and people, as well as their own faces, look strange and therefore they mis-identify people. Often they see sparks of light or spots floating before them and the world may suddenly look dim. They have out-of-the-body experiences.

They have a much higher incidence of these perceptual changes, more thought disorder both in content and process, and more incongruities in affect and behavior, than non-malvarians. The amount of depression is much the same for both malvarians and non-malvarians and this shows on the HOD scores in which the two groups are similar only in respect to the depression score.

Dr. Hoffer and Dr. Osmond were particularly puzzled by the number of chronic schizophrenic patients who did not have the abnormal chemical substance in their urine and who showed a low score on the HOD test. They speculated that there could be several explanations. An active process had stopped, leaving the victim psychologically and socially crippled; or there had been some permanent damage to brain cells which persists even though the substances are no longer excreted; the substances may never have been present in these patients, but different substances may have been, causing very similar clinical syndromes; or some patients may produce these substances at infrequent intervals, but often enough to perpetrate their disability so that patients and doctors alike lose heart and give up.

They enthusiastically discussed the possibilities raised by the test.

If malvaria were used as a diagnostic group, for example, then the diagnoses of neuroses, etc., would become more precise and more useful. Anxiety states or depressions with malvaria will do better when treated as malvarians, while those without malvaria may respond better to psychotherapy and medication or other treatment for anxiety or depression.

If the biochemical tests are used to indicate response to treatment, it will be easier to decide when some change in treatment is necessary.

If patients who recover from malvaria are tested regularly and started on treatment at the first sign of relapse, society can begin to develop a preventive psychiatry. Close relatives can, be examined at intervals and certainly should be if there is any sign of illness.

Finally, the genetics of malvaria can now be examined far more accurately than has been possible for schizophrenics.

The implications for public health are enormous. Mass TB surveys have helped catch many cases early and so permit treatment to begin at a stage in the illness when it is effective. Now surveys are beginning for lung cancer in men over 40, with the same purpose in mind. Screening of large numbers of people for malvaria could help many people avoid

spending years and decades in mental hospitals. This is preventive medicine.

Psychiatrists who have made suggestions for preventing schizophrenia have been mainly those who look upon it as a way of life. Their kind of preventive psychiatry would include trial marriages or easy divorces, teaching people how to "cope with their tensions," separating children from their parents, or changing the social customs of their times.

This is not the first n6r the last time that reformers have mixed medical and social issues. Talking about general paresis of the insane, Sir James Crichton-Brown (1871-72) reported, "This illness is one of the pestilent camp followers of civilization, the penalty for our boasted progress. This is a feverish and fidgety age and the result of all the ceaseless agitations and striving is that the body gives way under the strain. This illness is a reflection of the follies of the age: it is the miserable otium cum dignitate of the man of business."

There is massive evidence that schizophrenia is not., a way of life. Schizophrenia occurs with roughly the same frequency the world over. Its incidence has altered little during the last century when people have seen astonishing disruption and progress. One of the strongest features of this great illness is that social, economic, racial, political, and climatic factors have so little influence upon it. Oddly enough this extraordinary fact is rarely mentioned in textbooks and journals and has not the consideration it merits.

Schizophrenia and its sister illnesses are not invincible. Mass testing would finally force this ancient illness to yield to man's superior knowledge and skill. It would make early treatment and rapid recovery possible. It would be helpful in teaching those who are vulnerable, and their relatives, how to avoid illness. It would reduce the need for mental hospitals, halfway houses, homes for emotionally disturbed children, and other institutions. It would clear up the confusion among patients, families, and the public, produced by psychiatrists and mental health associations who make repeated statements that mental illnesses are "just like any other illnesses" and then proceed to blame families and the environment.

Only public preventive health services with their experience of and interest in social and preventive medicine are in a position to initiate, launch, and sustain programs of this sort, according to Dr. Osmond and Dr. Hoffer. These programs have the added advantage that they are not cluttered with some of the recent psychiatric notions about schizophrenia which blame the patient's family or society at large for the illness.

Malvaria and the HOD Test

Several thousand malvarian patients, including all diagnostic groups, were given the HOD test and the results compared to those found for acute schizophrenics. The approximate scores can be very quickly compared on the following table.

	Mean Scores		
	Neuroses	**Malvaria**	**Schizophrenia**
Depression	5 J4	8	8
Perception	4	10	9
Paranoid	2	4	4
Total	25	55	50

It was quite clear that malvarians are much closer to schizophrenia with their HOD scores than they were to neurotics. Dr. Hoffer and Dr. Osmond then studied the relation of malvaria to schizophrenia.

Relation of Malvaria to Schizophrenia

Not every schizophrenic is malvarian, and many people not diagnosed schizophrenic are malvarian. This fact, said Dr. Hoffer, has been used either to support or to condemn the concept.

"Critics who hoped we were reporting a diagnostic test for schizophrenia were disappointed, since it left them with nothing to attack. They have fallen back upon a demand for precision not expected of any other diagnostic test-that is, a perfect discrimination.

"Thus," he elaborated, "they have stated that 10 percent of normal people have malvaria, suggesting that this invalidates the concept. In fact, fewer than 5 percent of the normals are malvarian. They have confused patients who are physically ill but apparently mentally normal with actual normal subjects. The 10 percent malvarians in a physically ill group have not been examined from a psychiatric view. Many of them had cancer of the lung—a condition which is frequently associated with psychiatric and neurological changes.

"It is well known that physical symptoms are often the early warning signs of later serious mental illnesses. In a few cases which I have been able to follow, clear evidence for schizophrenia appeared many years after patients were operated on for abdominal complaints, etc. Therefore it would be highly unlikely for a large group of physically ill people not to contain a small proportion of malvarians. Unfortunately, due to the primitive state of our research and to the lack of interest of psychiatrists in a position to do these follow ups, much valuable information has been lost."

As was shown earlier, even the WR for syphilis has a large proportion of false positives. Even if every physically ill person who has malvaria is a false positive, this is still a very low incidence of false positives, Dr. Hoffer asserted.

"Of equal concern are the false negatives—well-known schizophrenics who are not malvarian. There are several reasons for this: Many acute cases are positive who when chronic become negative. When every schizophrenic is tested at the first onset of the illness, the incidence of false negatives will decrease markedly to about 10 percent. The reasons why many chronics are negative are not clear. Factors at work probably are:

"(1) the test is too insensitive to pick up minute quantities of mauve factor;

"(2) mauve factor is produced intermittently and there is none present on test day. Ideally a series of tests should be done at intervals of several days;

"(3) there are forms of schizophrenia which have different biochemical mechanisms. It is likely chronic schizophrenics who accumulated in mental hospitals are different and will require different chemical tests.

"The most likely hypothesis is that malvaria is an early or subclinical stage of schizophrenia. It is well known that every disease goes through a period of symptom formation. During this period only a few symptoms appear and they may occur in arrangements and complexes which suggest the disease but which can be very difficult to defend in a diagnostic conference against critical attack. The period of time between the first attack of the illness and its classical formation or development may vary from a few days to several years.

"Diseases which develop rapidly present fewer diagnostic problems. Diseases which develop slowly may present many difficulties, including an estimate of the duration of the illness. A retrospective review of most schizophrenic patients does not give a hopeful picture of diagnostic acumen. It is likely they have been ill close to two years before they have been diagnosed. Often this is because they and their families have not sought help, but too often they have gone through a sequence of diagnoses beginning with 'being nervous,' having, depression, and only

when they hear voices being called schizophrenic.

"Every diagnostic test which will help decide what the illness is during this developmental phase is therefore very important.

"Malvaria is therefore a measure of the early development of schizophrenia. Therefore neurotic malvarians, depressed malvarians, etc., are examples of early or of subclinical cases of schizophrenia."

The evidence Dr. Hoffer gave for this is: (1) The fact that on the HOD test malvarians resemble schizophrenics more than non-schizophrenics. (2) The fact that malvarians are treated like schizophrenics by psychiatrists who are unaware whether or not malvaria is present. This suggests that treatment is perhaps more sophisticated than diagnosis with many modern psychiatrists. (3) The clear genetic relationship with one-third of first-order relatives of schizophrenics or malvarians also being positive also supports this view. (4) The rapid response of malvarians to the megavitamin therapy regardless of their diagnosis. Malvarians not schizophrenic respond more quickly than do schizophrenics, again showing that it is an early or subclinical variant. (5) Most important of all is the fact that all malvarians have the same biochemical defect. In the same way all people who have in them actively proliferating spirochete have syphilis even though every syphilitic has different constellations of symptoms.

Corroboration

The first corroborative paper was published by Sohler et al. (1967).

"They used the Don Irvine technique which is slightly different from the one we used in Saskatoon and which tends to show more false positives," said Dr. Hoffer. "Using the original method of Hoffer and Mahon (1961) the following have found similar results: Dr. M. Galambos, formerly with the Training School, Prince Albert, Saskatchewan, Dr. M. Vogel, Calgary, Alberta, and Dr. W. E. Beebe, Detroit, Michigan. Other laboratories are beginning to show some interest.

"It will take many years before the concept of biochemical diagnosis is accepted in psychiatry. It may be necessary to re-establish the fact that no branch of medicine can aspire to be a science if it is going to give up the diagnostic method which has worked so well until now.

"The attack upon the malvaria hypothesis will take the following form:

"It will be said there is no such thing as mauve factor.

"It will be said that the test is of no value because not every schizophrenic had the factor and because a small proportion of normal subjects have it.

"It will be said that the mauve factor comes from stress.

"In spite of massive opposition, scientific facts have a habit of becoming established. The conservative leaders of any profession who provide stability to a body of knowledge are gradually replaced by younger, men to whom the newer ideas are less terrifying. They in turn develop a new orthodoxy, so progress moves in quantum leaps."

Since Dr. Hoffer made these predictions, several years ago, the mauve factor has been identified as a substance called kryptopyrrole (Irvine, 1973). Recently the term malvaria has been replaced by a term coined by Dr. Carl Pfeiffer, director, Brain Bio Center, Princeton, New Jersey, pyroluria (for patients excreting more than 20 mcg of kryptopyrrole, Sohler et al., 1974). According to Dr. Pfeiffer pyroluriac patients suffer many perceptual changes, fail to remember dreams, have white spots in the nails, a sweetish breath odor and left upper abdominal pain (Pfeiffer et al., 1974).

And so, as research continues, new diagnostic and treatment methods are developed.

REFERENCES

ALTSCHUL, R.. HOFFER, A., and STEPHEN, J.: Arch. Biochem. Biophys. 54, 558, 1955.

AXELROD, J., SZARA, S., and PERLIN, S.: Am. J. of Psych. 116, 1958.

CECIL, R. L., LOEB, R. F., GUTMAN, A. B., McDERMOTT, W., and WOLFF, H. G., Ed.: A Textbook of Medicine. W.B. Saunders Co., Philadelphia, 9th Ed., 1955.

CRICHTON-BROWN, Sir James: Journal of Mental Science. Vol. 17, 1871-72.

DENSON, R.: Nicotinamide in the Treatment of Schizophrenia. Diseases of the Nervous System 23:167, 1962.

HEACOCK, R. A., and MAHON, M. E.: Can. J. Chem. 36, 1550, 1958.

HEACOCK, R. A.: In Advances in Heterocyclic Chemistry, Vol. 5, pp. 205-290, Academic Press: New York, 1965.

HERJANIC, Dr. Marijan, MOSS-HERJANIC, Dr. Barbara L., and PAUL, W. Keith, RPN; Journal of Schizophrenia, Vol.1, No. 3, 1967.

HOFFER, A.: Canadian M.A.J. 81:235, 1959.

HOFFER, A.: Niacin Therapy in Psychiatry. Charles C. Thomas, Springfield, Illinois, 1962.

HOFFER, A.: Nicotinic Acid and/or Nicotinamide for Treating Schizophrenia. A Compilation of Saskatchewan Research Information. No date given.

HOFFER, A., and OSMOND, H.: A card sorting test helpful in making psychiatric diagnosis. J. Neuropsychiat. 2:306, 1961.

HOFFER, A., and OSMOND, H.: Malvaria; a new psychiatric disease. Acta Psychiat. Scand. 39:335, 1963.

HOFFER, A., and OSMOND, H.: How to Live with Schizophrenia. Johnson Publications, Ltd., London, and University Books, New Hyde Park, New York, 1966.

HOFFER, A., and OSMOND, H.: The Hallucinogens. Academic Press,

HOFFER, A., OSMOND, H., CALLBECK, M. J., and KAHAN, I.: J. Clin. Exper. Psychopath, 18, 131, 1957.

HOFFER, A., KELM, H., and OSMOND, H.: The Hoffer-Osmond Diagnostic Test. Robert E. Krieger Pub, *Co.*, Huntington, N.Y., 237 pages, 1975.

IRVINE, D. G., BAYNE. W., MIYASHITA, H., and MAJER, J. R.: Nature 224, 811", 1969.

IRVINE, D. G.: Kryptopyrrole in Molecular Psychiatry. Orthomolecular Psychiatry, Ed., Hawkins, David, and Pauling, Linus. W. H. Freeman and Company, San Francisco, 1973.

KAHAN, F. H.: Brains and Bricks. White Cross Publications, 1965.

KATZ, S.: "Heaven or Hell Drugs." Macleans, June 20, 1964.

KAUFMAN, Dr. W.: Common Form of Niacinamide Deficiency Disease: Aniacinamidosis. Yale University Press. Bridgeport, New Haven, 1943.

KAUFMAN, Dr. W.: Common Forms of Joint Dysfunction. E. L. Hildreth and Company, Brattleboro, Vermont, 1949.

KAUFMAN, W.: J. Am. Geriat. Soc. 3, 927, 1955.

KELM, H., GRUNBERG, F., and HALL, R. W.: Intern. J. Neuropsychiat. 1, 307-312, 1965.

N.Y., 1967.

HOFFER, A., and OSMOND, H.: New Hope for Alcoholics. University Books, New York, 1968.

HOFFER, A., and MAHON, M.: J. Neuropsychiat. 2, 331, 1961.

KELM, H., HOFFER, A., and OSMOND, H.: Hoffer-Osmond Diagnostic Test Manual, 1967. Distributed by Dr. John McKee, Behavior Science Press, Box AG, University, Alabama 35486.

KING, L. S.: "What is a diagnosis?" Journal of the American Medical Association 202, pp. 714-771, 1967.

OSMOND,. H., and HOFFER, A.: "On Critics and Research", Psychosomatic Medicine, Vol. XXI, No. 4, July-August, 1959.

PAYZA, A. N., and MAHON, M. E.: Analyt. Chem. 32, 17, 1960.

PFEIFFER, C. C, SOHLER, A., JENNEY, E. H., and ILIEV, V.: Treatment of Pyroluric Schizophrenia (Malvaria) with Large Doses of Pyridoxine and a Dietary Supplement of Zinc. J. Orthomolecular Psychiatry, Volume 3, Number 4, 1974.

PRITCHARD, Dr. M.: British Journal Psychiatry, Volume 113, 1967.

RINKEL, M., HYDE, R. W., and SOLOMON, H. C: Diseases of Nervous System 15: 259, 1954.

SOHLER, A., RENZ, R. H,, SMITH, S., and KAUFMAN, J.: International Journal of Psychiatry, #3, 1967.

SOHLER, A., HOSZTYNSKA, E., and PFEIFFER, C. C: A Rapid Screening Test for Pyroluria; Useful in Distinguishing a Schizophrenic Subpopulation. J. Orthomolecular Psychiatry, Volume 3, Number 4, 1974.

STEWART, C. N., and MAHOOD, M. C: Can. Psych. Assoc. J. 8, 133-137,. 1963.