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The Discovery of Kryptopyrrole and its Importance in Diagnosis of Biochemical Imbalances in Schizophrenia and in Criminal Behavior

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In this issue (JOM, Vol 10, No 1) Dr. Richard T. Kraus describes a notorious serial killer who is serving a 250 year sentence for the murder of eleven women. Unfortunately, serial killers are not a threatened species. On the contrary, they threaten society more and more, and with modern weapons of destruction seem to be even more effective. This case report may be the first in which four main factors which determine human behaviour are discussed in detail. Dr. Kraus describes “...a matrix of genetic, biochemical, neurological and psychological deficits”. I am particularly interested because the kryptopyrrole ("kp") which was found in this person’s urine was originally discovered in Saskatchewan about 1960 when I was Director of Psychiatric Research. The main biochemical research was completed in Saskatchewan by Dr. D. Irvine,(1) and in New Jersey by Dr. C. C. Pfeiffer (1) and his research group of biochemists.

This report provides a model of how criminal behaviour ought to be explored, with numerous references to the medical literature for all of the four variables. I will discuss mainly the biochemical findings and provide a brief history of its discovery. The presence of kp in urine is a valuable diagnostic aid especially for determining more specific treatment. It is most closely related to the schizophrenias but cuts across all diagnostic categories. I think it could become an important differential diagnostic test. It is simple to do, any competent medical laboratory can do it. The laboratory in Victoria has been
running them for me since 1976.

By 1960 the biochemical unit of the psychiatric research program in Saskatchewan was gearing up to investigate any possible relationships to the schizophrenias. One of the studies involved examining urine for several fractions and comparing the urine of patients and controls. We were then treating many alcoholics using psychedelic therapy. D-lysergic acid diethylamide (LSD), the hallucinogen, was well studied as a compound which could induce a model psychosis or a psychotomimetic experience. It occurred to me that inasmuch as LSD produced something

very similar (but not identical with) schizophrenia, perhaps it might also generate in the body of a person (not schizophrenic) the same type of biochemical abnormality which we thought was present in the patients. I asked Dr. N. Payza to examine the samples of urine obtained from an alcoholic who had been given LSD as part of his treatment.

The first morning specimen was obtained and another one around noon, usually the height of the experience. My idea was that if something appeared after LSD which was not present before, this might give as a lead. We were fortunate because the first patient we tested had a large amount of a substance that was not present in the morning specimen. We soon showed that it was not a breakdown product from the LSD itself, which meant it was created in the body by the impact of the hallucinogenic drug upon one of the biochemical systems. After we had improved the assay procedure we began to test patients. One day I took into the laboratory 12 specimens of urine. Six were obtained from schizophrenic patients, five were obtained from normal subjects and one was a blank. The code was kept secret. I asked the biochemical team to analyze these samples and to tell me which of the 12 were obtained from the schizophrenic patients. They accurately spotted all the schizophrenic samples. I concluded that schizophrenic patients, not given LSD, had the same substance in their urine as did some alcoholics who had been given LSD, but that it was not present in normal controls.

We needed large amounts of material for our chemical studies. Fortunately for us a chronic schizophrenic woman on the ward had huge quantities of this product. For a moment we considered calling the compound the Jensen factor. At first we called it the unknown substance (US), and later the mauve factor because when developed on the paper chromatogram it stained a beautiful mauve. When it was identified we called it, more accurately, kryptopyrrole. We named the disease characterized by large amounts of mauve factor “malvaria,” but Dr. Pfeiffer later gave it the more appropriate term **pyrolleuria.**

I immediately started two lines of investigation: (1) by Dr. Payza for short time, and then by Dr. D. Irvine who continued the research first at the Research Laboratory at the Saskatchewan Hospital in North Battleford, and later at University Hospital in Saskatoon. The objective was to determine the structure of the substance and its source. (2) To study its clinical correlates, i.e. could it be used to assist in diagnosis, could it have therapeutic significance, and could it be used to follow patients both to determine if they were improving, and to determine if they were getting worse.

Dr. Irvine showed that it was a pyrrole, later identified as kryptopyrrole. We began to cooperate with Dr. C. C. Pfeiffer at Princeton, New Jersey. Dr. H. Osmond, my colleague in the earlier Saskatchewan research, was then Director of Research for the state. The two laboratories did the basic work. Dr. Pfeiffer and his team discovered how to measure the amount of this substance in the urine using a fairly simple test, and they showed that

this substance bound with pyridoxine and zinc and when present in large amounts produced a double deficiency of this vitamin and the mineral. On the clinical side he described the syndrome pyrolleuria, a form of schizophrenia with clearly marked out symptoms and signs which could be diagnosed by the present of kp in the urine.

Several years later we had examined thousands of patients at three hospitals for the mauve factor.(2) It was present mostly in schizophrenic patients but was also present in one-quarter of other non schizophrenic patients including depressions, alcoholics, anxiety states, and in children with learning and behavioral disorders. It was rarely present in normal subjects, and was present in ten percent of a non psychiatric stressed population drawn from the surgical wards of the hospital. To my surprise it was found in most cases of lung cancer.(3) I found the following relationships:

1) Relationship to diagnosis - The mauve factor was found in the following categories of patients:

Diagnosis; percent with the diagnosis mauve factor

Normal subjects 0

Physically ill
Adults 10
Children 10
Mood disorders 20
Alcoholics 20

Schizophrenics
Early, not treated 75
Recovered 0
Not recovered 50

Thus it was clear that although it was most closely related to the schizophrenic
population, it could not be considered a test for schizophrenia. Probably there will never be such a test since the clinical diagnosis is subjective and there is wide disagreement among clinicians about the diagnosis. I therefore compared the results of testing for this compound with the results obtained on the HOD (Hoffer-Osmond Diagnostic) test.

2) Relationship to HOD Test.(4) This is a card sort test similar in principle to the MMPI but containing entirely different questions. Perceptual symptoms including hallucinations and illusions are specifically covered. The HOD test can be described as a perceptual test. Patients sorted 145 cards into true and false piles and these were recorded and scores obtained. We standardized this test on thousands of subjects and have reported the results widely. We found that there was a better relationship between the presence of high scores in the test and the presence of kp in

the urine than there was between kp and clinical diagnosis. Schizophrenics had much higher scores than did any other group of psychiatric patients, with the exception of patients with delirium tremens and normal subjects undergoing the LSD experience. In one study in New York, the investigating team found that the admission HOD test results were more closely correlated to the final discharge diagnosis than they were to the admitting diagnosis, even though none of the clinicians were able to see the results of the HOD test.

3) As an indicator for treatment. By 1960 we had completed four double blind controlled prospective studies on schizophrenic patients comparing niacin, niacinamide and placebo.(5) Based upon these studies and upon open clinical studies going back to 1951, I had concluded that schizophrenic patients responded better to any treatment when they were given adequate doses of vitamin B3. Forty years later this is still my conclusion, as it is of every physician who uses the same treatment. The only physicians who disagree are those who have never used the treatment and who have even refused to examine earlier studies. There is no patent on vitamin B3, and without a patent there is no financial incentive for any company to promote this treatment. Since schizophrenic patients, most of whom had the factor in their urine, responded better when treated with vitamin B3, I concluded that any psychiatric disease, no matter what they were diagnosed clinically, might also do better with this vitamin. This was confirmed by a large series of open clinical studies. I will not term these studies anecdotal, which has become the politically correct term for denigrating any studies that are not double blind, since all clinical studies depend upon the history or herstory of patients and how they respond, i.e. upon anecdotes. The only difference is that in double blind studies the anecdotes are collected by physicians or others who are blinded by not knowing what treatment is being given. At least this is the theory of this type of procedure. In fact, the vast majority of these studies are so imperfectly blinded that few clinician or nurses have much difficulty deciding whether the patient was on placebo or something more active.

Worshippers of the double blind remind me of the emperor whose nakedness was seen only by a child not yet blinded by tradition. This report by Kraus is an excellent example of the type of anecdotal history which has contributed so much to medicine.

The presence of the mauve factor in urine became a valuable indicator to use vitamin B3. Later, when Dr. C. C. Pfeiffer showed that kp bound pyridoxine and zinc and described the syndrome pyrolleuria, this became another important indicator that vitamin B6 and zinc must be used. It is especially valuable for children, who are very difficult to diagnose because they vary so much one from the other.

4) Response to treatment. Patients who responded to treatment invariably became mauve factor or kp factor negative. However, there were many patients who no longer excreted this factor but who had not recovered. I have not examined whether these patients might have

responded to longer treatment. In my recent report (6) on chronic patients it is evident that many chronic patients need five to seven years of treatment. Perhaps some of the negative excretors after having been positive might have fallen into this group. Patients who were well and were kp free were followed for months or years. If they became positive at any time they also became clinically ill within a matter of weeks or months.

Generally, the presence of kp is associated with clinical conditions characterized by a high degree of perceptual disorganization. These are chiefly the schizophrenic patients, but also includes a substantial proportion of other psychiatric diseases also characterized by perceptual changes. Unfortunately psychiatrists do not search their patients' mental state adequately and miss many of these changes. They can be readily detected using perceptual tests such as the HOD test. (7) In other words, the presence of kp correlates strongly with high scores on these perceptual tests. Perhaps Dr. Kraus's detailed report will arouse interest in this test, sadly neglected for so many years.

In 1960 I examined a seven year old boy who had been diagnosed retarded and preparations were being made to send him to a special school. His parents were very concerned and asked me whether I would examine him. For over a year he had difficulty in school, could not read, and avoided going to school as much as he could, often staying away from home all day but not at school. His mother, a teacher, had been spending a lot of time giving him special instruction without improvement. He was also developing behavioral problems at home. I examined him early in 1960 and could not locate any particular problem, perhaps because I had not had much experience treating children. I then had his urine analyzed for mauve factor, kp, and to my surprise found a large amount. I called his father, a friend of mine, and said in jest "You are in luck, your son has schizophrenia." He answered, "Why does that make me so lucky?" I then told him I was kidding him, and added seriously he was certainly not schizophrenic, but since he had the same biochemical factor in his urine we had found in schizophrenics, and since they had responded well to vitamin therapy, this suggested that his son might respond in a similarly beneficial way.

I started him on niacinamide 1,000 milligrams after each meal. In the fall his father asked me would I like to know what had happened to his son. He then told me that two months after his son had started on the vitamin he had begun to read, that he had spent a few months reading voraciously and that he was no longer concerned about his behaviour. His son was normal and remained well. He took his niacinamide regularly until he was about 14. One day he asked his mother why he was taking the pills. She brought him to see me and I explained why I thought he should remain on the vitamin until at least age 18 at which time he could determine how well he could do without it. He is still well, happily married with children, and is fully employed in a responsible job.

This illustrates the use of the kp urine test for pyrolleuria, and the use of niacinamide in large doses to treat this condition successfully. I did not use vitamin B6 nor zinc in 1960. Pyridoxine is essential for the conversion of tryptophan to nicotinamide adenine dinucleotide, the vitamin B3 coenzyme. With a deficiency of pyridoxine, the synthesis of NAD in the body is reduced. A pyridoxine deficiency will produce a form of pellagra not distinguishable clinically from the pellagra caused by a deficiency of vitamin B3.

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(Also see References in Dr. Richard T. Kraus' paper.)

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