

Naturally Occurring Endogenous Major and Minor Tranquilizers

H. Osmond, M.D.¹ and A. Hoffer, M.D., Ph.D.²

Depending upon whom you heed and what you read, benzodiazepines are either the safest and most useful anxiety relieving drugs so far discovered, or among the more potentially harmful addictive substances. According to their detractors (Lader, 1978; Marks, 1978) benzodiazepines have become increasingly popular because of medical indiscretions and over vigorous advertising. Drugs are neither inherently harmful or helpful; it all depends on how they are used. Some drugs like the major tranquilizers have distressing, even dangerous, side effects; others such as the benzodiazepines lend themselves to misuse by habituation, while others like the water soluble vitamins have very few dangerous properties and no history of abuse.

When Dr. Joseph Tobin, M.D., then the Director of the New Jersey Bureau of Research in Neurology and Psychiatry, told us about his clinical studies with diazepam in the late 1950% he described a substance helpful to patients suffering from excessive

tension and/or anxiety. It was especially useful in patients who were not psychotic, could not tolerate phenothiazine, and did not respond to the barbiturates and other hypnotics then frequently employed for anxiety.

Valium and other diazepines became best sellers in the world drug markets, not only because Hoffmann-LaRoche, the patent owners, promoted them vigorously, but because these substances have real merits. Diazepines are quickly effective, have fewer serious side effects than their competitors and, equally important, while not suicide proof are nothing like as lethal as barbiturates. They can, of course, be abused, but then what drug or other treatment cannot be? When taken by prescription from knowledgeable physicians, diazepines are remarkably safe and have few unpleasant side effects.

At about the same time that Valium swept the world markets to become one of the most frequently prescribed drugs, we published the first full account of vitamin B3 as a treatment for schizophrenia (Hoffer, Osmond, Callbeck and Kahan, 1957). Vitamin B3, although introduced with well designed double blind studies, among the first in medicine, and the first in psychiatry, did

¹ Bryce Hospital, Station 3 Tuscaloosa. Alabama, 35401

² No. 3A - 2727 Quadra St., Victoria, British Columbia

not have rapid and widespread acceptance. Unlike Valium, whose devoted and solicitous parents, Messrs. Hoffman-LaRoche, extolled its virtues with the formidable techniques of modern advertising, vitamin B3 was an orphan drug, belonging to everyone because it was in the public domain; consequently it was in no one's interest to promote it by advertising or to advance it politically.

For B3 there were no ethical advertising campaigns aimed at doctors, no detail men, no sponsored conferences. It was difficult to get articles about it published in major medical journals, whose editors, at that time, considered vitamins and nutrition a fad. Scurvy, pellagra, beri-beri, and rickets were seldom seen in everyday practice, so that the means by which these great illnesses had been cured were no longer of much interest to editors. Then again, especially in long standing schizophrenia, B3 worked slowly; there was seldom any immediate response; the measuring devices available to psychiatrists at this time were too clumsy and time-consuming to be used frequently. It often took weeks or even months before schizophrenic symptoms began to be eroded. Nevertheless in spite of official neglect, not always benign, and sporadic persecution, Orthomolecular psychiatry, of which vitamin B3 was the first component, has slowly spread.

When, in 1975, specific receptor sites for opioids and their pain relieving polypeptides, called endorphins were discovered (Hughes et al.), investigators began to hunt for similar receptor sites for other psychoactive drugs.

Phenothiazines and Haldol bind to a dopamine receptor; this is one of the bases of the dopamine hypothesis of schizophrenia. It is a specific example of a more general amine theory first clearly presented by Osmond and Smythies (1952) and later extended to an amine derivative hypothesis, the amino-chromes, by Hoffer, Osmond and Smythies (1954). Haldol is a powerful dopamine receptor blocking agent; this may account for some of its activity.

The amines such as adrenaline, noradrenaline and dopamine are highly reactive molecules

which are readily oxidized to their respective indole derivatives: adreno-chrome, noradrenochrome and dopa-chrome. It is likely that the dopamine receptor site is involved in the oxidation of dopamine, perhaps by stabilizing it and preventing dopachrome formation, or by oxidizing it with dopachrome as the site activator. Adrenochrome is an endogenous hallucinogen which may play a role in the causes of schizophrenia (Hoffer and Osmond, 1967).

One of the most powerful dopamine receptor blockers is ascorbic acid. This will surprise those who believe that ascorbic acid has no effect on the central nervous system. Weight for weight it is as active as Haldol, but since only a very small proportion of any dose crosses into the brain, a lot must be given in order to get these small quantities in.

Ascorbic acid can not be made in the brain but its concentration there is higher than in any other organ except the adrenal glands. Apparently it enters through the choroid plexus. It should not be surprising that it plays a major role in brain function; the body would not make an effort to maintain a high level in the brain when for most people the whole body contains just enough to prevent scurvy but not enough for optimum health (Stone, 1972). One of its functions may be to regulate neural transmission involving dopamine.

Tolbert, Thomas, Middaugh, and Zemp (1979) found that ascorbic acid inhibits dopamine receptors in the brain, thus resembling Haldol. Both also inhibit dopa-mine-induced increases in cyclic adenosine monophosphate. Other evidence points to a vital role for ascorbic acid somewhere in the operation of neurotransmitters. We agree with Tolbert et al. who write "These observations have therapeutic implications in treatment of neurological and psychiatric disorders reported to be accompanied by functional dopamine excess."

We have seen several schizophrenic patients who responded to ten grams per day of ascorbic acid with marked relief from anxiety and tension, when no tranquilizer had been helpful. Indeed, one of our very

first cases received what were then considered very large doses of both B3 and ascorbic acid. What may be needed is some mechanism for increasing the transfer of ascorbic acid into the brain so that very large doses would not be needed.

Ascorbic acid may be a naturally occurring antianxiety substance. Perhaps this is why brain tissue is one of the major storage sites for ascorbic acid. Scurvy is characterized by severe tension and sometimes by psychosis. At the turn of the last century the differential diagnoses for dementia praecox (schizophrenia) included pellagra, general paresis and scurvy. Ascorbic acid, according to Stone (1972, 1978) should be considered a natural metabolite, not a vitamin.

Stone (1972,1978) concludes that ascorbic acid is a natural metabolite which man has lost the ability to make. About 60 million years ago our ancestors suffered from a mutation which removed an enzyme essential for the conversion of glucose into ascorbic acid. Pauling (1968) showed how such a mutation would confer a genetic advantage in an environment which provided ample quantities of ascorbic acid in the food. In an environment deficient in ascorbic acid we would lose any advantage and suffer scurvy ranging from the preterminal type to the subclinical form present in most people. Stone calls it chronic subclinical scurvy (CSS). If medicine gave up its conviction that ascorbic acid is a vitamin and needed only in small doses it would pay proper attention to the therapeutic and preventive value of ascorbic acid. It should be considered in the same class as the essential amino acids, an *essential nutrient*, and required in gram rather than in milligram dosages.

The benzodiazepines too have specific receptor sites. Once this became known, several laboratories strove to discover the naturally occurring substance attracted to the benzodiazepine receptor, comparable to the opioids and endorphins (Haefely, 1978; Skolnick, Marangos et al., 1978). Unlike the opioid receptors the diazepam (hereafter Dz) receptors are distributed primarily in the brain and spinal cord. Opioid receptors are found in the gut and in different areas of the brain; this suggests that Dz

receptors are more closely linked with brain/mental activity than are opioid receptors.

Only a few substances can attach themselves to the Dz receptors; neither the other types of tranquilizers nor commonly occurring brain chemicals such as the transmitters histamine, serotonin, glutamate, glycine, aspartate, met-enkephalin, are adsorbed by these receptors.

Among the diazepamines there is a close relationship between clinical activity and affinity for the Dz receptor. The most active ones are adsorbed the most strongly. Inosine, one of the B vitamin group is adsorbed and so are hypoxanthine, caffeine, theophyllin and aminophyllin. None of the above were comparable to the benzodiazepines, however.

Benzodiazepines reduce anxiety, are hypnotics, anticonvulsants, and muscle relaxants.

H. Mohler and his colleagues from Hoffmann-La Roche and Co., Ltd., Switzerland, appear to have won the race to identify the substance which attaches to the Dz receptors. In a recent article in *Nature* (1979) they reported that "nicotinamide is a brain constituent with benzodiazepine-like actions." Of the compounds tested "only nicotinamide showed the main neuropharmacological central effects characteristic of benzodiazepine, although because only 0.3 percent enters the brain after injection into the internal carotid artery, rather high doses of the compound are needed to elicit central effects after systemic application."

They concluded that "nicotinamide has properties in common with benzodiazepines (and barbiturates) in its action on spinal cord activity, its anticonflict, anticonvulsant, antiaggressive, muscle relaxant, and hypnotic action. It also seems to influence CABAergic mechanisms without binding to CABA receptors itself."

"If nicotinamide physiologically exerts benzodiazepine-like effects in the brain, its pharmacological potency should be high in view of its low concentration in the brain. This is supported by the electrophysiological experiments using in situ drug application in which the potency of nicotinamide was found to be equivalent to that of a highly

potent benzodiazepine."

Our clinical experiments since 1952 show that for adult patients at least three grams per day is required, and sometimes much more. It would be desirable if more reached the brain. Luckily niacinamide is a much safer substance than any other officially recognized psychoactive drug in general use today. As safe as ascorbic acid whose recently discovered neuroleptic properties we have discussed here. It is strange that vitamin B3 and the benzodiazepines, which seem to have so little in common from a structural and biochemical point of view, should have such similar psychopharmacological activities. Ironically, vitamin B3 was introduced into psychiatry by several double blind comparison experiments conducted nearly thirty years ago, long before diazepam was discovered to be clinically active, but it may now be an essential component of the diazepam activity in the central nervous system.

Nicotinic acid does not have any diazepam-like activity; this seems logical since nicotinic acid is merely an intermediate between tryptophan and nicotinamide adenine dinucleotide (NAD). The natural vitamin B3 in the body is NAD which contains nicotinamide, not nicotinic acid. Since nicotinic acid is not a major component quantitatively of vitamin B3 in vivo it is not surprising it has no receptor activity. We might, however, expect NAD to be at least as active as nicotinamide, provided that it could cross into the brain.

Dz receptors may be involved in the mechanism which causes those mental diseases responsive to vitamin B3 such as pellagra, schizophrenia and so on. What we now require is a way of getting more nicotinamide into the brain quickly. If B3 could be attached to a carrier molecule which could ease its passage across the blood/ brain barrier, much smaller quantities than now used might be very effective. Perhaps this is why NAD proved to be such a potent agent for that small series of acute schizophrenics whom we tested with it over a decade ago (Hoffer, 1966; Hoffer and Osmond, 1966). These then are important scientific findings, but what are some of their implications for clinical work, the treatment of

patients ?

Psychiatry today, according to its own presidents and officials, is beset with numerous problems; some are the legacy of those expansive claims made by psycho-dynamic and social psychiatrists during the late 1950s and 1960s, while others arise from the unexpected side effects found to occur in those psychopharmacological agents upon which the psychiatric policies of the last two and a half decades depended. The most distressing discovery for psychiatrists and patients alike has been the gradual realization that the major tranquilizers appear to cause a number of previously unknown illnesses. Liver damage and bone marrow depression with blood dyscrasias were discovered in the 1950s, but during the last decade three major neurological conditions of doubtful reversibility have forced themselves upon our attention. These are akinetic mutism (Rifkin, Quitkin, and Klein, 1975), tardive dyskinesia (Crane, 1974) and most recently a neuroleptic-induced psychosis which has yet no agreed name (Chouinard and Jones, 1980). It is also during the last few years that the diazepam has led to more abuse than had previously been thought.

Last year, during this era of psychiatric gloom and confusion, scientists have discovered that two safe, cheap substances previously considered as vitamins or auxiliary food substances have quite unexpected psychopharmacological properties, closely resembling those of tranquilizers but without their distressing side effects. How would one expect psychiatrists to respond to such good and timely news? Surely, even the most skeptical would view such a discovery with hopeful expectation and request more evidence. That would be the normal, commonsense response, but unfortunately these findings have occurred after a bitter and prolonged controversy about the clinical uses of megavitamins. Part of the trouble arises from the fact that some psychiatrists and their psychopharmacologist colleagues are of the opinion that "basic science discoveries" must precede clinical applications. This inevitable progress

from laboratory to bedside which is considered to be 'scientific' ignores the historic fact that even more frequently, clinical findings had preceded and initiated scientific advances.

It is not unusual for substances thought to be of little clinical importance to be found to have unexpected therapeutic properties. Over fifty years ago the Germans produced a red dye, prontosil, which inhibited the growth of deadly streptococci. Not long after prontosil was introduced to medicine with flourishes of Nazi triumph, British and French investigators showed that the active principle in the antibiotic was a common chemical found in most laboratories — sulfanilamide. This was not known to have bacteriostatic properties. The Germans tried to salvage the expensive trade name by marketing sulfanilamide as prontosil album — but to no avail. Doctors quickly accepted the astonishing fact that the lowly lab reagent had been transmuted into a powerful treatment, used widely until penicillin was developed.

It now seems that vitamin B3, vitamin C, and other vitamins and nutritive substances currently used by Orthomolecular psychiatrists are due for the same kind of reappraisal which the advent of prontosil necessitated for sulfanilamide. It is at least as likely that some vitamins should have hitherto unknown pharmacological properties as it was that sulfanilamide should inhibit the metabolism of streptococci, meningococci, and gonococci. In 1936 no one would have believed that this hitherto unimportant substance would exhibit these lifesaving properties.

Today scientists are beginning to ask questions about vitamin B3 and ascorbic acid and their effect on the brain. The answers which they are getting have been unexpected by and disconcerting to the establishment. Consequently the clinical issues are more political and social than scientific. These scientific findings give much greater credence to the clinical findings which Orthomolecular psychiatrists have made and published for more than one-quarter century. The onus lies upon those who disagree with those clinical findings to show that they have not occurred.

It should surprise no one that the psychiatric establishment has not hastened to admit the possibility of error. So far as we can judge they have developed a protective blind spot for these recent findings. In this they have been less realistic than the late John Foster Dulles who, when his foreign policy began to be assailed by unwelcome facts, announced coolly that the new

circumstances required him to make an "agonizing reappraisal." There are urgencies in foreign policies which do not trouble psychiatric establishments who are likely to employ soothing platitudes and urge delay by stating "the public should await further well designed studies." This will be comforting for the amour propre of older members of the establishment, who may not survive to learn the results of such studies, which would simply prolong and extend the damage already done for another ten to fifteen years.

Over fifteen years ago we showed using vitamin B3 (1962,1964) that the number and length of readmissions to hospitals can be much reduced, "five year cures" substantially increased and the suicide rate reduced to a much lower rate (Hoffer and Osmond, 1967; Osmond and Hoffer, 1978). There are still no studies refuting this work or showing that any other treatment can change the long term outlook of schizophrenics for the better over a ten year period.

When our ten year follow-up study was published in 1964, there were no similar studies of phenothiazines for comparison with it. However, during the last fifteen years there have been a number of studies published which indicate that phenothiazines have not changed the long term outlook of schizophrenics very much. Thus Prit-chard (1967) found no difference in England in long term outlook for schizophrenic patients treated before 1952/53, before the introduction of tranquilizers, and after 1956/ 57 when these drugs were used. Johnson (1976) concluded that forty-one percent of a group of schizophrenics relapsed in two years despite the use of long acting injectable tranquilizers. Bockoven and Solomon (1975) found that patients treated in 1967

with tranquilizers did not do as well as patients treated in 1947 before tranquilizers had been discovered. Mosher and Feinsilver (1971) concluded "more distressing is the fact that 15 to 40 percent of schizophrenics living in the community achieve what might be termed an average level of adjustment (i.e. being self supporting or successfully functioning as a housewife)." Carpenter, McClashan and Strauss (1977) concluded that for acute patients treated at the National Institutes for Mental Health with very little medication and emphasizing psychosocial care had the same prognosis as similar patients receiving the usual dosages of

tranquilizers.

We would consider their milieu therapy as a good measure of a natural remission rate in a sheltered, supportive environment. The one year relapse rate (requiring readmission) was 35 percent for the no-drug group and 45 percent for the tranquilizer group. The lower rate is the usual readmission rate accepted for acute patients and is identical with the relapse rate at one year that we found in 1953 with our first double blind controlled experiment for placebo with electroconvulsive treatment. When we used niacin or niacinamide for our comparison group the one year remission rate was 75 percent.

TABLE 1
Comparison of Follow-Up Results

Year Treated Year Evaluated	Hoffer and Osmond		Bland and Orn	
	1952	1962	1963	1977
GROUP	NIACIN	CONTROL (ECT)	TRANQUILIZER	
Number	16	27	43	
Number Readmitted				
0	12	10	9	
1	3	5	11	
2 - 5	1	7	17	
6 + more	0	5	6	
a) 0 and one year combined	15	15	20	
b) 2+ more	1	12	23	
Time in Hospital	0.9%	12.6%	15%	
In years	1.4	34	87+	
Time spent in hospital per patient, per decade, years	.09	1.26	1.44	
Suicide	0	1	1	
Suicide Rate	0	2.1/1000/yr.	1.7/1000/yr.	

Table 1 shows a ten year follow up of twenty-seven patients who received the standard treatment for the decade, while sixteen received, in addition, a five week course of niacin or niacinamide. To our own data we have added a recent fourteen year follow-up study of forty-five very similar patients from the province of Alberta, a province immediately west of Saskatchewan where we did our study (Bland and Orn, 1978). They did not use vitamins as part of

the treatment. It will be seen that our twenty-seven patients in the comparison group who did not get vitamin B3 and the forty-five patients from Alberta fared similarly. On average each one of them spent about one year out of ten in hospital. The sixteen patients who were given vitamin B3 fared very differently, spending only about one month in hospital during the decade of follow-up, on average. Those who are statistically minded will find there are significant

differences between the three groups.

This is a small bit of evidence, but so far as we know no one has tried to repeat it. It is supported by our 'five-year cures' reported nearly twenty years ago.

Long term follow-up studies must, by their nature, take many years, and are very expensive both in time and money. As we have shown, there are experimental designs which might circumvent those problems to some extent by using identical twin pairs (Burrell and Osmond, 1959; Hoffer, 1976), and our own studies with identical twins lend credence to the effectiveness of B3.

For about half a century the public has been voicing hopes that a preventive psychiatry would develop. Those who advocate this have sometimes failed to realize that with the disappearance of the pellagra psychoses and general paresis, we have two examples of successful preventive psychiatry. What the public and psychiatrists mean is that we do not have effective prevention for schizophrenia. Psychiatrists usually respond to those who urge preventive measures with ambivalence. There have been many attempts to prevent children from becoming schizophrenic by a variety of educational means, starting with some forms of child psychoanalysis. So far there is little to show that there is any treatment which is available, feasible, and likely to be acceptable to the public which could be used to protect vulnerable people and would guard against relapse. It is true that Friedhof (1979) in New York has suggested giving the mothers of potentially schizophrenic children substantial doses of tranquilizers; by so doing he hopes to change their brain chemistry by permanently impairing dopamine receptors. It seems unlikely that even if this worked that many mothers would use such drastic measures to avert a potential danger.

There is little difficulty in locating vulnerable people, thanks to genetic studies by Kallman (1946) and Eliot Slater (1953), Slater and Cowie (1971), nearly forty years ago, and by using psychological tests such as the HOD (Hoffer and Osmond, 1961; Hoffer, Kelm, and Osmond, 1975) or the EWI (El Meligi and Osmond,

1970), combined with the work of Irvine, Bayne and Miyashita (1969), Pfeiffer (1975, 1978), Pfeiffer, Sohler, Jenney, and Iliev, (1974), and Sohler, Holsztynska and Pfeiffer (1974), on krypto-pyrrole. We have also been able to show, using the HOD, that some patients are more susceptible to relapse than others. Unfortunately our current treatments are of a kind which are unsuitable for use in prevention.

Prophylactic phenothiazines are difficult to justify because first, there is little evidence that they are effective, and second, their many side effects, while more or less acceptable when combating a grave illness, would become intolerable if given for prevention. Not only are they liable to make learning difficult but blood dyscrasias, jaundice, tardive dyskinesia, akinetic mutism and neuroleptic psychoses are all liable to occur, especially if the prophylaxis is begun early and maintained over many years. We recently saw a case of tardive dyskinesia which had occurred at the age of 17; only a few such misfortunes would discredit phenothiazines as a prophylactic or preventive agent; indeed this may be one reason why we have not heard of them being employed in this way.

Megavitamins with their minimal toxicity and few side effects are well suited for this particular role (Hoffer, 1969); indeed one of many criticisms made of them in the past was that they were not active enough psychopharmacologically to be an effective treatment. This no longer holds, thanks to the recent findings discussed earlier. Medicine has a predilection for dangerous medicines and procedures especially in serious illnesses. When faced by death or disaster, heroic medicine requires doctors and patients alike to accept readily any measures, however painful or perilous, to save life and health.

There is, however, another medical tradition exemplified by the phrase "nil nisi bonum" - nothing unless good. In attempts to prevent illness this must surely be paramount. Megavitamins, attention to diet (Hoffer and Walker, 1978), exercise, learning how to recognize and cope with illness, using appropriate measurements (Hoffer and Osmond, 1966), getting treated as early

as possible, and becoming both a vigilant and responsible patient could be begun today for many schizophrenic patients. There are methods available now and these could be refined and improved rapidly.

Why then have these not been used and studied? Mainly, we believe, because the psychiatric establishment, like other establishments, is unwilling to admit that its members could possibly be mistaken.

This is not unusual: the great theoretical physicist, Max Planck, was once congratulated by a friend for having persuaded his critics of the correctness of his views; Planck answered something to this effect, "I never persuaded any of my opponents. They died off and their places were taken by younger people who found my ideas less unfamiliar." Theoretical physics is seldom beset by the same degree of urgency which obtains in clinical medicine. An increasing number of people are learning about Orthomolecular psychiatry, but every year that passes tens of thousands of young people develop schizophrenia. Our figures show that about one-third of those afflicted are gravely harmed for the rest of their lives.

Establishments tend to recruit those younger people whose values and attitudes resemble those of their elders; if they did not do so there would be no establishments. This conservatism ensures stability and usually works well, unless such stability impedes the emergence of better treatments or sustains harmful ones. The great bleeding pandemic of about 1800 to 1836 is one example of harmful stability, and the prolonged, undramatic resistance to penicillin may be another.

We contend that every year's delay in using Orthomolecular psychiatry results in battalions, brigades, and divisions of young people of both sexes becoming and remaining intractably ill. Since our ten year follow-up was published sixteen years ago, if we are correct, or even partially correct, hundreds of thousands of young people will have endured millions of human life-years of avoidable misery and suffering.

The treatments which were so promising in the early 1960's are badly tarnished today; because of this we believe that the psychiatric establishment has a duty to reexamine the

data from our earlier studies, to obtain the views of clinicians who have used our methods,' and to meet patients who consider that they have benefitted from our treatments.

Since Orthomolecular treatments are compatible with most other treatments, little difficulty or expense would be incurred by adding them to those favored by the establishment. These recent scientific findings give our approach a different scientific status, that of a strong hypothesis. The remarkable safety of most of the treatments employed by Orthomolecular psychiatrists makes their use obligatory under Claude Bernard's ruling about human experiment. He stated that treatments unlikely to harm and likely to help are obligatory.

It is probable that our establishment colleagues with what they consider proper caution and what we believe is mainly inertia, will once again try to fob off the public with carefully controlled double blind studies and long term follow ups. While this might have been an admirable course of action twenty years ago, it is much less so today, for by its very nature such a study could not take less than twelve years. It is also likely to be expensive. During that twelve years at the most conservative estimate perhaps 300,000 young people will have become intractably ill. This seems a high price to pay for meeting those standards of scientific rectitude, resulting from the incuriosity of the psychiatrists and bureaucrats whose opposition has done much to produce the present situation.

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