Thyroid and Schizophrenia

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Introduction

In 1952 the standard treatment for schizophrenia was electroconvulsive therapy (ECT) and sedative drugs. Insulin coma was slowly being replaced because it was too dangerous and needed too much medical and nursing services and skills. As Director of Psychiatric Research for the Province of Saskatchewan, I was given the mission of finding better treatment for these patients. In searching the literature I discovered that several psychiatrists had given their patients large doses of desiccated (natural) thyroid, using very large doses. I also found that histamine injections had been used and found to be effective.[1] We found that histamine treatment used exactly as had been described by the authors was helpful, and out of twelve patients I treated eight were very much better, and a few showed dramatic improvement over a short period of time. This treatment was safe but was also time consuming.

I did not pursue this any further because I had become interested in using large doses of niacin. I had also given a few of my patients large doses of thyroid, increasing the dose as had been described but watching for overdose by the pulse rate. I was amazed at how much thyroid my patients could tolerate and I did see improvement, but again I did not pursue this any further. I now think this was an error and this report will provide the clinical data which will suggest that thyroid treatment should be considered seriously for patients with schizophrenia who do not respond as quickly and as well as they ordinarily do on orthomolecular therapy without thyroid.

From *The Hallucinogens*

After we developed our adrenochrome hypothesis I became even more interested in the connection between thyroid and schizophrenia. Quinones in general, including adrenochrome, have anti-thyroid properties. I recorded my findings in our book, *The Hallucinogens*,[2] pages 299 to 302. Since this book is out of print and probably not available to most I will repeat much of what we wrote, but I will not list the references here.

"A large number of workers have shown that thyroid hormone either in the form of dried gland or as the pure hormone triiodothyronine does improve cure rates much above the natural untreated rates and other standard treatments used, including the tranquilizers. Recently a number of authors reviewed the literature and found that many more schizophrenic patients were rendered completely free of symptoms and signs when treatment with thyroid was maintained. This included not only periodic catatonics but other schizophrenics who had no regular periodicity but seemed to have the usual more or less random fluctuations seen in most patients.

"Danziger, in 1958, reported some astonishingly successful results which have never been repeated by other workers using conventional treatments. He selected a series of 120 schizophrenics between the years 1946 and 1956. Many of them had not responded to any other therapy including ECT, psychotherapy, or psychoanalysis. Of this group 45% recovered, that is, became normal in every respect. Thyroid medication was continued for at least 100 days since recovery was slow for many. Of the 80 patients who were given thyroid medication for at least 100 days and who had been ill 6 months or less, all recovered. Relapses occurred only if patients discontinued medication while at home. The proper dose of thyroid would be considered excessively high by many physicians. We have found that some of our patients were taken off thyroid by family physicians as they were beginning to recover from their

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schizophrenia. The dose range was 2 to 20 grains daily (120 to 1200 milligrams). Only 10 patients needed more than 600 milligrams.

"Recently a sixteen-year old girl from the United States was admitted for treatment of her schizophrenia. She had been severely ill for nearly 2 years and had not responded to prolonged psychoanalytic therapy for many months. She had failed to respond to treatment in a university psychiatric ward in Texas, in a large well-known psychiatric clinic of the west coast, to 6 months of continuous high doses of tranquilizers in an hospital, to a combination of nicotinic acid (3 grams per day), penicillamine (2 grams per day for 10 days) and ECT in a fourth hospital. When she was admitted to University Hospital she was a classical adolescent schizophrenic with changes in perception, gross thought disorder, inappropriate affect and activity. She was filled with hatred for her parents, something we rarely see in our patients not exposed to psychoanalysis. She also had malvaria.[3] She was immediately started on a second series of ECT plus nicotinic acid plus penicillamine and within 2 weeks had recovered clinically but her HOD,[4,5] scores remained very high. After 1 week she suddenly relapsed within a period of 24 hours and became catatonic. About this time Dr. L. Gjessing, son of Dr. R. Gjessing, visited our research at Saskatoon and brought us up to date on periodic catatonia. A review of her illness then showed that although she had not once recovered spontaneously from schizophrenia she had several times been very much improved after a series of ECT. She did not fit in the Gjessing syndrome but she had a periodicity imposed on her by her treatment.

"At this time she was started on desiccated thyroid and the dose was increased until her pulse rate hovered between 110 and 120 per minute. She was maintained on nicotinic acid and given small doses of haloperidol to control agitation. The thyroid was begun as her clinical condition was rapidly worsening into a catatonic stupor. Within a day her condition steadied and she slowly began to improve. When she was very much better she was discharged in December 1964, after two months in hospital, but her HOD scores were too high and the stigmata of schizophrenia were still present. Six months later she was nearly well. Her scores had become normal, she was being tutored at home in preparation for her return to high school and she was able to relate to her parents and friends in her normal manner. She quickly lost her hostility to her parents as she recovered and she was assured they had not made her ill. It was explained to her that ambivalence and hostility were merely symptoms of schizophrenia to be ignored, if possible, and controlled. She is still on 7 grains of thyroid per day. With this dramatic result before us a series of 12 schizophrenic were started on a similar program. All had been treated with nicotinic acid. All were at home and getting on reasonably well, but none were completely free of symptoms. From this group of 12 only 3 were not benefitted but of these one discontinued it before it could become effective on the advice of her family physician. Of the remaining 9, 6 were very much better and seem to be moving rapidly toward recovery and the other 3 are improving as the doses of thyroid are being increased. One of the 6 with a history of 16 admissions to University Hospital (Saskatoon) because he was constantly plagued by auditory hallucinations, is now nearly well and has been free of voices over 2 months. The usual maintenance dose is 5 grains of desiccated thyroid. All are, of course, still taking nicotinic acid.

"Lochner et al. in 1963 conducted a double blind controlled comparison study on 30 schizophrenic patients who had been in the hospital for 4 years or more, with a chronic history running 8 years or more. Of the group, half were given 200 micrograms of l-triiodothyronine each day

and the other half, placebo. Of the drug group 12 were improved and of the placebo group 2 were improved. ($P<0.01$). Out of 12 drug patients who changed, 7 increased motor activity, sociability, interest in their environment and performed better at work. They became more spontaneous, their thinking became more logical and relevant and they felt better. One subject who had not responded to any medicine in many years improved enough to work in the hospital kitchen. The remaining 5 who changed became overly active but revealed for the first time a good deal of pathology they had suppressed. Of the placebo group none improved but 2 became more active.

"It is clear from Lochner et al's review that thyroid medication has not come into general use simply because there is no acceptable rationale. The majority of schizophrenic patients had normally functioning thyroid glands. Reiss and Haig (1954) using radioactive tracer methods found that of 1539 subjects in a mental hospital in England 17% were underactive and 17% were overactive.

"But there is a peripheral insensitivity to thyroid hormone. Large doses of hormone did not increase oxygen consumption. It has been known for a long time that schizophrenic patients could tolerate large doses of thyroid and not show any evidence of hyperthyroidism. Hoskins (1932) reported that schizophrenic patients were resistant to large doses of thyroid. We have found that 5 grains must usually be given before the pulse rate is elevated to 100 or more. This is nearly twice the normal endogenous production of thyroid. Brody and Man (1950) found that the concentrated serum precipitable iodine for 578 schizophrenic patients was normal. They also suggested that the low basal metabolic rate of these patients was a function of a defective response to the circulating hormone.

"If tissues do not respond to normal levels of hormone this must be due to a metabolic block on the tissue receptors. The report of Brody et al. ruled out excessive destruction of hormone. The metabolic block might be due to a toxin as was suggested by L. Gjessing (1964) who believed that such a toxin could accumulate gradually until a critical level was reached. At this time the hypothalamus would be affected which would in turn stimulate discharge of large amounts of amines, increase thyroid activity slightly and precipitate the psychosis. The adrenergically altered metabolism would gradually break down the toxins and allow the patient to enter a quiet phase. The administration of thyroid and the elevation of oxygen consumption would increase the detoxification process and so prevent a buildup of toxin and so abort a relapse.

"Quinones are antithyroid. It is not surprising that adrenochrome which has a quinoid structure, can also interfere in thyroid function. It is likely the accumulation of substances like adrenochrome and adrenolutin is responsible for the curious relationship between schizophrenia and thyroid function. Rawson et al. (1957) stated that adrenochrome prevented metamorphosis of tadpoles. This is a property shared with other indoles and provides direct evidence that thyroid hormone and adrenochrome are antagonists."

When we wrote this in 1966 there was no direct proof that adrenochrome was found in the body. Now we do have this proof and this makes our suppositions even more powerful.

Thyroid Hormone Metabolism

The pituitary gland releases thyroid stimulating hormone (TSH) in response to a call from the body that more thyroid hormone is needed. The thyroid gland synthesizes tetraiodothyronine (T4), made from tyrosine and iodine. This is made by the combination of two diiodothyronine molecules (T2) and smaller amounts of triiodothyronine (T3). Enzymes in the gland release the T4 and T3 from thyroglobulin and both are released into the

circulation. T3 combines with T3 receptors and this controls the effect of this hormone on body physiology. The cell needs 5 to 7 times as much T4 to bind to nuclear reception to have the same effect as T3. By a feedback mechanism the amount of circulating hormones controls the secretion of TSH. Thus when there is enough T3 in the circulation little TSH is required and TSH values as measured in the laboratory are low. The thyroid gland produces much more T4 than T3. The conversion to T3 occurs in the liver, kidneys, pituitary and nervous system. The pituitary and nervous system are not dependent on liver and kidney to make the conversion. This is a simplified account of the formation of these hormones but I will ignore the other iodinated fractions such as T2 and reverse T3. These undoubtedly have physiological properties.

Hyperthyroidism means too much hormone is being secreted, with laboratory tests showing very low TSH, and very high T4 and T3 levels. In hypothyroidism the TSH is very high and the other values are low. But a hypothyroid states may exist in the presence of enough T4. This is called the euthyroid sick syndrome or low T3 syndrome. TSH is normal or slightly suppressed but T3 levels are low. This is a condition of normal thyroid gland activity with a reduced peripheral formation of T3 from T4. This condition is found in elderly populations and increased death rate from surgery. The conversion to T3 is decreased in aging and by severe stress coming from burns, calorie restriction, chemical exposure, chronic alcohol intake, excessive oxidation, liver and kidney disease, toxic metal exposure, sleep deprivation, excessive exercise. To synthesize these hormones the thyroid gland requires iodine, selenium, zinc, niacin, vitamin B_{12}, lipoic acid, and the antioxidants vitamin C and E. For a comprehensive discussion of the thyroid hormones see Kelly.[6]

Hypothyroidism With Normal TSH and T4 Values

Over 200 symptoms are associated with hypothyroidism. The most common symptoms and signs include weakness, fatigue, low energy, increased fat, cold intolerance, hair and skin changes and low body temperature. Rouzier[7] examined 671 patients for thyroid disease. A total of 262 patients had very low T3 levels and the rest were low. All had body temperatures less than 97° F. The addition of thyroid containing both T4 and T3 corrected body temperature to 98° with improvement in their well being. He found a good correlation between body temperature and T3 levels. Rouzier concluded that TSH alone should not be used as the sole criterion for determining thyroid deficiency. But this teaching goes against the grain of modern thyroid investigation and treatment. In Rawson's review written in 1966 the TSH test is not even mentioned.

Modern practice recommends that TSH alone is adequate and treatment should be given only when these values are very high and that the synthetic T4 only should be used. This is what had been standard clinical practice for many decades, ie., the use of clinical criteria for determining thyroid insufficiency should no longer be the main criterion, and the desiccated thyroid used for decades which contains both T4 and T3 and the other iodinated fractions of tyrosine should be replaced by the synthetic preparation. This was based upon the hypothesis that the preparations of desiccated thyroid contained varying concentrations of these two hormones and therefore were not suitable for clinical use. The new criteria for determining hypothyroidism, i.e., TSH values with little regard to clinical findings, has never been validated by comparing it with the older criteria. In science one usually does not give up a method until it has been shown that the new method yields results as good as or better than the old method. This is called validation.

Rouzier wrote, "We are often taught that administration of synthetic T4 compound is much more efficacious than the old, outdated, difficult-to-regulate Armour thyroid. The FDA recently fined Knoll Pharmaceuticals $90 million for manipulating results of studies to convince physicians that Synthroid (T4) is superior, whereas recent data indicates otherwise. Nevertheless prejudice still exists against the T3 and T4 combination, that which we find to be the far superior regimen. We looked at patients on Synthroid to evaluate adequately T4 to T3 conversion. Our data supports inadequate conversion of T4 to T3 on patients treated with synthetic T4. Our data supports use of a combination T4 and T3 (Armour Thyroid) as recently recommended by an article in the New England Journal of Medicine. Measuring and monitoring free T3, which is the primary active hormone is appropriate."

Bunevicius et al.[8] found that some patients did better on the combination subjectively and scored higher on standardized tests that those patients treated with T4 only. Hamilton et al.[9] found patients with normal TSH values who were low in T3 and who improved when given T3.

Baisier et al.[10] found that TSH values did not correlate well with clinical symptoms of hypothyroidism. These symptoms included fatigue, depression, a feeling of coldness, and five other symptoms. At least one of these was present in 97% of their patients. Studying 832 patients, 81% female, they found that urinary T3 values were the best indicator of hypothyroid function. They found, "...the determination of free T3 in the 24 hours urine has a far better correlation with the clinical thyroid statue of a patients than any other classical test, even under treatment with natural desiccated thyroid (T3 and 4), the level of 24 hours urine free T3 continues to correlate with the patients clinical state. The explanation is that TSH is grossly in feedback with serum T4 only, not so much with serum T3, while the patients well being depends on the free T3 that is disposable inside the cells." Skinner[11] examined 139 patients clinically hypothyroid but with normal TSH values. They recovered when treated with T3.

But many years earlier Dr. Broda Barnes,[12,13] found that the simplest test of all was the body temperature, and when patients had low basal temperatures they responded well to treatment with desiccated thyroid. The more recent work by Langer[14] summarizes the remarkably high incidence of hypothyroid disease which can be easily diagnosed by the clinical symptoms including basal body temperature and the response to desiccated thyroid preparations. A recent book by Shames and Shames[15] is very good. These authors recommend against depending solely on TSH values and insist on T3 testing as well. Any TSH value over 3 is suspicious according to these authors. They depend upon clinical criteria as well as Barnes' temperature test. They state that thyroid medication does not cause osteoporosis, it helps prevent it. I have not seen any persuasive evidence that it does cause osteoporosis but this is one of the common fears of the profession. They are confusing the impact of endogenous thyroid hyperactivity with exogenous use of thyroid hormones. These are different conditions and even if the endogenous form may be associated with osteoporosis this does not prove that exogenous thyroid has this effect. The osteoporosis associated with exophthalmic goiter is probably not caused by the thyroid but by the other metabolic factors that are associated with it. Dr. David Derry[16] reported that in over 25 years of practise using thyroid he had not seen any cases of osteoporosis, nor have cases been reported in the medical literature. Apparently osteoporosis became endemic beginning about 25 years ago following the introduction of TSH as the sole criterion for the use of thyroid. Toft[17] concluded that "The evidence that exogenous

subclinical hyperthyroidism is a risk factor for osteoporosis is therefore inconclusive." Rawson[18] in his careful review of thyroid function written in 1966 does not list osteoporosis even though he lists almost every other organ in the body as being affected by hyperthyroidism. Surely if this was a common finding he would have discussed it.

Derry suggests that the deficiency of thyroid hormone is a major factor and that iodine and thyroid hormone deficiency are endemic. This was partially created by the common restriction against the use of salt so that even the small amounts of iodine in iodized salt are no longer being consumed.

Gewirtz et al.[19] treated five women with normal levels of T3 and T4 and with elevated TSH levels or a low metabolic rate. They all responded to thyroid medication.

Langer devotes a chapter to the use of thyroid in the treatment of depression. Several case histories are given, double blind controlled therapeutic trials are referred to and then the authors conclude, "Unfortunately, hypothyroidism is still not widely enough recognized as a major cause of depression. It would be a mistake, however, to consider subnormal thyroid function and nutritional deficiencies as the only causes."

I have been using desiccated thyroid for patients not schizophrenic when I diagnosed hypothyroidism since 1960. My first patient was a man who had been treated with radioactive iodine for severe exophthalmic goiter. He was classical with bulging eyes, etc. After treatment he became hypothyroid and was placed upon T4. But no matter how often it was adjusted he still did not feel well and his exophthalmic eyes did not recede. I discontinued his synthetic thyroid, started him on desiccated thyroid and niacin. Within half a year he was normal and his eyes had receded back into their sockets. I have seen about ten patients who were all receiving adequate amounts of T4 as called for by the TSH test and of these, nine became well only after their thyroid was replaced with T3. I have seen only one patient who did not respond to desiccated thyroid but did become well on T4.

Schizophrenic Syndromes

A syndrome is a constellation of symptoms and signs by which it is identified clinically. The schizophrenic syndrome consists of perceptual changes combined with thought disorder. This is described in our book, *How To Live With Schizophrenia* and agrees with the definition first described accurately by John Conolly over 150 years ago. It is an excellent working definition and if it were used routinely by psychiatrists, much of the confusion about who is and who is not schizophrenic would vanish. It also correlates highly with the HOD test and with the urine test for kryptopyrrole. But it does not mean that there is only one cause for this disease. A large number of factors can precipitate this syndrome. Treatment becomes much more scientific when these causative factors are identified. The causative factors are those which produce the excess production of adrenochrome and similar oxidized derivatives from adrenalin, noradrenalin and dopamine. These are synaptic blocking agents as are the hallucinogens and this is what creates the disturbance in perception and in thinking. I will list some of these causal factors and discuss the thyroid problem as one of the causative factors.

Carl C. Pfeiffer[20] divides 29 medical causes into three categories: Well-Known, Less Well-Known and Almost Unknown. I will add two more: Syndromes Very Common In 1900 and Very Rare Today, and Syndromes Common in 1950 and Very Rare Today. The classic psychosis caused by thyroid deficiency is known as myxedematous madness.

(a) Syndromes Common in 1900 and Very Rare Today
1) Pellagra
2) Scurvy
3) General paresis of the insane (brain syphilis)
4) Dementia praecox, still present but is now called schizophrenia.

We in psychiatry cannot claim any credit for the disappearance of the first three syndromes. Improving nutrition and adding vitamin B_3 to flour helped eradicate pellagra, and knowledge about the importance of vitamin C removed that particular cause. Penicillin removed syphilis as a cause. These four syndromes were part of the differential diagnosis in a textbook written about 1900. We did remove dementia praecox by renaming it schizophrenia.

(b) Syndromes Common in 1950 and Very Rare Today
(1) Atropine intoxication from asthma cigarettes
(2) Mercury intoxication
(3) Rheumatic fever

Banning asthma (belladonna) cigarettes removed atropine as a cause, and mercury as a cause is very rare although I did see two cases about 25 years ago. Mad hatters were more common in Europe when liquid mercury was used to make felt hats. Rheumatic fever was considered in the differential before 1950. A few chronic schizophrenic patients at autopsy showed typical changes seen in brains of patients who died of rheumatic fever.

(c) Common Syndromes. Well-Known (Pfeiffer)
(1) Pellagra
(2) Porphyria
(3) Hypothyroidism
(4) Drug intoxication - Hallucinogens
(5) Homocysteinuria
(6) Folic acid/B_{12} deficiency
(7) Sleep deprivation
(8) Heavy metal toxicity

I have added the following:
(9) Vitamin B_3 dependency
(10) Cerebral allergy
(11) Omega 3 essential fatty acid deficiency
(12) Vitamin B_6 dependency
(13) Zinc deficiency
I think the first three causes I added are the most common and probably account for 90% of all schizophrenic patients.

(d) Less Well-Known (Pfeiffer)
(1) Hypoglycemia
(2) Psychomotor epilepsy
(3) Histapenia
(4) Pyroluria
(5) Wilsons's disease
(6) Chronic Candida infection
(7) Huntington's Disease

Schizophrenia Due to Hypothyroidism

Pfeiffer wisely included hypothyroidism as one of the causes of this syndrome. Psychiatrists have not paid enough attention to his classification. I hope this report will alert physicians to the state of thyroid metabolism which must always be taken into account. According to Pfeiffer about ten percent of schizophrenic patients are hypothyroid.

The mental state may include perceptual changes such as hallucinations, (aural and visual); thought disorder including obsessions, paranoid delusions, fear, suspiciousness, resentment; mood disorder including depression, mood swings and suicide ruminations. This conforms to the Conolly definition of schizophrenia.

Schizophrenic patients do respond to treatment with thyroid containing T3 but very large doses may have to be used. They are able to tolerate these doses. The biochemical evidence suggests that adrenochrome is antagonistic to thyroid hormone, perhaps to T3. If adrenochrome prevents T3 from functioning properly it would account for the hypothyroid symptoms and for the need for large doses to overcome this inhibition.

Conclusion

Schizophrenic patients should be examined for hypothyroidism. When there are clinical symptoms and signs of this condition, thyroid should be added to the program. This may be T4, or T3, or desiccated thyroid which contains both. Low TSH values should not prevent the use of thyroid. Some thyroidologists recommend that TSH be kept below 3. The blood values may be low or normal for TSH, and low for T3. Low T3 is more reliably related to hypothyroidism as seen clinically.

References

1. Hoffer A, Parsons S: Histamine therapy for schizophrenia: a follow-up study. *Can Med Assoc J ,* 1955; 72: 352-355.
2. Hoffer A, Osmond H: The Hallucinogens. Academic Press. New York, 1967.
3. This was our original term for patients who excreted kryptopyrole before it was identified. Pfeiffer later called it pyroleuria.
4. Hoffer A, Osmond H: The association between schizophrenia andtwo objective tests. *Can Med Assoc J,* 1962; 87:641-646.
5. Hoffer A, Kelm H, Osmond H: *The Hoffer-Osmond Diagnostic Test.* RE Krieger Pub Co. Huntington, New York, 1975.
6. Kelly G: Peripheral Metabolism of Thyroid Hormones: A Review. *Alternat Med Rev,* 2000; 5, 306-333.
7. Rouzier N: *Optimal thyroid hormone replacement therapy.* 2825 Tahquitz Canyon Way, B200, Palm Springs, CA 92262.
8. Bunevicius RG, Kasanavicius R, Zalinkevicius, Prange RJ: Effects of Thyroxine as Compared with Thyroxine plus Triiodothyronine in Patients with Hypothyroidism. *NEJM,* 1999; 340; 424-429.
9. Hamilton M et al: Safety and Hemodynamic Effects of Intravenous Triiodothyronine in Advanced Congestive Heart Failure. *Am J Cardiol,* 1998; 82: 443-447.
10. Baisier WV, Herloghe J, Eeckhaut W: Thyroid insufficiency. Is TSH measurement the only diagnostic test. *J Nutr Environ Med,* 2000; 19: 105-113.
11. Skinner GRB, Holmes D, Ahmad A et al: Clinical response to thyroxine sodium in clinically hypothyroid but biochemically euthyroid patients. J Nutri Environ Med, 2000; 19: 115-124.
12. Barnes BO, Barnes CW: *Heart Attack Rareness in Thyroid-Treated Patients,* Springfield Ill, CC Thomas, 1972.
13. Barnes BO, Galton L: *Hypothyroidism. The Unsuspected Illness.* Thomas Y. Crowell Co, New York, 1976.
14. Langer SE, Scheer JF: *Solved: The Riddle of Illness.* Keats Publishing, Inc. New Canaan, CT, 1984.
15. Shames RL, KH Shames: *Thyroid Power.* Harper Collins, New York, 2001.
16. Derry D: *Presentation to Association Complementary Physicians of BC,* Victoria, November 14, 2001.
17. Toft AD: Subclinical hyperthyroidism. 2001; NEJM 345: 512-516.
18. Rawson RW: The Thyroid Gland. *Clinical Symposia,* Ciba Company Limited, 1966; 18: 35-63.
19. Gewirtz GR, Malaspina D, Hatterer JA, Feureisen S, Klein D & Gorman JM: Occult Thyroid Dysfunction in Patients With Refractory Depression. *Am J Psychiat,* 1988; 145: 1012-1014.
20. Pfeiffer C, Holford P: *Mental Illness: The Nutrition Connection.* ION Press, London, UK. 1996.