The History of Iodine in Medicine Part I: From Discovery to Essentiality

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Part I: From Discovery to Essentiality

The essential element iodine has been kept in the Dark Ages over the last 60 years after World War II. In order to partially remedy the gross neglect of this essential element by the medical profession, poorly represented in medical textbooks and vilified in endocrine publications, the Journal of The Original Internist will start a series of publications on the history of iodine in medicine from discovery to the present. This series of publications is part of a book on the Iodine Project which was implemented by the author 6 years ago. Over the last 4 years, a series of publications by the author and collaborators have appeared in The Original Internist, rediscovering iodine as the Universal Medicine,[1-13] a status iodine held for over 100 years before World War II.

The first installment in this series will deal with the history of iodine from discovery to essentiality, covering a period of 100 years. The discovery of the stable halides, chloride, iodide, bromide and fluoride seems to have been a French enterprise. All 4 halides were identified by French scientists, (Table I) with H. Davy from Great Britain, sharing the discovery of chloride with Gay-Lussac in 1809-1810.[4,14]

Two years prior to the discovery of iodine, Gay-Lussac identified chlorine as a new element in 1809, and subsequently Davy claimed credit a year later in 1810 for this discovery. Of interest is the fact that Faraday was Davy's lab assistant and when Davy traveled abroad, Faraday doubled as his valet.

"Gay-Lussac and Thenard made a fundamental contribution to the realization that so-called oxymuriatic acid contained no oxygen and was an element … On the previous day, 26 February (1809), Gay-Lussac and Thenard had read a first draft of their memoir. In the first reading the authors had suggested unequivocally that oxymuriatic gas was an element. Their patron, Berthollet, unfortunately persuaded them to alter their remarks to make this not more than a possibility … Because of the pressure he exerted on Gay-Lussac and Thenard, Davy is usually credited with the discovery of the elementary nature of chlorine, which he announced in 1810."[14]

Bernard Courtois, a French chemist, was a saltpeter (potassium nitrate) manufacturer. Saltpeter was one of the compounds needed for the manufacture of gunpowder. Seaweed ash was used as a valuable source of sodium and potassium salts. Sulfuric acid was added to remove interfering compounds before the salts could be precipitated. One day toward the end of AD 1811, Courtois added too much acid to the suspension of seaweed ash. The iodides in seaweed were oxidized to iodine, which sublimated and formed a violet vapor above the preparation. The crystals obtained from condensation of the iodine vapor were analyzed by Courtois and he prepared several iodide salts. Courtois never published his findings. Some of these crystals ended up in the hands of Gay-Lussac and Ampere who gave some to H. Davy.

Although Courtois discovered iodine in 1811, it was Gay-Lussac who proved that it was a new element and gave it the name of "iode" from the Greek "ioeides", violet colored. Davy anglicized the name "iode" calling "iodin" which became "iodine" in the 1930's.[4] By 1813, Gay-Lussac had synthesized several products from iodine and fully characterized this new element, but he gave full credit to Courtois for the discovery of iodine. According to the Dictionary of Scientific Discovery,[14] Davy, in an attempt to eclipse Gay-Lussac in the characterization of iodine, did the unthinkable for a scientist of his rank:

"A large part of Davy's claim for the originality of his study of iodine depends on his complete honesty in claiming certain knowledge before that of Gay-Lussac and in particular in dating as 11 December a paper read to the Institute on 13 December (that is the day following Gay-Lussac's publication)".

Courtois did not benefit from his discovery. In 1831, he was awarded a prize of 6,000 francs for his discovery. By this time Courtois had given up the saltpeter business and, from the 1820's, attempted to make a living by preparing and selling iodine and iodine compounds. This enterprise also failed, and he died in poverty.[14]

Fifteen years after the discovery of iodine, Balard discovered bromine serendipitously while developing a method to measure iodine in seaweeds and other plants obtained from the Atlantic and Mediterranean Oceans.[14]

"The discovery of bromine, Balard's first and greatest achievement, actually was a by-product of his more gen-

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eral chemical investigations of the sea and its life forms. In the course of his studies, Balard devised a reliable test for the presence of iodine, the content of which he was determining in plants taken from the Atlantic and the Mediterranean. Chlorine water was added to the test solution, to which starch and sulfuric acid had already been added. The iodine was manifested by its characteristic blue color at the interface of the test solution and the chlorine water. Then Balard noticed that, in some samples, above the blue layer there appeared a yellow-orange layer, which had its own characteristic odor. He isolated the substance causing the yellow color, which proved to be a red liquid."

Although the names of the two previous halogens were based on their colors, chloros = greenish yellow for chlorine; and ioeides = violet colored for iodine, Balard did not choose the red color of liquid bromine but the odor instead, and obviously not a pleasant one, since the Greek word "bromos" means stench. As a side note, "spontaneous generation" iconoclast Louis Pasteur who left his name to "Pasteurization" was a student of Balard.

Some 60 years after the discovery of bromine, Moissan survived long enough to characterize the last stable halogen fluorine in 1886. Moissan received the Nobel Price for chemistry in 1906. Fluorine derives its name from "flux". The isolation of fluorine was a life-threatening endeavor and many scientists were maimed and killed trying to accomplish this feat. Fluorine is the most reactive of all the elements.

Only eight years after the discovery of iodine from seaweed, a Swiss physician, J.F. Coindet who previously used burnt sponge and seaweed successfully for the treatment of goiter, reasoned that iodine could be the active ingredient in seaweed. In 1819, he tested tincture of iodine at 250 mg/day, in 150 goiter patients with great success. He could reduce significantly the size of goiter within a week. He published his results in 1820. [15]

During the early 1850's, Chatin [16,17] studied the relationship between the prevalence of goiter and the concentrations of iodide in the soil, water and food supplies of different localities. He also studied the effect of iodine supplementation on endemic of goiter. He made the following observations: 1) goiter and cretinism are rare in localities which are rich in iodine; 2) they do occur frequently, however, in localities which are poor in iodine; 3) iodine supplementation is a specific preventative of goiter.

Between 1891 and 1892, a series of publications appeared in the British Medical Journal, reporting for the first time the effective use of thyroid extracts both parentally and orally in patients with hypothyroidism [18-20]. In 1895, Bauman [21] detected high concentrations of iodine in the thyroid gland and proposed that the active ingredient in the thyroid extracts contains iodine.

By the time Bauman identified large concentrations of iodine in the thyroid gland in 1895, pharmaceutical and apothecary preparations containing iodine, excluding thyroid extracts, were widely used as a panacea for all human ills. To quote Kelley [22]:

"In the first flush of enthusiasm for the newcomer, physicians and surgeons tested it and tried it for every conceivable pathological condition. The variety of diseases for which iodine was prescribed in the early years in astonishing – paralysis., chorea, scrofula, lacrimal fistula, deafness, distortions of the spine, hip-joint disease, syphilis, acute inflammation, gout, gangrene, dropsy, carbuncles, whitlow, chilblains, burns, scalds, lupus, croup, catarrh, asthma, ulcers, and bronchitis – to mention only a few. Indeed, tincture of iodine, iodoform, or one of the iodides, was applied to almost every case that resisted the ordinary routine of practice; and between 1820 and 1840 there appeared a remarkable series of essays and monographs testifying to the extraordinary benefits to be achieved by this new and potent remedy."

Unfortunately, these monographs disappeared from U.S. medical libraries. It is now very difficult to review the true history of iodine in medicine in extenso without access to these publications. Some 50 years ago, Nobel laureate Albert Szent Györgyi, the physician who discovered Vitamin C in 1928 and who was a medical student in the early 1900's, wrote [23]:

"When I was a medical student, iodine in the form of KI was the universal medicine. Nobody knew what it did, but it did something and did something good. We students used to sum up the situation in this little rhyme:

If ye don't know where, what, and why
Prescribe ye then K and I.

Our medical predecessors, possessing very few and crude instruments only, had to make use of two given by nature (the use of which has since gone out of fashion): eyes and brains. They were keen observers and the universal application of iodide might have been not without foundation."

The phenomenal growth of iodine containing products, from 10 preparations listed in the pharmacopoeias in

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1851 to 1,700 approved pharmacopoeial names assigned to iodine-containing products in 1956, is compelling evidence for the widespread applications of iodine in medicine [22]:

"In the Great Exhibition at the Crystal Palace in Hyde Park in May 1851 iodine and iodine compounds were publicly shown for the first time by ten pharmaceutical firms, … by 1890, to choose a date at random, the 6th edition of Martindale's Extra Pharmacopoeia sponsored 30 medicaments derived from iodine; the 'Iodine Centenary Volume' compiled by 'The Prescriber' in 1914 mentions 45 iodine preparations; by 1928 'Martindale' had extended its coverage to 128 iodine items: and, in an International Index published in 1956, and devoted exclusively to iodine pharmaceuticals, no less than 1,700 approved pharmacopoeial names, proprietary names, synonyms, and alternative designations are alphabetically listed."

By the early 1900's iodine was well established in medical and surgical practices, as described in the Encyclopedia Britannica 11th Edition published in 1910-1911 [24]. In Volume XIV, under iodine, on page 725-726, one reads:

"In medicine iodine is frequently applied externally as a counterirritant, having powerful antiseptic properties. In the form of certain salts iodine is very widely used, for internal administration in medicine and in the treatment of many conditions usually classed as surgical, such as the bone manifestations of tertiary syphilis. The most commonly used salt is the iodide of potassium; the iodides of sodium and ammonium are almost as frequently employed, and those of calcium and strontium are in occasional use. The usual doses of these salts are from five to thirty grains or more. (For the reader's information, one grain is approximately 60 mg. Therefore, the daily therapeutic dose was from 300 mg to 1800 mg iodide). Their pharmacological action is as obscure as their effects in certain diseased conditions are consistently brilliant and unexampled. Our ignorance of their mode of action is cloaked by the term deobstruent, which implies that they possess the power of driving out impurities from the blood and tissues. Most notably is this the case with the poisonous products of syphilis. In its tertiary stages-and also earlier-this disease yields in the most rapid and unmistakable fashion to iodides; so much so that the administration of these salts is at present (For the reader's information, this was written in early 1900) the best means of determining whether, for instance, a cranial tumour be syphilitic or not. No surgeon would think of operating on such a case until iodides had been freely administered and, by failing to cure, had proved the disease to be non-syphilitic. Another instance of the deobstruent power – "alterative," it was formerly termed – is seen in the case of chronic lead poisoning. The essential part of the medicinal treatment of this condition is the administration of iodides, which are able to decompose the insoluble albuminates of lead which have become locked up in the tissues, rapidly causing their degeneration, and to cause the excretion of the poisonous metal by means of the intestine and the kidneys. The following is a list of the principal conditions in which iodides are recognized to be of definite value: metallic poisonings, as by lead and mercury, asthma, aneurism, arteriosclerosis, angina pectoris, gout, goiter, syphilis, haemophilia, Bright's disease (nephritis) and bronchitis."

In a monograph published in 1940 by the Harvard University press, reviewing the history of iodine in medicine with 588 references, the author, William Thomas Salter [25] expressed his amazement at the surprisingly good results obtained with iodide in tertiary luetic (luetic means syphilitic) lesions and arteriosclerosis using daily amounts of gms of iodide for long periods of time and without any evidence of complications.

"After the discovery of iodine by Courtois in 1811, there was a great vogue for iodine therapy. … Likewise, in the 1820's it was first introduced in the treatment of syphilis, and that use of the medication has continued since. It still is employed in the treatment of various granulomata such as actinomycosis, blastinomycosis, and odd skin disturbances like lupus erythematosus. Occasionally, even today, a gumma is found and the response of such a tertiary luetic lesion to iodide therapy is very surprising, … The dosage used in these disturbances is often very high. Doses of several grams a day have not infrequently been administered for considerable periods. … This form of therapy, however, still remains important in the treatment of sclerotic lesions of the aorta due to syphilis, and has even been used over long periods for the treatment of generalized arteriosclerosis. One cannot help wondering what complication such therapy may produce in the endocrine system, but there is available no very clear-cut evidence of manifest endocrinopathy due to these heroic doses of iodine."

In the same year Salter's monograph on iodine was released by The Harvard Medical Press [25], Radish and Perloff [26] published in the Journal Endocrinology a manuscript entitled "The medical treatment of hyperthyroidism". The two medical treatment modalities used at that time were iodine alone and x-ray irradiation of the thyroid gland, with iodine alone being by far the most common approach.

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In the early 1900's, Professor Kocher came on the scene and had an adverse iodophobic effect on the treatment of hyperthyroidism. Professor Theodore Kocher carried a lot of weight, being the recipient of the Nobel Prize in Medicine and Physiology in 1909 for his work on "thyroid surgery", the only Nobel Prize assigned to research on the thyroid gland. The year after Kocher received the Nobel price, he reported that he suffered from hyperthyroidism following ingestion of iodide. Kocher then became the most famous medicoiodophobe in medical history. He was against the use of iodine/iodide for all forms of hyperthyroidism [4].

Whether Kocher suffered from Iodophobia Vera, true iodophobia, when the physician, although misguided, is sincere; or Iodophobiae Simulatio, that is simulated iodophobia with intent to deceive, remains a mystery. The timing was perfect. The Nobel Prize gave world recognition to Kocher who did not waist any time to use his fame in the promotion of iodophobia. Radish and Perloff commented:

"The relationship between iodine and the thyroid gland, particularly as regards function, was recognized as early as the beginning of the last century by Staub (1819), and Coindet (1820). After the syndrome of Flajani was classically described by Graves and von Basedow, iodine became the basis for treatment, with variable degrees of success, until that time when Kocher first described his hyperthyroidism presumably caused by iodine. This conception of the great Swiss surgeon caused such a sensation that the use of iodine was almost completely abandoned. Today, however, we are skeptical of the validity of Kocher's conclusions." [26]

Cowell and Mellanby in their 1925 publication gives up a glimpse of Kocher's influence over the thyroidologists of that time, bordering on intimidation:

"Kocher taught that the administration of potassium iodide must never be carried out in exophthalmic goiter, and on the whole, this advice has been taken. As evidence of this fact may be mentioned the discussion on the treatment of exophthalmic goiter at the Royal Society of Medicine in 1923. No speaker mentioned iodine or any preparation of iodine as being of any value in the treatment of the disease, and it can be inferred that therapy involving the use of iodine has been deliberately avoided." [2]

Kocher's influence divided the clinicians into 2 groups: the iodine group who favored the use of iodine preparations first in hyperthyroidism, referring the patient for x-ray or surgery only in non-responders; and the surgical school, discouraging the use of iodine and recommending surgery exclusively for hyperthyroidism. Kocher's influence crossed the Atlantic Ocean, as reported by Radish and Perloff:

"The conception that treatment of Graves' disease … is primarily surgical, is widespread despite the fact that American as well as European literature contains numerous reports of satisfactory results with non-surgical treatment in selected cases." [26]

Under the subheading "Treatment with iodine alone", Raddish and Perloff reported that iodine alone was used extensively by physicians for hyperthyroidism at that time. Clinics in Europe and the U.S. reported very high success rates with iodine alone:

"In Biedl's clinic about 10% of the cases with favorable results were completely and permanently cured, 40% entirely symptom free so long as iodine was administered, and 50% almost symptom free but still showing some manifestations of the condition. The 'toxic symptoms' of acute Graves' disease (diarrhea, restlessness, insomnia) reacted especially favorably to iodine. The fact that the percentage of cases treated by iodine alone in Means' clinic has increased remarkably during the last 3 years, shows that the pendulum may be once again swinging towards the medical treatment of hyperthyroidism in this country." [26]

Using iodine alone in patients with hyperthyroidism, Thompson et al [27] reported in 1930 a success rate of 88% and Starr et al (28) in 1924 reported a success rate of 92% with Lugol solution at daily doses of 6 to 90 mg.

During the first 100 years following the discovery of iodine, its clinical applications were purely empirical and the effective dose was arrived at by trial and error. The concept of essential trace elements was not yet established. In 1911, Gabriel Bertrand (1867-1962) proposed the concept of essential trace elements, necessary for normal growth and functions of plants, following a series of publications in the Comptes Rendus de L'Académie des Sciences published between 1894 and 1911. The evolution of Bertrand's concept of essential elements is described in the Dictionary of Scientific Discoveries [14]:

"In the years 1894-1897 Bertrand investigated the process of the darkening and hardening of the latex of lacquer trees. He recognized that the color change was caused by the oxidation of a phenol – laccol in the pres-

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ence of another substance, laccase. Other phenolic compounds, he found, underwent similar organic oxidation reactions, also in the presence of substances similar to laccase. In 1896 Bertrand first used the term "oxidase" for these oxidizing enzymes (including tyrosinase, which he had described). During the following year he published several studies of oxidases. Bertrand made another important advance in the analysis of enzymes when he observed that laccase ash contained a large proportion of manganese. Throughout the last half of the nineteenth century it had been known that plants contained minerals, and in 1860 it was demonstrated that in artificial situations plants could be grown in a water culture containing only metallic salts. Researchers still accepted the presence of minerals in the plant as incidental, however, and thought them the result of the presence of minerals in the soil. Bertrand's work in 1897, and especially his later claim that a lack of manganese caused an interruption of growth, forced a change in thinking on this matter. He concluded that the metal formed an essential part of the enzyme, and, more generally, that a metal might be a necessary functioning part of the oxidative enzyme. From this and similar researches he developed his concept of the trace element, essential for proper metabolism."

Ten years later, Marine applied Bertrand's concept of essential trace elements to the element iodine in human subjects. This was the first and last time an element was demonstrated to be essential for human health based on research performed in human subjects. Interestingly, all the other essential trace elements were studied only in laboratory and farm animals, not human subjects. The only element proven essential for human health based on studies performed in humans, turns out to be the most feared and neglected nutrient.

Based on extensive studies of overall performance and goiter in farm animals, D. Marine estimated the amount of iodide required for human subjects. However, for convenience, the nurses and physicians supervising this project were only concerned with the appearance of simple goiter following implementation of iodine supplementation. Again, for convenience and to keep the cost of supervising personals to a minimum, the iodide was not given daily but at less frequent intervals using larger amounts of iodide.

Marine chose a population of adolescent school girls from the 5th to 12th grade between the ages of 10 and 18 years residing in Akron, Ohio, a city with a 56% incidence of goiter [29,30]. His choice was based on the observation that the incidence of goiter was highest at puberty, and 6 times more common in girls than in boys.[30] He studied two groups of pupils devoid of goiter (thyroid enlargement by palpation) at the beginning of the project. The control group consisted of 2305 pupils who did not receive iodide supplementation; and 2190 pupils received a total of 4 gm of sodium iodide per year for a period of 2½ years. The amount of iodide was spread out in 2 doses of 2 gm each during the spring and during the fall. This 2 gm dose was administered in daily amounts of 0.2 gm of sodium iodide over 10 days. At 4000 mg of sodium iodide per 365 days, the average daily amount of sodium iodide was 12 mg, equivalent to 9 mg iodide, 60 times the RDA.

After 2 ½ years of observation, 495 pupils in the control group developed thyroid enlargement (22%). Only 5 cases of goiter occurred in the iodine-supplementation group (0.2%). Iodism was observed in 0.5% of the pupils receiving iodide supplementation. Iodism is characterized by the following signs and symptoms: skin eruptions; frontal sinus pressure with rhynorhea (runny nose); brassy taste associated sometimes with dyspepsia. In an area of Switzerland with an extremely high incidence of goiter (82 to 95%), Klinger, as reported by Marine, administered 10-15 mg of iodine weekly to 760 pupils of the same age group. The daily iodine intake in this group was 1.4-2 mg. The initial examination revealed 90% of them had enlarged thyroid. After 15 months of this program, only 28.3% of them still had an enlarged gland. None experienced iodism. In response to these studies, the Swiss Goiter Commission advised the use of iodine supplementation in all cantons. Iodized fat in tablet form containing 3 to 5 mg iodine per tablet was used for iodine supplementation.

In 1831, French chemist and agronomist J.G. Boussingault [31] proposed iodized sodium chloride (table salt) as a mean of preventing goiter. Such proposal was implemented first in Europe and then in the 1920's, in the USA. Following Marine's study, absence of goiter, not overall performance was the end point relied upon for assessing iodine sufficiency. Iodization of salt gave a false sense of iodine sufficiency and resulted in the public relying on iodized salt for supplementation instead of the previously used forms of iodine and iodide such as the Lugol solution in the recommended daily amount of 0.1 ml to 0.3 ml containing 12.5 mg to 37.5 mg elemental iodine.[4] In order to ingest 12.5 mg of elemental iodine from salt, one would have to consume 165 gm of salt; and obviously 3 times that amount of salt would be required for supplying 37.5 mg elemental iodine.[3,5] Beside, table salt in the U.S. contains iodide only, not iodine. Iodine is very important for normal function of breast tissue.[3] Therefore, supplementation should con-

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tain both forms, iodine and iodide. The evolution of iodine from discovery to essentiality is summarized in Table II.

The implementation of iodization of table salt in the U.S. was associated with appearance of autoimmune thyroiditis. In several communities worldwide, an increased incidence of chronic autoimmune thyroiditis was reported following implementation of iodization of sodium chloride [32]. In areas of the United States where this relationship has been studied, mainly in the Great Lakes Region, a similar trend was reported. In 1966 and 1968 Weaver et al [33,34] from Ann Arbor Michigan reported:

"The salient histopathological feature of the thyroid glands, removed at operation in a five-year period before iodine prophylaxis (1915 to 1920), was the paucity of lymphocytes in their parenchyma, and, more importantly, the absence of thyroiditis of any form" "It should be emphasized that the thyroid glands prior to the use of iodized salt were devoid of lymphocytes, and nodular colloid goiters with dense lymphocytic infiltrates were found after the introduction of iodized salt in 1924".

It is of interest to note that prior to iodization of salt, autoimmune thyroiditis was almost non-existent in the USA, although Lugol solution and potassium iodide were used extensively in medical practice in amounts 2 orders of magnitude greater than the average daily amount ingested from iodized salt. This suggests that inadequate iodide intake aggravated by goitrogens, not excess iodide, was the cause of this condition [2]. Of interest is the fact that autoimmune thyroiditis cannot be induced by inorganic iodide in laboratory animals unless combined with goitrogens, therefore inducing iodine deficiency.

Furszyfer et al [35], from the Mayo Clinic, studied the average annual incidence of Hashimoto's thyroiditis among women of Olmsted County, Minnesota during 3 consecutive periods covering 33 years of observation, from 1935 to 1967. They found the incidence to be higher in women 40 years and older versus women 39 years and less. However, in both groups, there was a progressive increase in the incidence of Hashimoto's thyroiditis over time. During the 3 periods evaluated, that is 1935-1944; 1945-1954; 1955-1967; the average annual incidence of Hashimoto's per 100,000 population were 2.1; 17.9; and 54.1 for women 39 years and less. For women 40 years and older, the average annual incidence over the same 3 periods were: 16.4; 27.4; and 94.1.

It is important to point out that the Mayo Clinic study started 10-15 years after implementation of iodization of salt in the area. Therefore, even during the first decade of observation, the prevalence of autoimmune thyroiditis was already significant. Again, it must be emphasized that prior to the implementation of iodized salt as observed by Weaver et al [32,33], this pathology of the thyroid gland was not reported in the USA, even though the Lugol solution and potassium iodide was used extensively in medical practice at that time in daily amount 2 orders of magnitude greater than the average intake of iodide from table salt [3].

In 1912, pathologist H. Hashimoto [36] published his histological findings in four thyroid glands removed at surgery: numerous lymphoid follicles; extensive connective tissue formation; diffuse round cell infiltration; and significant changes of the acinar epithelium. He called this pathology of the thyroid "struma lymphomatosa". This condition became known as Hashimoto's Thyroiditis. At the time of his publication in 1912, autoimmune thyroiditis was not observed in the U.S. population until the iodization of salt. Hashimoto's thyroiditis is now classified as goitrous autoimmune thyroiditis because the gland is enlarged, in distinction to atrophic autoimmune thyroiditis where atrophy and fibrosis are predominant. Both conditions are chronic, progressing over time to hypothyroidism in a significant percentage of patients [4]. Both conditions improved following a complete nutritional program emphasizing magnesium combined with iodine supplementation for whole body sufficiency [4].

Further evidence that iodine deficiency not excess is the cause of autoimmune thyroiditis follows. Experimentally induced autoimmune thyroiditis in laboratory animals by acutely administered iodide required the use of antithyroid drugs, essentially goitrogens, to produce these effects. These goitrogens induced thyroid hyperplasia and iodide deficiency. Antioxydants either reduced or prevented the acute iodide-induced thyroiditis in chicks and mice. Bagchi et al and Many et al proposed that the thyroid injury induced by the combined use of iodide and goitrogens occurs through the generation of reactive oxygen species. (See Ref. 4 for review).

A proposed a mechanism by the author for the oxidative damage caused by low levels of iodide combined with antithyroid drugs: Inadequate iodide supply to the thyroid gland, aggravated by goitrogens, activates the thyroid peroxydase (TPO) system through elevated TSH, low levels of iodinated lipids, and high cytosolic free calcium, resulting in excess production of H2O2. The excess H2O2 production is evidenced by the fact that antioxidants used in Bagchi's experiments did not inter-

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fere with the oxidation and organification of iodide and therefore neutralized only the excess oxydant. This H2O2 production is above normal due to a deficient feedback system caused by high cytosolic calcium due to magnesium deficiency and low levels of iodinated lipids which requires for their synthesis iodide levels 2 orders of magnitude greater than the RDA for iodine [4].

Once the low iodide supply is depleted, TPO in the presence of H2O2 and organic substrate reverts to its peroxydase function which is the primary function of haloperoxydases, causing oxidative damage to molecules nearest to the site of action: TPO and the substrate thyroglobulin (Tg). Oxydized TPO and Tg elicit an autoimmune reaction with production of antibodies against these altered proteins with subsequent damage to the apical membrane of the thyroid cells, resulting in the lymphocytic infiltration and in the clinical manifestations of Hashimoto's thyroiditis [4].

Based on this proposed mechanism where deficiencies of magnesium and iodine induce autoimmune thyroiditis, implementations of a complete nutritional program emphasizing magnesium combined with iodine supplementation was effective in patients with this thyroid pathology, including autoimmune hyperthyroidism. Even a patient with atrophic autoimmune thyroiditis responded to this program [4].

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Diet and Schizophrenia

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Introduction

Most of the research on treating psychiatric disease has been directed at neurotransmitters. Although this there has been *some* success with this approach, long-term prognosis with this approach is less than desirable. A growing body of data suggests that more natural approaches to Schizophrenia, bipolar disorder, and severe depression deserves further investigation and consideration. The orthodox mindset has searched (in vain) for the anatomical and physiological basis of Schizophrenia, but to date, no theoretical models really provide meaningful insight (or effective treatment).[1] The search for an anatomical basis for Schizophrenia has engendered an enormous, almost indigestible mass of data. No "common" genetic, morphological or microscopic abnormality has been found that is either necessary or sufficient for the diagnosis (except for ventricle enlargement, which is a non-specific finding). This has lead many to believe that Schizophrenia has less to do with genetic or anatomical factors, and more to do with dietary and environmental ones. The relationship of food to mental illness is top on the list of items that are particularly inflammatory to the orthodox medicine paradigm of mental illness.[2] But is it really that simple? This article will review four major dietary and nutritional considerations that are linked to Schizophrenia. These are: (1) Casein and Wheat (gluten) allergy (more correctly termed hypersensitivity); (2) Essential Fatty Acid Deficiency; (3) Niacin deficiency; And, (4) Glutamic Acid and Glycine supplementation. In addition, a few general/miscellaneous factors will be considered. The study of micronutrients and mental health is known as orthomolecular psychiatry, a term coined by two-time Nobel laureate Linus Pauling in a controversial 1968 essay. Pauling wrote that nutritional supplements, unlike psychotherapy or drugs, represent a way to provide 'the optimum molecular environment for the mind." Varying the concentrations of substances normally present in the human body, he wrote, may control mental disease even better than conventional treatments. Today the Society for Orthomolecular Health Medicine counts about 200 American members. One of the foremost practitioners, the Canadian psychiatrist Abram Hoffer, claims to have successfully treated thousands of schizophrenics with massive doses of vitamin C and niacin.

Casein, Gluten and Schizophrenia

Casein is a protein found in milk, especially high in cow's cheese and cow's milk. Gluten is a protein found in grains, and is especially high in common wheat. It is interesting to note that the two predominantly used grains (wheat and barley) in this country are genetically engineered and have 5 times the gluten content and only 1/3rd the protein content of the original wheat from which they were derived. This high gluten content is thought to be the culprit in allergic reactions, food intolerance, malabsorption, indigestion, mood disorders, arthritis and a host of other symptoms and diseases. When scholars have studied disease patterns and the decline of various civilizations, many of the degenerative diseases developed when cultivation of these grains became a major part of the their diet.

One consistent dietary factor linked to Schizophrenia is an allergy or sensitivity to wheat (specifically the wheat protein gluten).[3] Epidemiologic data illustrate that the incidence of Schizophrenia is much less in societies that eat no wheat or rye but do eat other cereal grains (e.g. maize and millet).[4] Historical and anthropological studies have shown a strong association between wheat consumption and the incidence of Schizophrenia.[5] For example, in Finland and Sweden during World War II, these countries faced severe shortages of wheat and rye. During that time, the incidence of new cases of Schizophrenics declined acutely; while in countries that did not face such shortages, it remained the same or increased. Also, Schizophrenia is extremely rare in cultures that traditional eat wheat-free diets (e.g. South Pacific inhabitants of New Guinea and Micronesia). However, when these cultures, under Western Influence, convert to a high-grain diet, the incidence of Schizophrenia rises sharply (about a 65% increase) to match that of other Western or Modernized Nations. Schizophrenia is also more prevalent (about 3 times)[6] in celiac sprue (a gluten allergy that causes gastrointestinal, neurological and immunological problems).[7,8,9] Studies have shown that Schizophrenics who are put on an exoprhin-free or low-exorphin diet are able to reduce their need for medications.[10] And double-blind challenges of introducing or removing exorphins from the diet of Schizophrenics shows a remarkable correlation between behavior and symptoms (improving when exorphins are removed or limited).[11] Furthermore, Schizophrenics who are assigned a lower gluten diet are discharged twice as quickly as those who are given a higher gluten diet.

One hypothesis to explain how gluten can cause behavioral changes (Note: gluten is also implicated in attention

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deficit, hyperactivity, and autism) is what I call the *Exorphin Dysfunction Hypothesis*. Exorphin means endorphins and enkephalins that come from outside (exogenous) the body. If you remember, endorphins and enkephalins are substances created within the body (endogenous) that have morphine like pain killing effects (and euphoric mood effects). [Note: A detailed review of endorphins and enkephalins are beyond the scope of this paper].

When cereal proteins (grains) are ingested, gluten fragments enter the blood stream. These gluten fragments have a very similar shape to the body's own endorphins (including enkephalin peptides). These gluten fragments, therefore, can act upon endorphin receptors in the brain, which are heavily clustered in the frontal lobes and the lower limbic regions of the brain (the same regions implicated in Schizophrenia according to the dopamine hypothesis). This can lead to mood disturbances, euphoria, dysphoria (disturbed or altered mood), irritation, perceptual distortions and even psychosis. Further lending credence to the Exorphin Dysfunction Hypothesis is studies using "mixed agonist/antagonists" drugs (e.g. cyclazocine and nalorphine) that artificially stimulate and suppress the body's endorphin receptors have been known to produce profound dysphoria bordering on psychosis in patients.

Gluten therefore, by its *molecular mimicry* of endorphins (and enkephalins) reacts with the brain's endorphin receptors in the same deleterious way as cyclazocine or nalorphine. Casein proteins in dairy products are also thought to have similar amino acid sequences to enkephalin, and also capable of interacting with brain receptors.

It is interesting to note, that the degree to which this occurs is highly individual along a spectrum from no disturbance to severe sensitivity. The factors that make a person more susceptible to Exorphin Dysfunction are not fully known, but hypothesized to be genetic, environmental, nutritional, bacterial (e.g. alternations in gut flora or infections), viral, and structural (e.g. alterations in the gut barrier integrity). Furthermore, some Schizophrenics appear more sensitive to Exorphins than others; with research showing 20% being severely sensitive to even minute amounts of exorphins in the diet.

From the above studies it would seem reasonable to assume that gluten and casein have a negative effect some individuals with Schizophrenia, which is reversible upon instituting a wheat and dairy free diet. This is one many examples of illness being the result of individual maladaptation to certain foods which are nonpathogenic in the majority of the population. Elimination diets should be a valuable adjunct in ruling out cryptic gluten sensitivity in Schizophrenia.[12]

Essential Fatty Acids and Schizophrenia

Over the past 100 years a dramatic change in our diet has occurred. We have invented an industry of prepared foods made in factories and shipped to consumers via supermarkets. With this "invention", shelf-life became a premium. EFAs, on the other hand, kill shelf-life because they have a tendency to go rancid when exposed to heat, light and oxygen. At the same time, large commercial oil manufacturers began producing the refined vegetable oils we are now so familiar with. Currently, 4 oils (soybean, cottonseed, corn, and canola) account for 96% of the vegetable oil use in the U.S. The omega-6:omega-3 ratio of these combined oils is between 12:1 and 25:1. An estimate of the omega-6:omega-3 ratio in our diet 100 years ago is between 3:1 and 5:1. This dramatic shift toward omega-6 oil consumption, coupled with the alteration of the fats via hydrogenation and oxidation is thought to be one of the leading factors in the rise of chronic illnesses.[13]

Another consistent dietary factor linked to Schizophrenia, is the under consumption of (or increased need for) essential fatty acids (aka the "good" fats).[14, 15, 16] Fatty acid deficiency has been linked to a variety of mental disorders, such as Schizophrenia, bipolar disorder and depression. Among criminals (whom have a higher incidence of mental illness), treatment with essential fatty acids decreases behavior problems in prison by 1/3rd or more.[18,19]

"Some researchers suspect that even mild deficiencies can affect the psyche long before any physical symptoms appear. Stephen Schoenthaler, a sociologist at California State University at Stanislaus, has been exploring the link between nutrients and mental health by giving basic vitamin and mineral supplements to prison inmates and juvenile detainees. Again and again, since the early 1980s, Schoenthaler has found that when inmate nutrition improves, the number of fights, infractions, and other antisocial behavior drops by about 40 percent. In each case, he has found, the calmer atmosphere can be traced to the mellower moods of just a few hotheads. The inmates most likely to throw a punch, he has discovered, are the ones with the least nutritious diets and the lowest levels of critical nutrients…in the late 1990s, an Oxford University physiologist named Bernard Gesch decided to put the theories to a more rigorous test. Gesch divided 231 prisoners in one of Britain's toughest prisons

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into two groups. Half were given a standard vitamin and mineral supplement each day as well as fish-oil capsules and omega-6 oil from evening primrose. The other half received placebos. The results, published in 2002 in *The British Journal of Psychiatry*, drew headlines on both sides of the Atlantic. They were also almost identical to Schoenthaler's. Over the course of approximately nine months, inmates taking supplements committed about 35 percent fewer antisocial acts than the group taking placebos. A few weeks after the study started, the prison warden told Gesch that the administrative report that month showed no violent incidents had occurred. As far as he was aware, this had never happened in the history of the institution…"[20]

The exact mechanism of the role of essential fatty acids in these disorders is not fully know, but can be hypothesized to be: (1) Disruption of prostaglandins (local hormone like messengers); (2) Changes in cell membrane structures and neurotransmitter receptor shape; (3) Changes in intracellular transport (e.g. the influx of calcium into the cell); (4) Changes in cell electrical charge or conductance. Researchers have suggested that present-day refining and food selection patterns have led to widespread deficiencies of omega-3 fatty acids in some industrialized countries, with a consequent increase in the incidence and prevalence of many medical and psychiatric disorders.[21] The hypothesis that changes in essential fatty acid metabolism and, or availability being responsible for Schizophrenia is known as the "membrane phospholipids" model of Schizophrenia and may provide a unifying conceptual framework for not only understanding schizophrenia but also bipolar disorder, dyslexia, schizotypal personality disorder, other schizophrenia-like syndromes and possibly other psychiatric disorders.[22,23]

"Early in life, an out-of-kilter stress response could cause healthy tissue in the body to break down over time, initiating chronic inflammatory reactions. Since certain inflammatory cells depend on high amounts of omega-3 fatty acids, shortages of these nutrients could arise. Without sufficient fatty acids, cell membranes (including those of brain neurons) may form defective structures, triggering a "vulnerability to develop chronic psychiatric diseases such as schizophrenia, dyslexia, autism, and depression…This chain of events would help explain why a chronic maladaptive stress response and omega-3 fatty acid deficiency are common findings in individuals with these conditions."[24, 25]

Studies over the last 20 years and thousands of research articles have demonstrated the essential role of the omega-3, omega-6 and omega-9 fatty acids. Since the brain tissue is primarily composed of fatty acids, it makes sense to consider its fatty acid make up when examining affective disorders. [Of particular interest is the fact that the brain is 70% fat by dry weight].

All cell membranes, particularly neuronal membranes, are made up of a high percentage of phospholipids (fats). The membranes of dendrite and synapses are 80% lipids by weight. Neurotransmitters, and indeed all substances which are expressed, reabsorbed at the synapse, or move within the neurons, must cross these membranes. This is true of the excitatory amino acid systems, as well as dopamine, serotonin, acetylcholine and nor epinephrine.

The treatment of psychiatric patients (Schizophrenia, bipolar, depression, ADHD) with essential fatty acids has resulted in significant reduction in symptoms, and sometimes complete remission of symptoms—without drugs. In a landmark 1999 study, Harvard psychiatrist Andrew Stoll found that bipolar patients who were given large doses of omega-3s did significantly better and resisted relapse longer than a matched group of patients who were given placebos. Case studies and double-blind studies have consistently demonstrated sustained improvement of both positive and negative symptoms in patients with chronic schizophrenia consuming certain fatty acids who were not being treated concurrently with conventional antipsychotic medications.[26,27]

It is interesting to note that the onset of mental illness or psychotic episodes can be brought on by dieting (calorie restriction) and more importing food avoidance (the limitation or avoidance of fats). Without sufficient fatty acids, cell membranes (including those of brain neurons) may form defective structures, triggering a "vulnerability to develop chronic psychiatric diseases such as schizophrenia, dyslexia, autism, and depression," the researchers explained.[28]

Essential fatty acids actually work by turning on health-promoting genes and interacting with receptors that can only be stimulated by these types of fats. The wrong types of fat either can't turn on the right genes, turn on the wrong genes, or cause the signaling of the wrong messages.[29] The demonization of all fats is not only misguided, but extremely harmful to our health as different fats have different personalities. It is important not to stereotype all fat as "bad" so that we do not under consume the "good" fats that are one of the most versatile and powerful health promoting substances ever discovered. Essential fatty acids are an essential component of anyone's diet who wishes to be and remain healthy."[30]

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In summary, recent studies are showing excellent treatment results of psychiatric conditions through the use of essential fatty acids.[31, 32] It is almost unbelievable that the treatment of these conditions, so long resistant to other forms of treatment, can be managed with the help of a simple, available and inexpensive nutritional supplement.[33] In addition, sometimes patients will present with an essential fatty acid deficiency, but may be suffering from a single or multi-nutritional deficiency, either solely or concurrently. This is because certain nutrients are necessary for the processing of essential fatty acids, especially nicotinic acid (niacin, vitamin B3), antioxidants (also vitamin E and C), magnesium, and zinc (part of the desaturaze enzyme necessary to break down fatty acids). Deficiency of any one of these nutrients (or a combination of) can manifest as an essential fatty acid deficiency and as mental disorders.

Nicotinic Acid (Niacin)

Nicotinic Acid functions in over 50 known metabolic reactions, most of which are enzymatic. Its bioactive forms—NAD+, NADH, NADP, and NADPH—play important roles as catalysts in the energy production process in the cells, the breakdown of proteins and fatty acids, the synthesis of fatty acids, and the formation of steroid hormones and red blood cells.[34] Niacin for the treatment of Schizophrenia is derived from the hypothesis that metabolites of adrenaline and nor adrenaline are toxic and have neuro-mental consequences and that Niacin helps metabolize these. In addition, Niacin, through its role in energy production, nitric oxide modulation, and essential fatty acid metabolism, is thought to be mechanisms through which it is beneficial.[35]

One of the first associations between Nicotinic Acid and mental illness was its link to the disorder of Pellagra in the early 1900's. Pellagra is a disorder of the four D's—dermatitis, diarrhea, dementia and death. However, Pellagra (like all diseases) can occur along a spectrum of symptoms and does not always appear in the "text book" style so often quoted. The disease can consist of any of the following: bilateral, symmetrical skin lesions; hyper pigmentation of the skin; thickening of the skin; inflammation of the tongue and mouth; indigestion; anorexia; neurasthenia; diarrhea; irritability; amnesia and delirium [and mood disturbances].[36, 37] Pellagra was at epidemic proportions in the early part of the century and its cause was unknown. A member of the U.S. Public Health Service, Joseph Goldberger, M.D., researched the crisis and noticed that poorer people were more likely to get the disease, as were people in prisons, asylums and orphanages, where there was a limited diet [this same association is seen in Schizophrenia]. Goldberger began experiments on prison inmate volunteers, giving them the poor diet he associated with pellagra. Within months many developed the disease. The symptoms were reversed when foods rich in vitamin B3 were added to the diet. Nicotinic acid (niacin), when its use was introduced, cured hundreds of thousands of pellagra patients of their psychoses (dementia), as well as of the other physical manifestations of their disease (diarrhea and dermatitis).

It is interesting to note that Nicotinic Acid was once considered a standard treatment for mental disorders. A fact evident by Dr. William Kaufman's inadvertent discovery in 1951 that 758 psychotic patients treated with Nicotinic Acid had the added benefit of greatly improving the symptoms of all forms of arthritis and DJD (Degenerative Joint Disease)—even partially or fully reversing ankylosed joints.[38] Recent research has confirmed a powerful role of Nicotinic Acid in treating joint pain, inflammation and lipid disorders (high cholesterol, low HDL, high LDL, and high Lipoprotein(a)).[39]

Niacinamide's primary mechanism of action is through its inhibition of PARS and TNF-α. Because inhibition of PARS suppresses inducible NO synthase, which reduces the generation of NO and peroxynitrite, niacinamide is able to interrupt this self-amplifying, positive feed-forward cycle. Reactive oxygen species (ROS), most notably peroxynitrite and hydroxyl radicals, induce DNA strand breaks that lead to the activation of the repair enzyme PARS. Unfortunately, PARS activation triggers a futile energy-consuming cycle, resulting in massive depletion of cellular NAD and ATP, leading to functional alterations of the cell and eventual cell death. PARS also regulates the expression of a number of genes, including the gene for collagenase and inducible nitric oxide (NO) synthase. Thus, PARS activation is inversely associated with joint tissue integrity. A related chain of events involves the activation of tumor necrosis factor-α (TNF-α), a cytokine that produces higher amounts of ROS (which further activates PARS); stimulates production of other cytokines; and inhibits the synthesis of cartilage matrix and contributes to cartilage loss. Not surprisingly, high levels of TNF-α are found in the synovial fluid and joints of certain individuals.

Mohler has reported: "nicotinamide has properties in common with benzodiazepines (and barbiturates) in its action on spinal cord activity, and its anticonflict, anticonvulsant, antiaggressive, muscle relaxant, and hypnotic action". Kennedy3 reported: "this drug (niacinamide) has a qualitatively similar effect to diaze-

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pam on the turnover of serotonin, nor adrenaline, dopamine and GABA in those areas of the brain that are thought to be deranged in anxiety".[40, 41]

As early as circa 1940, researchers reported treating dozens of patients successfully with moderately large doses of niacinamide (½ to 1 ½ grams). None of these patients, interestingly, had any overt signs or symptoms of pellagra (niacinamide deficiency) or any other vitamin deficiency.

More recently many other investigators have reported on the use of nicotinic acid and nicotinamide for the treatment of mental disease. In several studies collectively involving over approximately several hundred psychiatric patients, it was found that those who received niacinamide were less likely to be readmitted after discharge, and spend only ½ the time hospitalized. Hoffer and Osmond, who since 1952 have advocated and used nicotinic acid in large doses, in addition to the conventional therapy, for the treatment of Schizophrenia. Hoffer has collected data on more than a 1,000 patients treated with this approach.[42] The dosage recommended by Hoffer is 3 to 18 grams per day, as determined by the response of the patient, of either nicotinic acid or nicotinamide, together with 3 grams per day of ascorbic acid. Hoffer contends the vitamins neutralize an oxidized compound that causes hallucinations when it accumulates in the brains of patients.

Niacinamide is tolerated well by schizophrenic patients and is safe. Some patients experience the "niacin" flush; however, within several days, the flush is no longer evident. Furthermore, new forms of niacinamide, such as sustained release and inositol hexanicotinate, have eliminated this problem. Sedatives and tranquilizers can be used with niacin, but the effect of phenothiazines may be potentiated.[43, 44]

Glutamic Acid (Glutamine) and Glycine

Glutamine is an amino acid that is present at rather high concentration in brain and nerve tissue and plays an essential role in the functioning of these tissues). Research has implicated dysfunction of glutamatergic neurotransmission in the pathophysiology of schizophrenia. Dysfunction of glutamatergic neurotransmission (through N-methyl-D-aspartate (NMDA) receptors) may play an important role in the pathophysiology of schizophrenia, especially of the negative symptoms and cognitive impairments associated with the disorder, and is a promising target for drug development.[45] Glutamatergic neurons are the major excitatory pathways linking the cortex, limbic system (emotional centers), and thalamus, regions that have been implicated in schizophrenia. Further lending credence to the glutamate hypothesis of Schizophrenia is that the illicit drug PCP ("angel dust") induce psychotic effects in humans that closely resemble positive, negative, and cognitive symptoms of schizophrenia and behavior effects of PCT can be reversed by glycine.[46]

Glycine, a small nonessential amino acid, functions as an obligatory coagonist at NMDA ative symptoms of schizophrenia. In one double-blind, placebo-controlled study of twenty-two treatment-resistant schizophrenic patients, treatment Glycine administration resulted in a 30% reduction in negative symptoms. These findings support hypoglutamatergic hypotheses of schizophrenia and suggest a novel approach for the pharmacotherapy of negative symptoms associated with this illness.[47] Other studies have repeatedly confirmed these results.[48, 49, 50, 51]

General Nutritional Factors

Other vitamins and substances influence the functioning of the brain. Beyond the nutrients already discussed, strongly associated with Schizophrenia is deficiencies or increased need for magnesium, vitamin C, B-vitamins (e.g. thiamine, folic acid, B12, riboflavin), zinc, and the amino acid glycine.[52, 53, 54, 55, 56, 57, 58]

Magnesium: Although the evidence is inconsistent, some studies have found magnesium deficiencies in depressed patients. In addition, the mineral may work by enhancing the efficacy of other mood-stabilizing drugs.

B-vitamins: Folic acid is a B vitamin essential to mood regulation and the development of the nervous system. Patients deficient in these appear to respond poorly to antidepressants. In one 2000 British study, 127 patients taking Prozac were also given either 500 micrograms of folic acid a day or a placebo. The folic acid group did significantly better, in particular the women, who fared 30% better than the placebo group. Plasma folate levels below the tenth percentile of controls was associated with a 4- to 7-fold increased risk of having schizophrenia. There was a significant dose-response relationship between plasma folate concentrations and the risk for schizophrenia, and a protective effect by high plasma folate levels.[59] Vitamin B12 is another vitamin strongly associated with mental illness, especially dementia and psychosis. Numerous researchers and dozens of articles have shown a higher incidence Of low B12 concentrations in the blood of mental patients than in the population as a whole illness.[60, 61]

In a person dialogue with Dr. John Vlok Dommisse, one

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of the world's foremost experts on Vitamin B12 and mental illness, he writes:

"I have published a long paper, a chapter in a book on anti-aging medicine, and a long letter on the psychiatric manifestations of vitamin B12 deficiency (1991, 1996a & b) and was the published 'expert' in a long 'The Expert Speaks' interview published in the March 1998 issue of Clinical Pearls News, a nutritional and preventive medicine abstracts journal. (Dommisse) In all these publications I mention the review article from St Louis that shows which are the commonest psychiatric syndromes caused by this vitamin deficiency: mood disorders; dementia; paranoid psychosis; and violent behavior (Zucker et al, 1981). Various authors have documented the psychotic (Hart/McCurdy), depressive (MacCallum), and consecutive affective and psychotic conditions in the same patient (Verbanck/LeBon). Doctors Levitt and Joffe, working at the Clarke Institute of Psychiatry in Toronto (where I trained, years earlier), published a report about vitamin B12 deficiency causing the psychotic form of depression, in the British Journal of Psychiatry in 1988 (Levitt/Joffe). *They also reviewed the medical literature and found that psychotic depression is more often caused by B12 deficiency than by any other known or unknown cause* [emphasis mine]. This fact is hardly ever borne in mind when psychiatrists confront a case of psychotic depression and, when they do think of it and order a serum B12 level, they will more often than not still miss the deficiency because the lab "normal range" is so low that their patient's B12 level almost always appears to be in the "normal range". At least six neurological and psychiatric papers, in top medical journals, have shown that the normal range should be regarded as at least 500-1,300 pg/ml (rather than 200-1,100), since the cerebrospinal fluid level can be deficient when the serum level drops below 500, and neuropsychiatric symptoms often occur at serum levels between 200 and 500 pg/ml (VanTiggelen et al, Lindenbaum et al, Mitsuyama/ Kogoh, Nijst et al, Ikeda et al, Regland). As for the still held misconception that the neuropsychiatric effects of B12 deficiency are always accompanied by a macrocytic anemia, it is humbling to know that this notion was already debunked in 1905 (Langdon)! Since then, many papers have stressed this point, including those by Strachan and Henderson 1965, Evans et al (1983) and Lindenbaum et al (1988)."

Vitamin C: Vitamin C deficiency (even sub-clinical) can manifest symptoms of mental illness. In 1957 Akerfeldt reported that the serum of schizophrenics had been found to have greater power of oxidizing N,N dimethyl-p-phenylenediamine than that of other persons. Several investigators then reported that this difference is due to a smaller concentration of ascorbic acid in the serum of schizophrenics than of other persons. This difference has been attributed to the poor diet and increased tendency to chronic infectious disease of the patients, and has also been interpreted as showing an increased rate of metabolism of ascorbic acid by the patients. It may be that Schizophrenics have an increased metabolism of ascorbic acid, presumably genetic in origin, and that the ingestion of massive amounts of ascorbic acid has some value in treating mental disease.

Inositol: This sugar molecule appears to make the brain's receptors more sensitive to serotonin, one of the chemical messengers that mediate mood. In a series of short-term placebo-controlled trials, researchers at Ben Gurion University of the Negev in Israel found that large doses of inositol—12 to 18 grams a day—helped alleviate depression, panic disorder, and obsessive-compulsive disorder.

Summary

More and more data is suggesting a role of nutrition in the cause, prevention and treatment of mental illness. If one eliminates milk/cheese, wheat, caffeine, alcohol and sweets, it would make a big difference on the symptoms of chronically mentally ill patients. In addition, palliative or curative effects may be possible by consuming a multi-vitamin/multi-mineral [with a good amount of B-vitamins] and adding a supplement program consisting of the following:

- Essential Fatty Acids—Fish Oil (EPA/DHA) 3-6 grams/day [Note: I recommend Kirunal, an EPA enhanced fish oil which provides an EPA to DHA ratio of 3:1 (which is the ratio shown beneficial in studies). Standard fish oil supplements provide a 2:1 ratio of EPA to DHA].
- Essential Fatty Acids (250 mg of GLA/day)
- Niacinamide 1-6 grams/day
- Vitamin C 1-5 grams/day
- Glycine 10-60 g/day
- L-Glutamine 3-10 grams/day
- Inositol 3-18 grams/day

[Note: This is a pretty "hefty" supplement program, and the doses here are doses consistent with studies. No study to date, has seen if there is a "synergistic" effect between these supplements, thus allowing one to take less of each. In my experience, many patients often achieve clinical results with less than the above, especially when doing all the above. Start with the low dose and increase each until clinical response. *Indicates ab-

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solutely the most essential parts of the program.]
In my experience, the presence of skin lesions, joint problems, gastrointestinal disturbances and concurrent mood disturbances strongly suggest a nutritional component to the disease. What is also of concern in mental illness is that these patients tend to self-medicate with illicit drugs, especially alcohol. The problem with drugs and alcohol is they further interfere with the nutritional process by affecting digestion, storage, utilization, and excretion of nutrients.[62]

Of course, not everyone with a vitamin deficiency grows violent or sinks into a clinical depression. So why might a nutritional supplement help only some people? Possible explanations include "inborn errors of metabolism" (genes that require a person get more than the "average" of nutrients for proper function), changes in the blood-brain barrier permeability, frank or subclinical (aka sub-optimal) nutrient deficiency and toxins.

Nobel Prize winner Linus Pauling said, "The methods principally used now for treating patients with mental disease are psychotherapy chemotherapy and convulsive or shock therapy." However, we have seen that perhaps, a more "natural" approach can compliment or replace these invasive approaches, which are often wrest with numerous side-effects and poor compliance.

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