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Goitre studies revisited, as a marker for schizophrenia, link diets with inadequate seafood, seaweed and protein to schizophrenia

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ABSTRACT

Gaining an understanding of the aetiology of schizophrenia may influence the growing number of children being prescribed antipsychotic drugs. Urbanization features foremost in the literature, however historical documents point to malnourishment. A unique set of data has been uncovered, with the potential to broadly answer this question. Goitre studies, preceding treatment with antipsychotic drugs, acted as a marker for schizophrenia. A review of these studies enabled environmental, public health and dietary variables to be compared between populations in mental hospitals (control) and the rest of New Zealand. Mineral deficiencies in soils enter the food chain through vegetables. In areas of depleted soil mineralization, inadequate diets were present amongst some New Zealanders; relative to those in mental hospitals. Dietary minerals are imperative for enabling the antioxidant defence system to counter stress and maintain neuronal health. The highest concentrations of these minerals, which are required for thyroid hormone production and antioxidant defences, are present in seafood, seaweed, proteins. Here we discuss the relevance of this finding to neuropathology at onset, first episode of psychosis, the prevalence and incidence of schizophrenia and affective disorders. Further work educating stakeholders of the need to eat for brain health would be beneficial for our children.

Keywords: mental health, environmental risk, thyroid hormones, antioxidant defence, selenium, iron

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INTRODUCTION

The incidence of antipsychotic drug prescribing to children is on the rise; without the benefit of long term evaluations of the effect on growing brains, or mechanisms of toxicity[1]. The aetiology of schizophrenia is unknown; which could potentially arrest this trend. Risk factors associated with the incidence and prevalence of schizophrenia has been documented. Urbanisation features prominently in the literature. Although 2/3 European studies link urbanisation to psychosis, it is not a ubiquitous finding[2]. Higher prevalence of schizophrenia has been linked to higher latitudes and developed countries[3]. The incidence of schizophrenia has been coupled to females and migrant communities [3]. In clinical settings, traumatic head injuries are known to increase the risk of schizophrenia (65.00%) [4]. Concurrent heavy use of alcohol, illicit substances (74.00%)[5] or anorexia commonly present with psychosis.

Historical documents point to malnourishment rather than urbanisation as an explanation of schizophrenia. William Shakespeare and his audience knew the layered clothing sign of schizophrenia, which he documented around 1605 in King Lear. His character, poor Tom ate poorly. This came on the back of an English famine in 1586. In 1908, the minister in charge of mental hospitals reported to the New Zealand Parliament that the cause of mental illness is 'lessened resistance [which] may be acquired by early or prolonged malnutrition'[6]. Amongst chronic schizophrenics, 50% of people (in 1943) were described as underweight, independent of calorie intake[7]. An increased risk of schizophrenia has been reported in offspring from prenatal exposure to nutritional deficiencies such as, the Dutch hunger winter (1944-45) and the Chinese famine[8,9]. Prior to schizophrenia, the psychiatrist Emil Kraepelin, viewed dementia praecox as a metabolic disorder and tested the injection of thyroid gland extracts and gonads, without sucess[10].

A unique set of data has been uncovered which may shed light on the aetiology of schizophrenia. Sir Charles and his team examined thyroid glands, measured goitres and categorized their findings from a total of 34 sites around New Zealand. A total of 80, 750 thyroid examinations were conducted across New Zealand, of which 31.20% demonstrated clinical goitre[11]. New Zealand had seven public mental hospitals in operation at this time. In addition to the large volume of goitre examinations, the researchers collected 471 soil samples from around New Zealand[11]. This data set includes a range of environmental, public health and dietary variables across both urban and rural settings within New Zealand. It has been proposed that environmental factors associated with urbanisation increase the risk of schizophrenia prior to its onset[12]. Significantly, these goitre studies produced a unique set of data that precedes modern pharmaceutical treatments for mental illnesses and the use of chemical fertilizers in soils. This data set enables us to broadly examine aspects of New

Zealand life in 1926. In the late 1930s, the precursor of electroconvulsive therapy was implemented in New Zealand institutions. The 1950s saw lithium, the first antidepressants, followed closely by antipsychotic agents. This data may therefore contribute to our collective understanding of schizophrenia and affective disorder.

The relationship between endemic goitre and low levels of iodine in the New Zealand soil (<10 pp 10^7) was established by Sir Charles Hercus and his team, to support iodine supplementation[11]. Goitre is hypertrophy of the thyroid gland. The use of goitre as a marker for schizophrenia is strongly supported by the available literature. For instance, the sporadic congenital disorder, cretinism, produces stunted physical and mental growth associated with congenital hypothyroidism. Myxoedema is the appearance of wax-like dermatological changes as a consequence of oedematous tissue. Pretibial myxoedema is associated with the hyperthyroidism of Grave's disease, whereas myxoedema is synonymous with severe hypothyroidism. Myxoedema is latently expressed in the brain; months or years after physical symptoms[13], to share commonalities with psychiatric presentations. Cognitive, behavioural and affective changes progress to psychotic features such as, perceptual disturbances, loose associations, delusions, visual and auditory hallucinations, and paranoia[13]. Clinical treatment of myxoedema is reported to precede improvements in mental state for some people with schizophrenia [14]. A significant correlation is reported between goitre and paranoid schizophrenia (77.00%) or affective disorders (57.60%)[15].

Moreover, people exhibiting symptoms of mental illness were not born into the institutions where they were housed for extended periods. It can therefore be asked; if there were any variables amongst the New Zealand community that differed from those in the mental health institutions of the time. If so, is there any relationship that has been maintained through time and may be viewed in the modern context of schizophrenia? Links between urbanisation and the development of schizophrenia have been widely explored in the literature. Goitre was first described amongst New Zealand's European settlers in 1882 (30 years after Christchurch settlement)[16] and amongst remote Maori tribes in 1815.[17] Given the strong correlations between schizophrenia and goitre;[15] this work may challenge the relationship between schizophrenia and urbanization. This work therefore aims to answer if there was any variable(s) in the general New Zealand population or environment; that may shed light on the emergence of schizophrenia?

Quality of the original data

The depth and breadth of the goitre studies originally undertaken by Sir Charles Hercus and his team was assessed; to establish if the data was of sufficient quantity and quality for re-analyses. The large volume of data supported validity of the findings despite a positive bias,

documented by a single researcher, who did not influence the outcome[11]. Two populations of New Zealanders were compared; those with an established mental illness and those without. The population in New Zealand mental hospitals were the control as their condition was pre-existing. In each population, environmental variables were compared such as, underlying geological structures, soils, atmosphere and waterways. Endemic illnesses, sanitation, drinking water and diets were also compared. The weakness of this method was the nature of the available data. The data had already been collected and was presented in a summarised form. This presentation limited the amount of statistical analyses. Direct comparisons were not always obtained due to missing data. This was sufficient, however, to broadly answer our question and for a review of the literature to progress.

Demographics of the mentally ill population

It is difficult to ascertain the numbers of inpatients diagnosed with dementia praecox or schizophrenia, as mental disorders were not categorized according to the standardized diagnostic criteria of today. It is clear that schizophrenia was present amongst the mental hospital populations. For instance, the introduction of iodine was met with an escalation of paranoid symptoms, as it was thought the food had been poisoned[18]. Psychosis rates in New Zealand (1925-1935) were quantified as 5.61-6.06 per 10,000 of the European settlers and 1.47-1.65 per 10,000 of the Maori population respectively[19] (Table 1).

Table 1: Demographic snapshot of mental health in New Zealand

Demographics	**Mental Hospitals (1925-26) (n=7)**	**New Zealand population (1920)**
Population n (Maori)	6066 (77) (1925), 6204 (1926)	1.24 million (53,000)
Occupation	Farmers and labourers (males) and domestic duties (females) were highly represented, comparative to other occupations	Complete spectrum
Diagnosis and prognosis	Bipolar disorder, major depression, schizophrenia, drug-induced psychosis, alcoholism, epilepsy and tertiary syphilis. Recovery rate 40.83% (1925), 30.00% (1926) Readmission rate 70.00% (1926) Suicide rate n = 4 (1925) and zero (1926) Mortality rate 31.82%. (1925), 5.2% (1926)	

*(Young, New Zealand Mental Hospitals of the dominion (report on) for 1926 and 1927)

Environmental variables across New Zealand

Underlying volcanic and sedimentary geological structures have not altered across New Zealand for 10,000 years. Vast areas of New Zealand soil support mineral deficiencies derived from underlying geological structures, leachate or wind-blown volcanic ash, pumice clouds. For instance, alluvial greywacke on the Canterbury plains and volcanic ash in the Urewera ranges. New Zealand soils were low in selenium (M =1.48, SD = 0.56) and brown soils were found to have low iron oxide levels[20] (M = 5.33, SD = 6.22). The goitre studies highlighted iodine deficient soils. By the 1920s, deficiencies of sulphur were recognized in the New Zealand soil. Natural mineral salts and superphosphates were used to correct these sulphur imbalances[21].

Saline contaminated areas exhibited less goitre amongst the population proportionate to distance away from the source. For instance, Heathcote (31.00%) and Lyttleton (20.00%) had less goitre than Christchurch city (64.00%)[20]. Tidal water systems were responsible for this finding. Close to Christchurch estuaries the artesian water supply was contaminated with saline[22]. The incidence of goitre was lower in proximity to these river systems[20]. However atmospheric prevailing winds were the other source of minerals. At Lincoln, prevailing winds brought seawater to influence the soil-iodine content[11].

Environmental variables within New Zealand mental hospitals

The mental hospitals were built in areas of poorer soil than their surrounding townships.

Public health factors within the New Zealand population

New Zealanders enjoyed a good standard of sanitation. For instance, there was no evidence of intestinal toxaemia or faeces in the water supply of Christchurch[11]. Christchurch has an aquifer, derived from snow-fed mountain water that is filtered through the local greywacke gravels[11]. However hydatid disease, typhoid, goitre, cretinism and myxoedema were all endemic to New Zealand[11]. Researchers noted that in a single classroom, 83.50% of children had been held back a year because of myxoedema[11].

Public health factors within the New Zealand mental hospitals

Water supplies and sanitation were well maintained at each mental hospital. Despite this, there was an outbreak of tuberculosis in the mental health system (80-100 patients in 1925)[23] a figure that was reduced to 25 patients by 1926[24].

Diets amongst the general population of New Zealand

A wide variety of foodstuffs were available to New Zealanders[25]. For instance, grains, fruit, vegetables and dairy products were supplied to Christchurch from local sources on the Canterbury plains and Banks Peninsula[11]. The researchers quantified seasonal variations in the mineral content of vegetables grown in the local soils. There was also no palatable seaweed in the diet, suboptimal intake of fish secondary to high prices[16] and supply issues for

Otago[20]. The diet of 710 families, who represented all strata within New Zealand society (70 occupations)[20] was documented. For instance, diet A was low in protein (42.82g/day), adequate in iron (0.00973g/day) and low in iodine (8.11*u*g/day)[20]. The other diets demonstrated adequate levels of protein, iron and iodine. Diet B included meats and tinned fish[20]. Diet C contained meat but no fish[20]. Diet D consisted of fish, eggs, but no meat[20]. The supply of adequate fruit and leafy vegetables to children was very low as children's' diets were high in meat, bread, potatoes and tea[20].

The diet in New Zealand mental hospitals

Treatment for mental illness at this time consisted of improving living standards, exercise and diet[26]. A professional dietitian (from September, 1925) ensued dietary requirements were met. The mental hospital farms produced these fruits, vegetables and cereal. Meat proteins at this time were reduced to manage bipolar disorder and epilepsy. Rationale for this policy was described in government reports as a high protein diet was thought to drive inflammatory sexual manifestations[24]. Residents in New Zealand mental hospitals enjoyed a meal of fish per week[20]. From 1926 iodized salt was introduced at the Christchurch mental hospital into bread, dairy foods and bacon[25]. These dietary based treatments did not improve discharge rates at Christchurch mental hospital (8.76%, 1925 and 6.80%, 1936) [23]. The diet enjoyed in mental hospitals contrasts markedly to the experience of Maori living in the North Island's Urewera ranges.

Specific comparisons between goitre and non-goitre tribes of the Urewera ranges

History records the New Zealand government (1866) confiscated acreage (for providing sanctuary to a fugitive); leaving the Tuhoe tribes without access to coastal seafood reserves. This historical fact explains significant differences in variables between the Ngai Tuhoe living inland and those on the coast. Inland geological structures were low in minerals such as, iodine, selenium and iron (siliceous rhyolite, pumice and thermal springs)[11]. Successive ash plumes had rendered the soil low in mineral composition. The inland tribes were living in primitive sanitary conditions, under nourished and in relative isolation[11]. Goitre was present (18.00% of adults and 30.00% of children across 300 thyroid examinations)[11]. By 1925 the Tuhoe still lived separate lives from the European settlers, but traded sugar and white flour[11]. Their diet was devoid of seafood, seaweed, low in protein, fat and high in carbohydrates[11]. In stark contrast to the inland tribes, the coastal region had swamp deposits,[11] that were rich in minerals. Here goitre was unknown[20]. Seafood was a dietary staple amongst the tribe and included mineral rich mussels and kelp-eating fish[20].

Environment as a risk factor

There were pockets of New Zealand where soils, atmospheric conditions and the underlying geological structure; did not support the availability of iron, selenium and iodine to the food chain. For instance, the North Island's volcanic plateau inland of the Urewera ranges or the Canterbury Plains near Christchurch. This finding confirms the linkage made between schizophrenia and geographic locations where there is low selenium in the soil[27]. Differences in the distribution and bioavailability of iodine and selenium were highlighted in Christchurch. Here prevailing wind conditions and distance from the saline waterways influenced the incidence of goitre [20,22]. With distance away from the sea, aquatic ecosystems allow the bioaccumulation of selenium to occur in animals[28]. Under these conditions, if a person does not eat sufficient protein or seafood, then dietary intakes of selenium, iron and iodine will be deficient.

Dietary supplementation

Food was locally sourced across the study. Selenium supplements are given to grazing animals. Selenium supplementation should not be necessary in humans as we obtain minerals and nutrients from a variety of sources. This study affirms that some diets were low in protein; communities had supply issues with seafood and there was an overall absence of eatable seaweed. These same areas also exhibited high levels of goitre within the communities, indicative of concurrent mineral deficiencies in the soil. This is not an entirely unexpected finding as accumulative evidence is increasingly linking mental illness to various mineral and amino acid deficiencies. For instance, depression, bipolar disorder, anxiety disorders, attention deficit and hyperactivity disorders and autism [28].

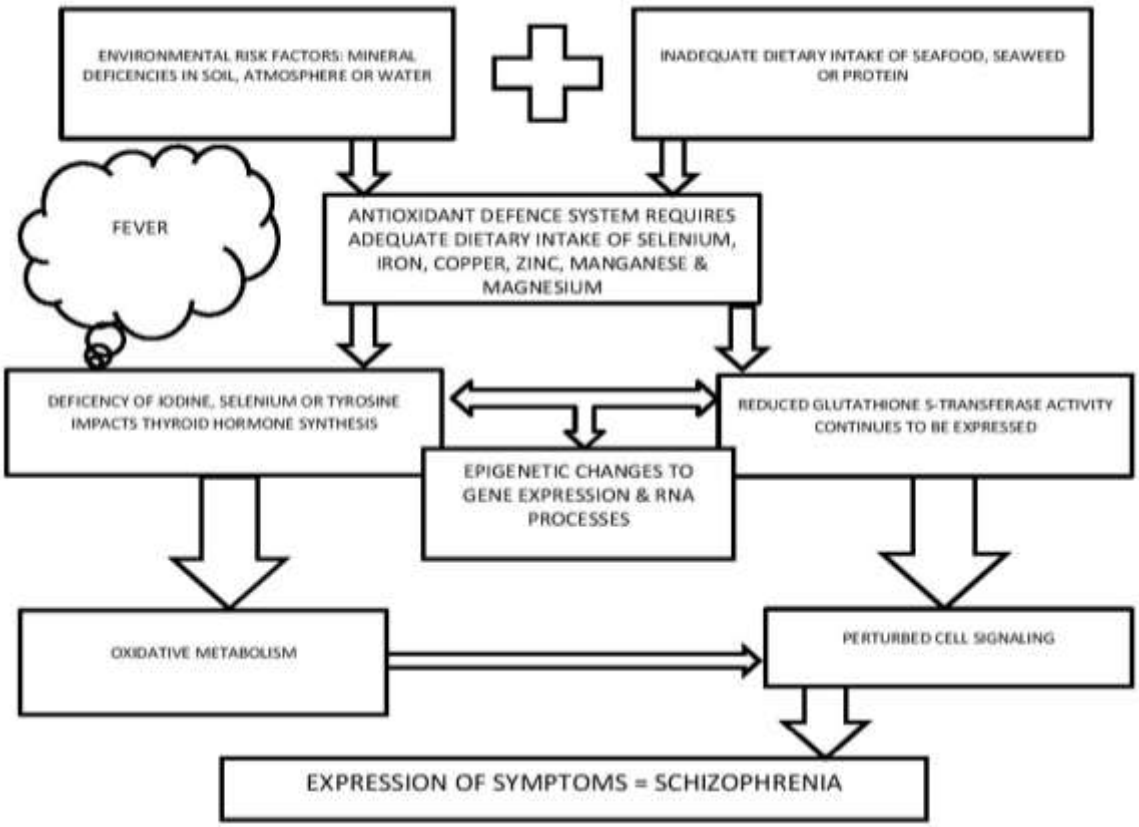
Prevalence and incidence of schizophrenia

Higher prevalence of schizophrenia has been linked to higher latitudes and developed countries[3]. These findings can be easily explained by distribution and bioavailability factors. At high latitudes, ocean selenium levels exhibit seasonal and regional variations[30] to presumably influence the food chain. In under developed countries protein-energy malnutrition is also a concern (linked to low levels of iron, iodine, zinc and vitamin A); which is addressed by various millennium treatment goal schemes[31]. Conversely in developed countries there appears to be a lack of work to address this concern, particularly amongst young girls prone to erratic dietary habits, illicit substance users and alcoholics. Similarly, there is a lack of education amongst females and migrants who may engage in poor dietary habits. The incidence of schizophrenia reportedly favours females and migrants[3]. The consumption of dietary protein as a determinant of body weight[32]; may be particularly germane to women. This theme is continued amongst migrant communities, where

improvements to diet have been explored as a marker for physical and economic adaptation to the new country[33].

Neuropathology of schizophrenia

We can speculate these findings do have relevance for schizophrenia as fluctuations in thyroid hormones are linked to severity of symptom domains in 49% of people diagnosed with schizophrenia and thyroid hormones are accepted as treatment for schizoaffective disorder[34]. The presence of ketone bodies in schizophrenia[35] adds weight to the notion the brain is in a state of near starvation. There is literary support for schizophrenia as a metabolic disorder. Perturbed metabolism associated with psychosis, is regulated by thyroid hormones requiring adequate dietary selenium, iodine and tyrosine. Seafood, seaweed and protein contain the highest concentrations of the minerals and amino acids, essential for thyroid hormone production and to maintain a healthy antioxidant defense system (Figure 1). Selenium and iron deficiencies enable heavy metal accumulation (lead, chromium and cadmium) in newly diagnosed schizophrenia[35]. There is substantial evidence of an impaired antioxidant defense system in schizophrenia by the first episode of psychosis [36-38]. Specific minerals that are obtained from dietary sources such as, iron, selenium, zinc, copper, manganese[40] and magnesium, are also required for antioxidant defense. These minerals form components of metabolic pathways, antioxidant enzymes or transport proteins[41]. Antioxidant enzymes such as, glutathione peroxide and superoxide dismutase are significantly reduced in schiozphrenia[40]. Iron, selenium[36] and copper[43] levels are also reduced in schizophrenia, while manganese[43], lead, cadmium and chromium[36] levels are increased. Selenium and the amino acid, tyrosine, have dual functions in the production of thyroid hormones and signal transduction[44].



Adequate levels of selenium, iron, copper, zinc, manganese and magnesium are required for the regulation and maintenance of antioxidant defences to support neuronal health. Environmental deficiencies of these minerals impart a risk to mental health. Inadequate dietary intake of these minerals impact antioxidant defences linked to schizophrenia. A) Perturbed thyroid hormone synthesis alters gene expression including glutathione S-transferase activity. B) Fever may exacerbate demand for thyroid hormones. C) Thyroid hormone levels influence oxidative metabolism; for which impaired mitochondria and oxidative stress mediate schizophrenia D) reduced glutathione S-transferase activity & perturbed cell signalling are germane to positive and negative symptoms E) schizophrenia.

Figure 1: Inadequate dietary intake of protein, seafood, seaweed in the context of schizophrenia

The mechanism by which these dietary minerals may influence schizophrenia is absent from the literature. Some minerals are cofactors of superoxide dismutase, associated with stress response to hypoxic brain injury[45]. Reduced superoxide dismutase levels equate with non-specific learning difficulties[39] described in the prodromal phase of schizophrenia. Iron is a contributor to mitochondrial electron transport, redox reactions and gene expression which regulate antioxidant defences. Depleted iron and selenium intakes are known to exacerbate iodine deficiency to impair thyroid hormone synthesis[46]. Thyroid hormone signalling is known to adjust energy expenditure accordingly[34]. We know that fever drives demand for thyroid hormones. For instance, the thyroid gland reacts to the presence of fever by increasing metabolic requirements[11]. Sir Charles was concerned that endemic diseases such as, myxoedema or bacterial toxins would increase metabolic demand to drive demand on the

[antioxidant] defence system[20]. Selenium, iodine and tyrosine also have well defined roles in autoimmune disorders such as, thyroiditis.

Deficient levels of thyroid hormones influence energy and phospholipid metabolism, antioxidant defences and oxidative metabolites in the adult brain. Astrocytes and neurons utilize these thyroid hormones to regulate myelination, oligodendrocyte function, cytokines and for modulation of neurotransmitter systems implicated in schizophrenia, involving dopamine, serotonin, glutamate and GABA[34]. Mitochondrial antioxidant defences are also regulated by thyroid hormones to suggest a mediatory role in schizophrenia. Thyroid hormones have a profound effect on mitochondrial energies and form complex relationships to oxidative stress[47]. These thyroid hormones also utilize hormone-activated transcriptional factors to modulate gene expression[48]. Low thyroid hormone levels therefore influence a broad range of epigenetic-led alterations to gene expression including glutathione S-transferase family members[49]. Rodent models demonstrate that glutathione S-transferases act as transporters and binders for thyroid hormones in both neurons and glial cells[50]. Reduced glutathione S-transferase activity also impacts the uptake and release of hydrocortisone[50], associated with stress-driven decompensation in schizophrenia. Stress is a well-established trigger for the onset of acute psychotic episodes. Ironically impaired glutathione S-transferase activity also affects the uptake and release of thyroid hormones and neurotransmitters[46]. Thyroid hormones are required in the brain for the expression of sensory perception, neuronal excitability, mental speed and ion channel regulation[51] (Figure 2).

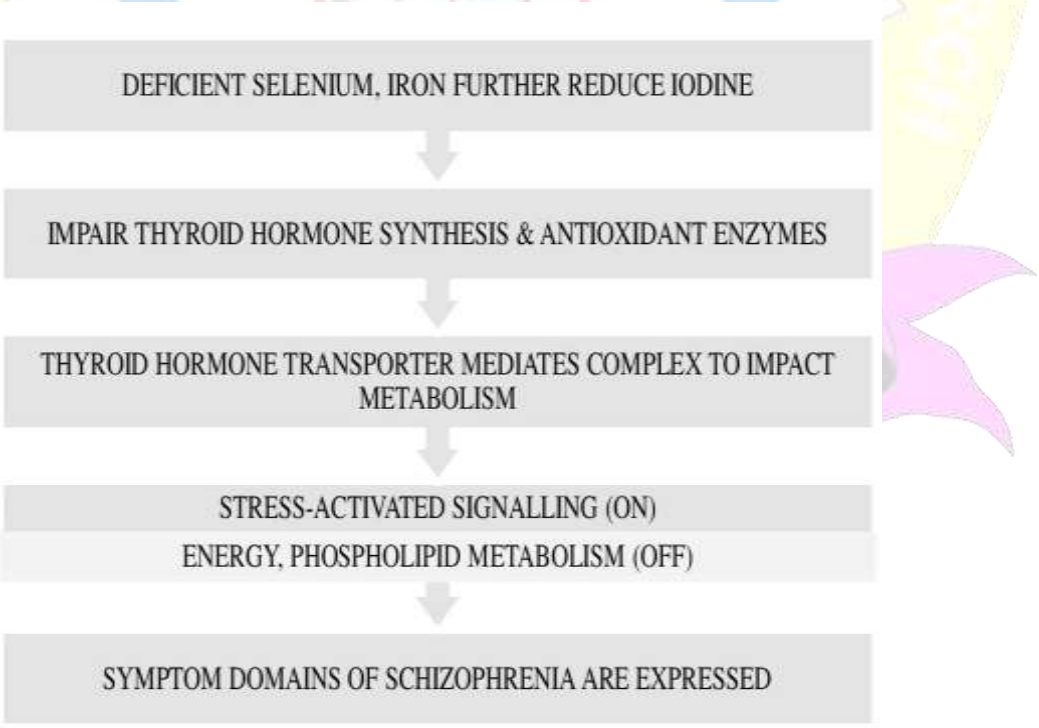


Figure 2: Onset of Schizophrenia

To overcome omissions the available data, government reports of the time were accessed. For instance, Dr McKillop documented some of Sir Charles' raw data in his annual government report. The data was also limited by the technology of the time. Modern repositories have verified these earlier findings in relation to soil deficiencies and underlying geological structures.

A review of goitre studies revealed mineral deficiencies in the environment. It is postulated that in low mineral soils, adequate dietary intake of seafood, seaweed or protein (meat or eggs) would conceivably protect the population from any detrimental effects on the brain. Environmental factors would merely represent a risk factor for the development of schizophrenia under these conditions. The main finding is dietary deficiencies of seafood, seaweed and protein amongst the New Zealand population; in areas coinciding with low mineral salts. These foodstuffs are known to contain high levels of the minerals and amino acids essential for the production of thyroid hormones, healthy antioxidant defences and neuronal health; germane to neuropathology at the onset, prevalence and possibly incidence reporting of schizophrenia and schizoaffective disorder. Further work is required to educate stakeholders of these findings by asking the question; do you EAT, for brain health? This information may influence the current trend of prescribing antipsychotic drugs to children prophylactically.

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