

What really causes  
schizophrenia

HAROLD D. FOSTER

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*Dedicated to Delta 3.5*

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*Whoever wishes to investigate medicine properly, should proceed thus: in the first place to consider the seasons of the year, and what effects each of them produces... Then the winds, the hot and the cold, especially such as are common to all countries, and then such as are peculiar to each locality. We must also consider the qualities. In the same manner, when one comes into a city to which he is a stranger, he ought to consider its situation, how it lies as to the winds and the rising of the sun: for its influence is not the same whether it lies to the north or the south, to the rising or to the setting sun. These things one ought to consider most attentively, and concerning the water which the inhabitants use, whether they be marshy and soft, or hard, and running from elevated and rocky situations, and then if saltish and unfit for cooking, and the ground, whether it be naked and deficient in water, or wooded and well watered, and whether it lies in a hollow, confined situation, or is elevated and cold: and the mode in which the inhabitants live, and what are their pursuits, whether they are fond of drinking and eating to excess, and given to indolence, or are fond of exercise and labour, and not given to excess in eating and drinking.*

Francis Adams, *The Genuine Works of Hippocrates*, 1849  
(on Airs, Waters, and Places), vol. 1, p. 190

# WHAT REALLY CAUSES SCHIZOPHRENIA: AN EXECUTIVE SUMMARY

How difficult is the schizophrenia jigsaw? How complex is the puzzle? In *The Madness of Adam and Eve*, Horrobin<sup>1</sup> points out that:

*While in familial and personality terms the problem is devastating, in biochemical terms the problem cannot be very serious. After all, the young person functioned near normally for fifteen, twenty-five or thirty-five years before becoming ill. Moreover, all schizophrenic patients vary in the severity of their illness, often, as documented earlier, becoming near normal while the body temperature is elevated. The fundamental biochemical problem, therefore, cannot be too serious and must be reversible.*

This is an extremely intelligent and encouraging characterization. It seems fair to ask, however, if the problem is so biochemically simple, why have thousands of doctors and scientists spent countless billions of dollars, over more than 100 years, in endless unsuccessful attempts to discover the etiology of schizophrenia?

The logical answer to this question must be that they are trying to hammer jigsaw puzzle pieces into spaces where they do not fit. Conventional drug treatment rests, to a large degree, on the “dopamine hypothesis,” that is on the belief that excess dopamine accentuates and decreased dopamine reduces the positive or hot symptoms of schizophrenia.<sup>2</sup> The evidence for high levels of dopamine in schizophrenia is poor<sup>3</sup> and Parkinsonism (the mimicking of Parkinson’s disease) has occurred frequently in patients treated for this hypothesized excess. Since Parkinson’s disease is known to stem from a dopamine

deficiency, it seems likely that drugs causing a similar illness in schizophrenics are creating a lack of this neurotransmitter, rather than correcting an excess of it.

If too much dopamine is not the root cause of schizophrenia, what is? Certainly genetics must play a significant role because 50 percent of patients with this illness come from families with a history of the disorder.<sup>4</sup> This preponderance cannot be explained by abnormal child rearing since adoption has no impact on the risk of subsequently becoming schizophrenic. There is, beyond a doubt, therefore, a strong genetic component to schizophrenia, but it cannot be as straightforward as the inheritance of certain characteristics such as eye colour, since, as Myers<sup>5</sup> points out, “about half of the twins who share identical genes with a schizophrenic victim do *not* develop the disorder.” One must agree with Nicol and Gottesman’s<sup>6</sup> assessment that some individuals “have a genetic predisposition to the disorder but that this predisposition by itself is not sufficient for the development of schizophrenia.” The schizophrenia gene(s), therefore, is not destiny but it is enhanced risk.

This book discusses four genetic aberrations<sup>7-10</sup> that occur more frequently than normal in subgroups of schizophrenics. These include the low enzyme activity variant of the catechol-O-methyltransferase gene, the GSTM1\*O allele (required to produce a form of glutathione S-transferase) and possibly the C677TT variant of the gene for methylenetetrahydrofolate reductase. Beyond this, many schizophrenics appear to have inherited an unusual Nogo (reticulon 4, RTN4, or RTN-X) variant gene from both parents. What these four genetic aberrations appear to have in common is that they all result in higher than normal exposure to adrenochrome, a metabolite of adrenaline, or in an abnormal susceptibility to its negative impacts. Since all of these variants are quite widely distributed in the human populace, it seems likely that abnormal levels of adrenochrome

must carry some evolutionary advantage(s). That is, there appear to be not one, but at least three and maybe four balanced genetic morphisms involved in this mental illness. It is argued here that the genetic aberrations increasing the risk of schizophrenia appear to promote religious sense, technical and artistic creativity, and leadership.<sup>11</sup> They also seem to provide a greater resistance to a wide range of cancers, especially that of the lung.<sup>12</sup> While they may be extremely destructive in individuals prone to develop schizophrenia, such genes are highly beneficial for humanity as a whole.

In a recently published book, *The Invisible Plague: The Rise of Mental Illness from 1750 to the Present*, Torrey and Miller<sup>13</sup> argue that throughout human history, the baseline rate of insanity was approximately one case for each 2,000 members of society. Using a great diversity of records, ranging from mental health surveys to psychiatrists' diaries, they are able to prove beyond reasonable doubt that industrialization has been accompanied by dramatic increases in mental illness. In England, Ireland, Canada, and the USA, for example, "the prevalence of insanity, as a rate per population, increased at least sevenfold between the mid-18th and mid-20th centuries." In the USA and especially in Ireland, the increase was greater. Torrey and Miller<sup>24</sup> argue that "we are now in the midst of an epidemic of insanity so insidious that most people are even unaware of its existence." The invisible plague appears worst in Ireland where the number of insane persons per 1,000 population has reached almost 8.0. This seems to be about 16 times the pre-industrial global baseline.

One does not have epidemics of genetic diseases, simply because the human genome does not alter rapidly enough to cause them. The current epidemic of insanity, associated with both schizophrenia and bipolar disorder, that has developed over the past 250 years is a very strong argument that the

triggers that increase the negative impacts of the genetic aberrations linked to this mental illness have become more common. These appear to include anything that either stimulates the body's production of adrenaline or promotes its metabolism to adrenochrome and its derivatives. Such triggers include stress and its associated "fight or flight" response system, excess sugar consumption, and exposure to substances causing allergic reactions.

Besides being an hallucinogen, adrenochrome is a highly reactive neurotoxin that, in schizophrenia, undermines at least three major biochemical systems. It is an antagonist of the hormone triiodothyronine and can damage the thyroid. In chronic schizophrenics, this gland impairment appears permanent. Adrenochrome also has a Jekyll and Hyde relationship with serotonin and, so, impacts on tryptophan and its other chief metabolite niacin. At low levels, serotonin appears to stimulate adrenochrome formation, while at higher levels it retards the process. Adrenochrome also generates numerous free radicals causing oxidative stress, eventually exhausting the schizophrenic antioxidant defence systems, creating deficiencies of glutathione peroxidase, superoxide dismutase, and catalase. Complicating the impacts of high adrenochrome conversion from adrenaline are the numerous interactions that normally occur between triiodothyronine, serotonin, and the three major components of the antioxidant defence system.

If the adrenochrome hypothesis is correct, the "ideal" treatment for schizophrenia should involve eight steps, designed to reduce the production of adrenaline and slow down its metabolism to adrenochrome and other toxic indoles. Such a treatment should also attempt to reduce the further biochemical abnormalities that result from either an excess of adrenochrome and its metabolites, or from other impacts of the four genetic aberrations that appear associated with this mental illness.

Since many schizophrenics are over-oxidizing adrenaline because of allergic reactions to the environment, they need extra-special surroundings because of such sensitivities. Ideally, a treatment clinic would be like the Lange Meridian Center,<sup>15</sup> which was built using Bau-Biologie principles. Step two involves genetic and biochemical screening to identify the most likely effective treatment protocol. Allergy testing is also essential, as is a low sugar diet. The western diet has been increasingly dominated by sugar. The per capita consumption in the USA, for example, has increased by roughly a factor of 20 since 1822.<sup>16</sup> Hypoglycemia, consequently, is now rampant. This elevated dietary intake of sugar stimulates the body to release insulin which, in turn, drives the blood sugar levels down, encouraging the adrenal glands to release adrenaline. In schizophrenics this is oxidized to produce abnormally high levels of adrenochrome and its metabolites. The fifth step in the treatment of schizophrenia should involve medications that must quickly reduce the destructive impacts of excess adrenochrome and its derivatives. They must also address the other biochemical anomalies directly related not to such indoles, but to the genetic aberration encouraging their overproduction. In schizophrenics with the MTHFR C 677TT variant, for example, the patient will also be suffering from depressed methionine and elevated homocysteine.

There appear to be several avenues for lowering excess adrenochrome levels. These include high doses of niacin or niacinamide and the use of other natural methyl acceptors thiamine (vitamin B<sub>1</sub>), riboflavin (vitamin B<sub>2</sub>), and ubiquinone (Coenzyme Q<sub>10</sub>). Niacin is usually the treatment of choice.

Another adrenochrome antagonist, triiodothyronine, appears very effective in treating schizophrenia. As shown by Danziger,<sup>17</sup> every one of the 80 schizophrenics who had been ill for 6 months or less, who took between 120 to 1,200 milligrams of desiccated

thyroid daily for at least 100 days, recovered, suffering relapses only if they later discontinued their medication. These doses may seem high, but it should be remembered that schizophrenics are known to be very resistant to thyroid medications. This is probably because all chronic schizophrenics appear to be suffering from badly damaged thyroid glands.

Treatment might also involve attempts to directly raise body levels of another adrenochrome antagonist, serotonin. If serotonin is not provided as a supplement, its metabolism could be encouraged by the consumption of foods that are high in tryptophan, such as beans, cod, pork, soybeans, and cheese (provided that the patient is not allergic to them). In addition, every effort should be made to repair the antioxidant defence system, increasing glutathione peroxidase, catalase, and superoxide dismutase activity.

Since there appear to be several genetic aberrations involved in schizophrenia, subgroups of patients also will suffer from distinct biochemical imbalances that need correction. The sixth step of the treatment protocol should address these. To illustrate, schizophrenics with the MTHFR C677T variant of the gene encoding for methylenetetrahydrofolate will suffer from an excess of homocysteine and a deficiency of methionine, even if treatment reduces adrenochrome levels. Beyond the provision of methionine, since the remethylation (or detoxification) of homocysteine requires folic acid, vitamin B12, zinc, and trimethylglycine, it is likely that schizophrenics with this genetic aberration will require high doses of these nutrients.<sup>18</sup>

Adrenochrome excess and the other biochemical abnormalities that occur in schizophrenia can eventually cause serious damage to the thyroid gland<sup>19</sup> as well as to the brain itself. Long term chronic patients are, therefore, much more difficult to treat successfully. This task might not be impossible, but it will

almost surely require higher doses of orthomolecular nutrients, taken for longer periods, before improvement is apparent.

One of the major problems in chronic schizophrenia is the development of brain atrophy, associated with large fluid filled spaces known as ventricles. Buckman and coworkers<sup>20</sup> provided evidence that blood levels of the selenoenzyme glutathione peroxidase have a strong negative correlation with computer tomography scan measures of such brain damage. Simply put, the less blood glutathione peroxidase, the greater the brain damage in chronic schizophrenics. Obviously, one treatment strategy worth trying is supplementation with the four nutrients, selenium, cysteine, glutamine, and tryptophan, that the body requires to produce glutathione peroxidase.<sup>21</sup> Injected glutathione may be of value. There is also growing evidence that eicosapentaenoic acid can repair ventricle damage in chronic schizophrenics, leading to an improvement in their mental health.<sup>22-24</sup>

It is clear that damage is not restricted to the brain in chronic schizophrenics. All of these patients also appear to suffer from extensive thyroid abnormalities.<sup>25</sup> I do not know how to repair a damaged thyroid gland. If this is impossible, significant behavioural improvements can only be expected when using a protocol that includes continuous desiccated thyroid gland supplementation.

The eighth and final step in the treatment of schizophrenia involves treatment for the soul. Recovering schizophrenics are still one of the few groups society feels free to abuse, ostracize, and discriminate against. While it is socially acceptable to admit to cancer, heart disease, multiple sclerosis, or Parkinson's disease, admitting to schizophrenia invites fear and derision. To recover, schizophrenics need employment, respect, and compassion. Too often they receive rejection, abuse, and insult.

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*There are causes for all human suffering, and there is a way by which they may be ended, because everything in the world is the result of a vast concurrence of causes and conditions and everything disappears as these causes and conditions change and pass away.*

[The teachings of Buddha by  
Bukkyo Dendo Kyokai,  
112th revised edition]

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*The lunatic, the lover and the poet  
Are of imagination all compact:  
One sees more devils than vast hell can hold,  
That is, the madman: the lover, all as frantic  
Sees Hellen's beauty in a brow of Egypt:  
The poet's eye, in a fine frenzy rolling,  
Doth glance from heaven to earth, from earth to heaven;  
And as imagination bodies forth  
The forms of things unknown, the poet's pen  
Turns them to shapes and gives to  
airy nothing  
A local habitation and a name.*

*William Shakespeare, A Midsummer Night's Dream*

## SCHIZOPHRENIA: FROM BEDLAM TO BABEL

*But strange that I was not told  
That the brain can hold  
In a tiny ivory cell  
God's heaven and hell.*

Oscar Wilde (1854-1900)

Schizophrenia may be the cruellest disorder,<sup>1</sup> afflicting “young adults, often beginning insidiously and progressing until the ambitions, potentials, and hopes of early years are disregarded in disarray. In their place lie broken thoughts, inappropriate or stunted emotions, and internal voices, or other misperceptions that can make existence a living hell.” Unfortunately, it is not rare. Schizophrenia is the commonest serious mental illness of the Developed World. In the USA, it accounts for some 24 percent of all admissions to mental hospitals.<sup>2</sup> Initially, the disease is often episodic with acute phases interspaced with remissions, but it often becomes chronic.

Schizophrenia is an imprecise diagnosis, in some ways similar to one of heart disease or cancer. It is not a single illness but a spectrum of conditions that have similar symptoms, a symptom complex of abnormal brain function. Schizophrenia usually consists of a combination of disorders of thinking process, perception, emotions, and sensory stimuli. It is a mental disorder that is often associated with apparently inexplicable anxiety, rapid mood swings, and fatigue.<sup>3</sup> Typically, schizophrenics suffer from auditory, olfactory, or visual illusions and hallucinations. Their senses of touch, taste, and smell may be distorted. It is hardly surprising with such handicaps that

schizophrenics behave in strange ways, or say totally meaningless or inappropriate things.<sup>4</sup>

Schizophrenia can be divided into four subtypes: simple, hebephrenic, catatonic, and paranoid.<sup>5</sup> Simple schizophrenia is characterized by confusion, withdrawal, and apathy. Hebephrenic schizophrenia is an unusual mixture of silliness, hypochondria, and delight in bizarre adornments and childish pranks. In contrast, catatonic schizophrenics huddle in grotesque positions, often refusing to move, to take food, or visit the bathroom. They also may display muteness and stupor. Paranoid schizophrenics are dominated by feelings of persecution, suspicion, and bitterness. Everything is sinister or threatening. They may respond to simple gestures or circumstances with violence. Schizophrenic symptoms are often described as either positive or negative.<sup>6</sup> Positive symptoms are so named because they involve the presence of altered behaviours, including delusions, hallucinations, extreme emotions, incoherent thoughts and speech, and excited motor activity. In contrast, negative symptoms encompass a lack of normal behaviours, such as the display of emotion, social interaction, speech, and movement.

## BEDLAM

Schizophrenia's history is one of man's inhumanity to man. It is not a coincidence that the word Bedlam has two meanings. One of these, a corruption of Bethlehem, is as Bedlam, a popular name given to England's oldest insane asylum, Bethlem Hospital. Mental patients have been "treated" there since as early as 1403, but it was not until 1547 that its admissions were limited to the insane. For centuries, Bedlam was known for the brutality and lack of respect shown to its patients.<sup>7</sup> It functioned largely as a tourist attraction that "Everybody who

lived in London or ever came to London visited as a matter of course.”<sup>8</sup> The hospital was an entertaining “zoo and freak show ... in which the inmate was regarded as a beast or monster.” Having paid their entrance fees, 17<sup>th</sup> century visitors exploited patients by getting them drunk and harassing them, finding great amusement in the “Ravings ... cursing and swearing” they provoked.<sup>9-10</sup> As might be expected, then, Bedlam also has come to mean any scene of confusion and uproar.<sup>11</sup>

As Charles Darwin’s theory of evolution gained greater support in the late 1800s, many people decided it held the key to “improving humanity.” Social Darwinians sought to explain crime, alcoholism, poverty, prostitution, homelessness, and, of course, insanity as the price paid for the inheritance of “defective germ plasma.”<sup>12</sup> That is, all society’s problems were seen as genetic. The way to solve them was through eugenics, a systematic attempt to increase desirable and decrease undesirable genetic traits in the population. To illustrate, British scientist Francis Galton<sup>13</sup> promoted these ideas in two basic ways. “Positive eugenics” encouraged the healthiest and most intelligent to marry and procreate. “Negative eugenics” included the institutionalization, castration, and sterilization of those, including schizophrenics, who were considered “defective” or “undesirable.” Galton’s ideas were most readily accepted in the USA, Canada, Scandinavia, and, of course, Germany.<sup>14</sup> They formed Hitler’s rationale for liquidating the occupants of Germany’s mental hospitals and all those supposedly showing eugenic social or racial inferiority, including homosexuals and Jews. In the USA, during the period 1907 to 1940, a total of 18,552 insane individuals were sterilized. Half of these procedures were carried out in California, with a quarter more taking place in Virginia and Kansas combined.<sup>15</sup> Sterilization of the mentally ill continued in the USA until the mid 1970s. At one time or another during the 20<sup>th</sup> century, 33 states had statutes permitting involuntary sterilization.

Such assaults on the mentally ill and the retarded did not lead to improvement in their lives. *Life* magazine ran an exposé of the cruel and unjust treatment of America's insane under the headline "Bedlam 1946: Most US Mental Hospitals are a Shame and a Disgrace." Its author, Albert Q. Maisel,<sup>17</sup> described institutions that had been allowed "to degenerate into little more than concentration camps on the Belsen pattern." Patients were given food like that "usually found in most garbage cans." Attendants had little or no training and provided medications on whim. Scores of deaths of patients followed beatings by such "guards." Torrey<sup>18</sup> described one of *Life's* photographs of naked patients, in wards with beds packed so tightly together that the floor was not visible, as looking like "a drawing done by William Blake to illustrate Dante's *Inferno*."

Then came Deinstitutionalization. This was supposed to be accompanied by the provision of alternative community facilities for the mentally ill. However, "what took place was simply depopulation of the state hospitals. It was as if a policy of resettlement had been agreed upon but only eviction took place."<sup>19</sup> In the words of a *New York Times* editorial,<sup>20</sup> deinstitutionalization became "a cruel embarrassment, a reform gone terribly wrong." Now the bulk of the insane in the USA are living on the streets, under bridges and in parks, alleys, and in homeless shelters. Increasing numbers of the untreated seriously mentally ill end up in prisons and jails as the violent acts perpetrated by them increase. The situation is similar in Canada and most other countries. In the USA, approximately one-third of all homeless people are seriously mentally ill; that is, they are schizophrenics or suffering from bipolar disorder.<sup>21</sup> If they cannot function effectively under normal circumstances, how can they cope without food or shelter, living on the streets?

In truth, only one out of every five young people who experience an initial episode of schizophrenia will ever recover enough

to live anything approaching a normal life, without drugs or on low drug doses.<sup>22</sup> Even the most modern drugs are incompatible with a normal lifestyle. Rarely do schizophrenics who take them work and pay income taxes because, on average, the available drugs for the treatment of schizophrenia result in only a 15 to 20 percent reduction in symptoms. Drugs frequently also cause serious side-effects that include involuntary movement, very much like that seen in Parkinson's disease. These adverse effects lead to many schizophrenics discontinuing treatment and, of the four out of five who do not achieve near normality, only one is likely to take his or her prescribed medication continuously. Of the remaining three, only one will maintain contact with support services. The other two often join the homeless, live in seclusion at home, or commit suicide.

## BABEL

According to Genesis, the Tower of Babel was erected on the Plain of Shinar in Babylonia by Noah's descendants.<sup>24</sup> Its builders intended to find the backdoor to Heaven, but Jehovah, angered by their presumption, decided to stop construction. This he did by inflicting them with a diversity of languages. Meaningful communication became impossible and Noah's descendants were then scattered over the face of the earth. This story from the *Old Testament*, which was perhaps inspired by the fall of the famous temple-tower of Etemenanki, gave rise to the English word "babble."<sup>25</sup>

Bedlam and Babel appear together in this chapter's title to highlight the link between the continuing inhumane treatment of the mentally ill and the inability of the diverse disciplines that study them to communicate. As Horrobin<sup>26</sup> has pointed out:

*Schizophrenic patients have been ill served by the narrow ultra-specializations of the second half of the twentieth century. Each has seen the illness from its own very limited perspective. [Give a child a hammer and everything becomes a nail.] Those inclined to psychological and psychoanalytical levels of explanation have blamed dysfunctional families for the disease. Those interested in a broader sociological picture have blamed society as a whole. Those interested in drug action have blamed the neurotransmitter function. Almost no one has taken any interest at all in the whole-body manifestations of the illness, which careful clinicians in the first half of the century had noted. Almost no one has attempted to integrate what is known in a coherent and integrated fashion.*

As a consequence of this domination of the schizophrenia research agenda by narrow specialists, the recovery rate from the illness is no better today than it was a century ago<sup>27</sup> yet like so many of our other mysteries “the truth is out there.” In an attempt to discover it, this book seeks clues to the causes of schizophrenia from all available sources. That is, they are collected not just from the social and physical sciences, but also from conventional and unconventional medicine and from the testimonies of recovered patients and their relatives.

Money is not a good measure of the wasted lives of schizophrenics or of the pain and suffering their illness causes to families, friends, and to society as a whole. Nevertheless, it gives some idea of the enormous losses involved. In England in 1992, the hospitalization of schizophrenics cost £652 million, amounting to 5.4 percent of the National Health Service hospital budget. When indirect expenses, such as those for social services, courts, lost wages, and family expenses were added to the total, the annual cost of insanity (schizophrenia and bipolar disorder) in England was at least £3 billion.<sup>28</sup> In Canada each year, schizophrenia is responsible for \$1.1 billion in direct and

\$1.2 billion in indirect costs, for a total of \$2.3 billion.<sup>29</sup> In the USA in 1991, schizophrenia has an annual price tag of \$65 billion and bipolar disorder of over \$45 billion.<sup>30</sup> As a consequence, taken together these two illnesses cost the USA \$110 billion in 1991. Insanity is the single most expensive disease category under both the Supplemental Security Income and Social Security Disability Insurance programs. USA federal income supplement payments to schizophrenics account for a large part of this \$110 billion. No matter where or how you measure it, schizophrenia is an enormous social burden that must be lifted.

## SUMMARY

Several conclusions can be drawn from schizophrenia's clinical expression. In its early acute stages, this mental illness is episodic. That is, its symptoms increase and decrease markedly over time. Eventually, in most cases, it becomes chronic, without remission. These fluctuations suggest that there may be a social or environmental "trigger(s)" promoting acute schizophrenic episodes. Differences between the four major subtypes of the condition also imply that there is unlikely to be a common cause for all forms of schizophrenia. The illness, therefore, is probably a syndrome, associated with several environmental "triggers," and/or genetic abnormalities.

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*Within the scientific community those who succeed tend to be reserved and cautious and stay within carefully prescribed activities. The bold, the daring lone ranger may be romanticized by other parts of American culture, but that glorification does not extend to the internal workings of science. Funds are given to those who stay well within the confines of their field, not those who push the envelope.*

*Devra Davis, When Smoke Ran Like Water:  
Tales of Environmental Deception and the  
Battle Against Pollution, New York: Basic Books, 2002.*

*At the end of the seventeenth century, insanity was of little significance and was little discussed. At the end of the eighteenth century, it was perceived as probably increasing and was of some concern. At the end of the nineteenth century, it was perceived as an epidemic and was a major concern. And at the end of the twentieth century, insanity was simply accepted as part of the fabric of life. It is a remarkable history.*

E. Fuller Torrey and J. Miller<sup>1</sup>

## HISTORY OF SCHIZOPHRENIA

Nobody has done more to shed light on the history of schizophrenia than E. Fuller Torrey. This chapter draws very heavily on his scholarship and is only a shadow of it.<sup>2,3</sup> Of particular value are his books *Schizophrenia and Civilisation*, which became available in 1980, and *The Invisible Plague: The Rise of Mental Illness from 1750 to the Present*. The latter has just been published (2002), with Judy Miller as a co-author. If you are truly interested in schizophrenia's history, it will be extremely worthwhile to read Torrey's books and articles on the topic.

Mesopotamian tablets dating back to the second millennium BC describe symptoms of paranoid delusions, mania, and depression.<sup>4</sup> Similarly, the *Bible*, in Deuteronomy 28, warns of the penalty for breaking God's commandments: "The Lord will smite you with madness and blindness and confusion of

mind.” Occasional references to insanity also occur in early Indian texts on Ayurvedic medicine, from the 1st century AD. They can also be found in ancient Greek and Roman literature. Hippocrates, for example, described insanity following childbirth (postpartum psychosis) and insanity accompanying epilepsy. He also identified the delirium that is secondary to high fevers (phrenitis). Greek mythology is full of characters visited by madness, as punishment by the gods.

Insanity was again described by Islamic physicians, including Al-Razi (Rhazes) and Ibn Sina (Avicenna) during the 7th and 8th centuries. Ibn Sina, for example, discussed mania in his writings and reviewed the case of a patient having delusions of being a cow. When Islamic medicine was at its peak, hospitals in Cairo, Alexandria, Damascus, Aleppo, Baghdad, and Fez had wards for the treatment of the insane.<sup>7</sup>

In Christian Europe during the Middle Ages, there was little systematic study of medicine. Nevertheless medieval physicians were well aware that mental illness could result from “humoral imbalance, intemperate diet and alcohol intake, overwork and grief.”<sup>8</sup> As Europe’s Middle Ages gave way to the Renaissance, insanity became more obvious, largely because of its appearance in King Charles VI in France and his grandson King Henry VI in England. Charles VI, for example, became mentally ill in 1392, at age 24. Over the next 30 years he had a series of remissions and relapses. Such insanity was often given a religious interpretation and prayer became an accepted form of treatment.<sup>9</sup>

Clearly, for more than two thousand years there is evidence that humanity has been afflicted by insanity. However, in both *Schizophrenia and Civilisation*<sup>10</sup> and *The Invisible Plague*,<sup>11</sup> Torrey makes a strong case that the prevalence of insanity, in the form of schizophrenia, began to increase rapidly with the onset

of the Industrial Revolution. To cite directly from the former book:<sup>12</sup>

*It was as if somebody rang a bell precisely at the turn of the nineteenth century to herald the official entrance of schizophrenia. Whereas up to that point there appear to have been at best a few scattered cases in the literature, classical schizophrenia was suddenly being described by different people in different places all at about the same time. Such an entrance for a disease is rather dramatic. Almost from the first historical suggestions of schizophrenia, an accompanying theme can be heard in the background: Insanity (and schizophrenia) were rapidly increasing. The persistence of this idea throughout the nineteenth century and into the twentieth is one of the most striking facets of the short history of schizophrenia.*

This dramatic increase in schizophrenia was probably first documented, in 1829, by Halliday<sup>13</sup> who claimed insanity had more than tripled in England during the previous 20 years. A similar increase in prevalence was obvious in France where, after an extensive analysis, Renaudin<sup>14</sup> established that there had been a major increase in insanity between 1835 and 1854, especially in younger, more prone to schizophrenia, age groups. In 1861 Griesinger remarked on the growing number of insane in Germany, while 6 years later Belgrave<sup>15</sup> asserted that the same phenomenon had occurred in Denmark. Even stronger proof of an increase in schizophrenia, during the 19th century, was provided by the Australian physician, Tucker.<sup>16</sup> He visited 400 asylums, mainly located in Europe and the USA, during the period 1882 to 1885. His report *Lunacy in Many Lands* described his 3-year odyssey, concluding that the vast majority of superintendents of asylums believed that insanity had recently increased and this “must be accepted as a fact.”

Statistical evidence to support the view that insanity was on the rise during the 19th century began to accumulate in 1840,

in the USA, with the first census that identified the “insane and idiotic.” Later censuses recorded these two categories independently. From these data, Gorwitz<sup>17</sup> calculated that, in 1840, the USA prevalence rate for insanity was 50.7 per 100,000. By 1860 it had risen to 76.7, reaching 183.3 per 100,000 population by 1880. It would appear, therefore, that in the USA there was more than a threefold increase in insanity, during a 40 year period, in the middle of the 19th century. During the same time span, the number of inmates in insane asylums rose from 2,561 to 38,047. By 1904<sup>18</sup> there were 150,151 such patients.

On the basis of this evidence, Torrey<sup>19</sup> concluded that “schizophrenia, as we know it, is probably of recent origin, and the reasons for this have to do with the spread of civilization and its concomitants.” This relationship between Western industrial civilization and schizophrenia appears to be continuing today. In India, for example, there have been several studies published since 1966 which support the view that the disease is most prevalent among the more highly educated and/or westernized castes.<sup>20</sup> Similarly, in northern Ghana, between 1937 and 1963, as Westernization occurred, the prevalence of schizophrenia rapidly increased.<sup>21</sup> In Papua and New Guinea, more than a 20-fold difference in schizophrenia prevalence was identified among districts, those where the disease was most common having the greatest contact with Western civilization.<sup>22</sup>

In a more recent book, *The Invisible Plague: The Rise of Mental Illness from 1750 to the Present*, Torrey and his co-author Judy Miller<sup>23</sup> argue that throughout human history, the baseline rate of insanity was approximately one case for each 2,000 members of society. Using a great diversity of records, ranging from mental health surveys to psychiatrists’ diaries, they are able to prove beyond reasonable doubt that industrialization has been accompanied by dramatic increases in mental illness.

In England, Ireland, Canada, and the USA, for example, “the prevalence of insanity, as a rate per population, increased at least sevenfold between the mid-18th and mid-20th centuries.” In the USA and especially in Ireland, the increase was greater. Torrey and Miller<sup>24</sup> then argue that “we are now in the midst of an epidemic of insanity so insidious that most people are even unaware of its existence.” The invisible plague appears worst in Ireland where the number of insane persons per 1,000 population has reached almost 8.0. This seems to be about 16 times the pre-industrial global baseline.

## SUMMARY

The abnormally high levels of schizophrenia amongst the Irish, both in Ireland and abroad, support a genetic component to schizophrenia.<sup>25</sup> Nevertheless, studies in Canada, Norway, Saudi Arabia, and the Sudan have shown that inbreeding associated with consanguineous marriages does not increase the prevalence of schizophrenia. Similarly, inbreeding rates are highest in Japan, Brazil, India, and Israel but none of these countries has abnormally high rates of schizophrenia.<sup>26</sup>

One does not have epidemics of genetic diseases, simply because the human genome does not alter rapidly enough to trigger them. The current epidemic of insanity, associated with both schizophrenia and bipolar disorder, that has developed over the past two centuries is a very strong argument that neither disease is primarily genetic in origin. Schizophrenia’s rise, especially in urban areas, suggests that, at the very least, it has a “trigger” or “triggers” that is (are) most common in industrialized regions.<sup>27</sup>

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*Most secrets of knowledge have been discovered by plain and neglected men than by men of popular fame. And this is so with good reason. For the men of popular fame are busy on popular matters.*

Roger Bacon (1220-1292)

The seeds needed to produce most crops are planted months and sometimes years before the harvest. Many diseases also have significant latency periods. The “trigger” that causes multiple sclerosis is acquired in childhood or adolescence, long before any of its symptoms appear. We know this because the disorder is far more common in the north of the USA than in the south. Adult migration between these high (northern) and low (southern) prevalence zones<sup>1</sup> does not seem to effect whether or not a person develops multiple sclerosis. However, risk is not defined at birth, and migration north or south during childhood, or adolescence, increases or decreases the chance of eventually developing the disorder. Shingles is an acute infection of a particular sensory nerve that causes an outbreak of blisters and severe pain. It occurs only in adults who have had chickenpox as children and is caused by the same virus, reactivated after being dormant in the body for decades.<sup>3</sup> Does schizophrenia have a similar “incubation” or “latency” period, before clinical symptoms appear in early adulthood, but long after the disease has been acquired? If so, just when are the seeds of “the cruellest disease of the Western World”<sup>4</sup> planted?

## THE WOMB

Although the symptoms of schizophrenia rarely become obvious until early adulthood, some unfortunate individuals appear destined for this mental illness from before birth. They often display minor physical abnormalities that begin to develop in the fetus during the first trimester of pregnancy. Such characteristics may include an abnormal head size, asymmetrical, malformed or low-seated ears, a high steeped mouth, furrowed feet, and/or webbed fifth finger. Infants who later become schizophrenic often display an unusually long third toe and/or a gap between the first and second digits.<sup>5</sup> Some similar characteristics occur in Down's syndrome and other genetic disorders. They also may be linked to fetal exposure to teratogens (such as alcohol), dietary deficiency, and rubella infection.<sup>6</sup>

## BIRTH

Life is never easy for schizophrenics. Even delivery may be unusually complicated and dangerous.<sup>7</sup> The births of future psychotics, for example, have often been associated with toxemia, bleeding during pregnancy, and the threat of spontaneous abortion and asphyxia.<sup>8</sup> If one twin dies during the perinatal period the other's chance of becoming schizophrenic is increased.<sup>9</sup> Future schizophrenics typically have low birth weights<sup>10</sup> and are born prematurely.<sup>11</sup> Labour is often prolonged.<sup>12</sup>

## THE ACUTE PHASE

Three new technologies provide windows into the brain, providing numerous clues on the origins and nature of schizophrenia.<sup>13</sup> CAT (computerized axial tomography), for example,

is used to take X-ray photographs of the brain that are capable of revealing any damage. PET (positron emission tomography) scans for brain activity by showing differences in the consumption of glucose. This sugar acts as a chemical fuel, with active neutrons “burning” more. Using a form of radioactive glucose, PET scans can identify where the brain neutrons are the most active. As Myers<sup>14</sup> points out, this gives new meaning to the phrase “food for thought.” MRI (magnetic resonance imaging) is based on the fact that the centres of atoms spin. In MRI, the head is placed into a strong magnetic field which aligns the spinning atoms of the brain. A brief pulse of radio waves is then used to momentarily disorientate them. As they return to their normal spin, such atoms generate signals which, after computer-processing, produce detailed pictures of the soft tissues of the brain. All these techniques have been used to study the brains of schizophrenics and to compare them with those of controls who do not have the illness.

Such technologies have identified abnormalities in those parts of the schizophrenic brain that are related to memory and recognition of speech that are visible by the time an individual has their first psychotic episode. Compared with a control group, magnetic resonance imaging has established that schizophrenics have smaller bilateral hippocampal and left planum temporale volumes. Beyond this, patients with paranoid psychosis have smaller amygdala volumes than those with non paranoid psychosis. Such differences in brain structure and function occur together in the early stages of schizophrenia.<sup>15-16</sup>

Brain scans have also shown that if only one identical twin is schizophrenic, he or she has the larger brain cavities (termed ventricles). In contrast, the thalamus, a control centre that routes brain signals, is smaller than normal in the schizophrenic twin brain.<sup>17-18</sup> Any malfunction in the thalamus may contribute to the overflow of sensory stimulation that is experienced



confirmed that fluid-filled brain ventricles, seen in acute schizophrenics, are enlarged in those with chronic mental illness.<sup>25</sup> The presence of such evidence of brain atrophy in chronic schizophrenia has been linked to levels of the important antioxidant enzyme glutathione peroxidase. The lower the activity level of this enzyme in platelets, the larger such structural brain abnormalities appear to be.<sup>26</sup> There are other malfunctioning organs in schizophrenia besides the brain. Skoliarova<sup>27</sup> has described a series of autopsies that were conducted on schizophrenics within 20 minutes to 5 hours after death. Regardless of the type of schizophrenia involved, there was always a clear visible deterioration of the thyroid gland, rarely seen in other patients. It follows, therefore, that some symptoms seen in chronic schizophrenics must be caused by a malfunction of the thyroid.

## SUMMARY

The decline into schizophrenia begins in the womb, where it is marked by frequent first trimester appearance of minor physical abnormalities, very similar to those seen in fetal alcohol syndrome,<sup>28</sup> such as a webbed fifth finger. Second trimester “mis-wiring” of the fetal brain also often occurs. Births tend to be difficult and prolonged, commonly associated with toxemia and other maternal health problems. Birth weights are typically low. Such abnormalities cannot be solely of genetic origin because there are many recorded cases of only one identical twin being schizophrenic.<sup>29-30</sup> It follows, therefore, that there must be some “trigger” or “triggers” affecting the fetus early in pregnancy, that promotes the future development of schizophrenia. Its impact must be subtle because the anatomical changes seen in this mental illness are relatively minor. Some, however, become more obvious later in life, especially if schizophrenia has become chronic. They then often include a damaged thyroid gland and overdeveloped brain ventricles.

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*The next big step in psychiatry is not likely to come from further refinements of the drugs and psychotherapies that define the field today. It will come, instead, from discoveries about human genetic variations and the ways they affect the brain. Just as eye-opening stories from psychoanalysts' couches guided psychiatry in the first half of the twentieth century, and the products of smelly chemistry laboratories guided it in the second half, so will knowledge about individual genetic differences guide psychiatry over the next fifty years.*

Samuel Barondes, in John Brockman (Ed.),  
*The Next Fifty Years: Science in the  
First Half of the Twenty-First Century*,  
New York: Vintage Books, 2002

## THE GENETIC BASIS OF SCHIZOPHRENIA

*Mind, mind alone,  
Is light, and hope, and life and power.*

Ebenezer Elliott (1833)

Think carefully before you dismiss the dirty, ragged, homeless, bag lady, mumbling incoherently while searching in garbage cans for her next meal. There, but for the Lord's grace, go you and I. God may not play dice with the universe, but every mating is a gamble and every fertilized egg a genetic lottery.

The odds against any one person, picked at random from the general population, being schizophrenic are roughly 1 in 100, a long shot.<sup>1</sup> The odds of any four randomly selected people all being schizophrenics are, therefore,  $100^4$ , that is 1 in 100 million. Nevertheless, all of the identical Genain quadruplets began to suffer from this mental illness in high school and have been in and out of hospitals ever since.<sup>2</sup> These women, of course, shared not only identical genes but also very similar environments. Nevertheless, the Genain family experiences seem to confirm a significant role for genetics in schizophrenia. Not that this evidence was really needed, since a genetic link was established firmly by family and twin studies<sup>3</sup> conducted in Europe during the period 1920 to 1987. Such research showed that relatives of schizophrenics were more likely than normal to develop the disorder, the closer the relationship, the greater the likelihood. According to Myers,<sup>4</sup> the lifetime risk of developing schizophrenia for relatives of a victim of the illness are roughly as follows: grandchildren (5 percent); uncles and aunts (2 percent); half siblings (6 percent); siblings (8 percent);

siblings with one schizophrenic parent (17 percent); children (13 percent); fraternal twins (18 percent); identical twins (48 percent); and the offspring of two schizophrenics (47 percent). Such figures, of course, gave impetus to the eugenics movement that sought to “improve” the human genome by preventing the reproduction of schizophrenics.

Genetics must play a significant role in schizophrenia because 50 percent of patients with this illness in the USA come from families with a history of the disorder.<sup>5</sup> This preponderance cannot be explained by abnormal child rearing since adoption has no impact on the risk of subsequently becoming schizophrenic.<sup>6</sup> There is, beyond a doubt, therefore, a strong genetic component to schizophrenia, but it cannot be as straightforward as the inheritance of certain characteristics such as eye colour, since, as Myers<sup>7</sup> points out, “about half of the twins who share identical genes with a schizophrenic victim do *not* develop the disorder,” one must agree with Nicol and Gottesman’s<sup>8</sup> assessment that some individuals “have a genetic predisposition to the disorder but that this predisposition by itself is not sufficient for the development of schizophrenia.” The schizophrenia gene(s), therefore, is not destiny but it is enhanced risk. In a paper written in *Nature* in 1964, Julian Huxley and his three co-authors<sup>9</sup> argued that the high frequency of schizophrenia found in the general population (roughly 1 percent) could not be maintained by genetic mutation alone, but was evidence of a balanced polymorphism. After all, the fertility of schizophrenics is only about 70 percent of that found in unaffected members of the community.<sup>10</sup> If the schizophrenia trait did not provide some counterbalancing advantage, the number of those suffering from the associated mental illness would decline very rapidly to a much lower level that could be maintained by mutation alone.<sup>11</sup> If true, this means that the high prevalence of the gene(s) partly responsible for schizophrenia can only occur because this trait confers both unfavourable and favourable

properties. When two selective forces oppose one another in this way, the frequency of the two genes stabilize, in what is known as balanced polymorphism.<sup>12</sup> What this would mean in this case is that inheriting the schizophrenia trait in its heterozygous form does not lead to schizophrenia and also carries with it some selective advantage, such as resistance to another disease. Conversely, those inheriting the schizophrenia trait in homozygous form would very likely become mentally ill. This type of trade-off situation occurs with the “sickling” trait which in its heterozygous form gives considerable protection against malaria but in its homozygous form causes deadly sickle cell anaemia.<sup>13</sup>

The argument for balanced polymorphism in schizophrenia makes a great deal of sense and is reviewed in detail in a later chapter. It is, however, currently out of favour with geneticists, most of whom feel that schizophrenia “is not a single disease entity but may reflect common symptomatology caused by several distinct genetic abnormalities.”<sup>14</sup> That is, they are looking for a variety of genetic aberrations, not one key trait. At least two recent papers give detailed overviews of progress to date.<sup>15-16</sup> These references can be consulted for details. The following discussion draws heavily from the article by Sawa and Snyder<sup>17</sup> that appeared in *Science* in April 2002.

One way to simplify the genetic complexity of a disease or disorder is to concentrate on individuals who have an obvious rare inherited form of it. Children who have a deletion of 22q11 suffer from an illness that used to be called velocardiofacial syndrome or DiGeorge syndrome but is now termed 22q deletion syndrome (22qDS). They are characterized by learning disabilities, cardiac defects and hypernasal speech (that is linked to abnormalities in the palate) and have abnormal facial features. Interestingly, 25 to 30 percent of such children become schizophrenic as adults.<sup>18</sup>

There is growing evidence that the gene causing the symptoms of 22qDS, that is DiGeorge syndrome, may be that encoding catechol-O-methyltransferase (COMT), one of the two principal enzymes that degrade catecholamines, such as dopamine.<sup>19</sup> The activity of dopamine in the brain is normally terminated by reuptake by a transporter protein. This protein is relatively inactive in the prefrontal cerebral cortex, suggesting that it is here that catechol-O-methyltransferase has the primary responsibility for the inactivation of dopamine. Mice deprived of the ability to produce catechol-O-methyltransferase tend to confirm this because they develop elevated dopamine levels but only in the prefrontal cortex.<sup>20</sup>

Weinberger and coworkers<sup>21</sup> have examined a common genetic polymorphism of catechol-O-methyltransferase in which valine has been replaced by methionine. The methionine type of this enzyme has only 25 percent of the activity of the valine form. This means that an individual with the Val-COMT allele (coding the valine-catechol-O-methyltransferase form of the enzyme) would be expected to have less dopamine in their prefrontal cortex. It has been found that schizophrenics and their unaffected brothers and sisters who have the Val-COMT allele perform poorly on memory tests, a brain function that depends heavily on the prefrontal cortex. As Sawa and Snyder<sup>22</sup> point out "It is remarkable that COMT [the gene encoding the enzyme catechol-O-methyltransferase], which regulates dopamine, is localized to 22q11 where a microdeletion is associated with a profound increase in susceptibility to schizophrenia." However, Sawa and Snyder may be stretching their point as, according to Kern and Bernards, the enzyme catechol-O-methyltransferase metabolizes epinephrine to the inactive metabolite, metanephrine, not dopamine.<sup>23</sup>

Five recent studies,<sup>24-28</sup> from countries as different as Finland, Wales, the USA, and Israel, have also stated that homozygosity

of a low enzyme activity variant of the catechol-O-methyltransferase (COMT) gene is related to aggression in schizophrenics. Kotler and coworkers,<sup>29</sup> for example, found a significant excess (46.7 percent versus 21.0 percent) homozygosity of this low enzyme activity variant in 30 mostly male (28 out of 30) homicidal schizophrenics in a maximum-security psychiatric facility in Israel, as compared to 415 controls (Pearson chi (2)=10.53, P=0.005, df=2). No such difference in COMT genotype was found between a further 62 non-violent schizophrenics and the same 415 number control group. However, a significant excess (46.7 percent versus 25.8 percent) homozygosity of this low enzyme activity variant was identified when homicidal and nonviolent schizophrenic patients were compared. It seems apparent from these results that the most dangerous group of schizophrenics, specifically those that are homicidal, includes numerous patients with a specific genetic anomaly that influences how catecholamines degrade. Analysis of data from both Finland and the USA<sup>30</sup> further suggests that the same genetic trait is also abnormally common in schizophrenics who commit suicide in a violent manner.

A recent paper by Park and coworkers<sup>31</sup> also tends to confirm that there is an association between genetic polymorphism of catechol-O-methyltransferase and susceptibility to schizophrenia. This study involved comparisons of 103 Korean schizophrenic in-patients and 103 age and sex matched controls. They concluded that:

*... subjects with at least one low activity associated COMT-L allele showed a tendency of elevated risk for schizophrenia (OR = 1.7, 95% CI = 0.9-3.1) compared with those homozygous for the high activity associated COMT-H alleles. Moreover, when cases were stratified by family history of schizophrenia, a significant combined effect was seen: the cases with concurrent family history of schizophrenia and the COMT-L allele*

*containing genotypes had an almost 4 fold (OR = 3.9, 95% CI = 1.1-14.3) higher risk of schizophrenia compared to controls with the COMT-HH genotypes.*

Further evidence of genetic abnormalities in schizophrenia affecting the regulation of catecholamines recently has been provided by Harada and coworkers.<sup>32</sup> These researchers collected DNA samples from 87 unrelated Japanese patients with schizophrenia and 176 controls from the same district, to explore for any association between schizophrenia and polymorphism of the GSTM1 gene. To quote them directly (I have deleted their references):

*The glutathione S-transferases (GST's:EC 2.5.1.18) belong to a family of multifunctional enzymes that catalyze the conjugation reaction between reduced glutathione (GSH) and a variety of xenobiotics including carcinogens, environmental contamination, anti-cancer agents, antibiotics, and products of the oxidative process. Amongst the four major classes of GST's ( $\alpha$ ,  $\mu$ ,  $\pi$ ,  $\theta$ ), the  $\mu$  class GSTM1 and the  $\theta$  class GSTT1 display significant polymorphism, including an absence of the gene. The human  $\mu$ -class GST's assigned to Chromosome 1p13.3 are subgrouped into GSTM1, M2, M3, M4, and M5. Recent experimental evidence have indicated that GST1 and M2 classes catalyze a glutathione conjugate of catecholamine o-quinones, including aminochrome, dopachrome, adrenochrome and noradrenochrome under physiological conditions. GSTM2 displays stronger activity for dopachrome and noradrenochrome than GSTM1, and in contrast, GSTM1 displays catalytic activity of adrenochrome at levels 1.5 times greater than GSTM2, and the remaining classes of GST's ( $\alpha$ ,  $\pi$ ,  $\theta$ ) possess very low or negative catalytic activity for all o-quinones.*

Harada and colleagues<sup>33</sup> analyses of DNA from the 87 schizophrenics and 176 controls clearly established that an abnormal form of GSTM1 was much more common in schizophrenics than in those without the disorder. Specifically:

*The frequency of the GSTM1\*0 allele was significantly higher amongst the patients with schizophrenia compared to controls ( $P = 0.00075$ ). Moreover, the incidence of the GSTM1\*0 was significantly higher amongst the schizophrenic patients classified as disorganized type ( $P = 0.0008$ ), relative to the control sample. Our findings suggest that the GSTM1\*0 is associated with an increased susceptibility to schizophrenia, particularly disorganized type of the disease. It is therefore likely that the GSTM1 gene deletion constitutes to vulnerability for disease states of this kind, rather than being the direct cause of schizophrenic conditions.*

The evidence from Japan, therefore, strongly suggests that abnormalities in the gene coding for glutathione S-transferase which is involved in the regulation of the catecholamines, particularly adrenochrome, appears to play a significant role in schizophrenia.

There may be other genetic aberrations in schizophrenia, though the evidence is still contradictory. Methylenetetrahydrofolate reductase (MTHFR) catalyzes the conversion of 5,10-methylene THF to 5-methylTHF.<sup>34</sup> The latter substance is the major type of circulatory folate and the predominant carbon donor for the remethylation of homocysteine to methionine. Patients who are severely deficient in MTHFR suffer from developmental delay, motor and gait dysfunction, seizures, and schizophrenic episodes and other neurological abnormalities. Many such problems are probably the consequence of elevated homocysteine,<sup>35</sup> although abnormally low MTHFR activity can also cause depressed levels of circulatory folate, and lower availability of methionine.

The gene for MTHFR is located on chromosome 1 at 1p36.3. Most of the allelic variants discovered to date are rare and cause severe MTHFR deficiency resulting in homocystinuria. Two

alleles, however, C677T and A1298C, are common variants that are not associated with homocystinuria.<sup>36</sup> Arinami and coworkers<sup>37</sup> examined the possibility of a role for C677T polymorphism in MTHFR in schizophrenia, major depression, and bipolar disorder. The TT variant was found to occur in 12 percent of 419 controls, 21 percent of 297 schizophrenics ( $P < 0.0006$ ;  $P < 0.002$  after Bonferroni correction), 28 percent of 32 patients with severe depression ( $P < 0.02$ ), and a statistically insignificant 13 percent of bipolar disorder cases. Regland and coworkers<sup>38</sup> also screened 11 schizophrenics with high homocysteine levels to see if they carried C677T. Seven of these patients were found to be homozygous for C677TT. Another male patient was heterozygous.

Similarly, Deng and colleagues<sup>39</sup> have reported that MTHFR C677T is more common in Chinese families that have a member that developed schizophrenia before reaching 25 years of age. Beyond this, Joobar and colleagues<sup>40</sup> have shown that the C677TT variant of this gene is more common than expected in those schizophrenics who respond well to neuroleptics.

Taken as a whole, the evidence seems to suggest that some schizophrenics have a variant of the MTHFR gene that reduces their ability to metabolize homocysteine effectively. Nevertheless, there have been negative studies<sup>41-42</sup> that have not found this variant overrepresented in a sample of schizophrenics and the issue is not settled.

Evidence has been put forward recently for a fourth genetic aberration in many schizophrenics. Novak and coworkers<sup>43</sup> from the University of Toronto studied post-mortem frontal cerebral cortices from 81 schizophrenics and from a control group of 61. They discovered that 17 out of 81 schizophrenics had inherited an unusual Nogo (reticulon 4, RTN4 or RTN-X) variant gene from both parents. In contrast, only 3 percent of

the control group were homozygous for this genetic variant. Nogo did not seem linked to schizophrenia if heterozygous, that is if the variant was inherited from only one parent.

One of the functions of the Nogo gene is to produce proteins that inhibit growth of brain nerve endings.<sup>44</sup> The variant gene, found to be more common in schizophrenics, has three extra chemical bases, known as CAA, in a region where protein production is regulated. It is possible that these extra CAA bases cause the variant Nogo gene to overproduce proteins, reducing the number of nerve endings in regions of the brain associated with schizophrenia. This, of course, might make it more susceptible to damage from toxins.

## SUMMARY

Is schizophrenia genetic? Are genes destiny? The truth appears to be that certain genetic aberrations, especially those which cause abnormalities in the degradation of catecholamine neurotransmitters, seem likely to increase the risk of developing schizophrenia. However, there are strong lines of evidence that prove schizophrenia is more than just the injustice of genetic inheritance. From the middle of the 19th century to the middle of the 20th, in the Developed World the majority of schizophrenics were confined to mental asylums for most of their reproductive years. Suicide rates amongst them were much higher than in the normal population and many were sterilized in the name of eugenics. As a result, their rates of procreation were very low and so the transmission of any “schizophrenic genetic trait” to the next generation occurred infrequently. Nevertheless, at exactly the same time, as Torrey and Miller<sup>43</sup> have shown, schizophrenic prevalence in the Developed World continued to rise steadily. Indeed, “the epidemic of insanity that has occurred over the past two centuries is a

strong argument against these diseases [schizophrenia and manic-depression] being primarily genetic in origin.” Then again, as in sickle cell anaemia, the schizophrenic trait may be a balanced polymorphism, so that despite its obvious disadvantages, it carries with it huge, as yet unappreciated, social benefits.<sup>44</sup>

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*There are no final answers in science, only varying degrees of probability.... Science is not the affirmation of a set of beliefs but a process of inquiry aimed at building a testable body of knowledge constantly open to rejection or confirmation. In science, knowledge is fluid and certainty fleeting. That is at the heart of its limitations. It is also its greatest strength.*

Michael Shermer, *Why People Believe Weird Things*,  
New York: Henry Holt and Co., 2002

*While a more subtle and quiet offence which may pass unnoticed in the historical moment, ideocide is ultimately, in its continually expansive accumulative enormity, a far more pernicious crime against all humanity than any “simple” genocide.*

Stuart Troy<sup>1</sup>

We had just agreed to give the student her master's degree. The tension in the examination room had receded and the committee members began to chat. “It just goes to show,” said the biochemist, “that health in the end always boils down to biochemistry.” Being a geographer, I was sure he was mistaken. In the end, everything is spatial and if you cannot explain this distribution pattern you have accounted for nothing. In a mellow mood, I let his comment pass unchallenged. It's probably just as well that I did because, after considerable reflection, I decided that he may well be right. After all, pathogens cause abnormalities in biochemistry, and so too do toxins. Genetic aberrations result in biochemical abnormalities and so too does trauma. Vitamin, mineral, and other nutrient deficiencies and excesses correct or interfere with normal biochemical activity. Drugs, herbs, and supplements attempt to reverse biochemical imbalances, while even stress and exercise impact on the body's biochemistry. Clearly, if we don't know or cannot explain the abnormal biochemistry of schizophrenia, how can we identify its causes?

## THYROID HORMONES

Federal health officials are seriously considering giving potassium iodide pills to every Canadian living within 10 kilometres of a nuclear power plant.<sup>2</sup> Potassium iodide pills are used to flood the thyroid gland, so preventing it from absorbing iodine 131, a radioactive isotope released in large quantities during nuclear power plant disasters. An interesting development, but what does it have to do with schizophrenia? Fetuses irradiated by the exploding atomic bomb dropped on Nagasaki City subsequently developed a higher than normal prevalence of schizophrenia.<sup>3</sup> This illness was more common in those exposed in their second trimester than in their third. The closer pregnant women were to the hypocentre of this exploding atomic weapon, the higher the subsequent prevalence rate of schizophrenia in their offspring. A similar phenomenon can be seen in the Ukraine, amongst those most affected by the Chernobyl nuclear power plant disaster.<sup>5-6</sup> Survivors from the permanently evacuated Exclusion Zone and clean-up workers who entered it now have a schizophrenia incidence rate that is about five times as high as that of less irradiated Ukrainians (5.4 per 10,000 in Exclusion Zone workers and evacuees compared to 1.1 per 10,000 in the Ukraine in 1990). Those exposed to radiation levels of 0.30 sievert or more have the highest risk of subsequently developing schizophrenia.<sup>7</sup> These observations strongly suggest a role for a malfunctioning thyroid gland in schizophrenia, a possibility that has been confirmed by the direct measurement of thyroid hormones in schizophrenics. Thyroid gland problems may also have a genetic dimension since De Lisi and coworkers<sup>8</sup> have shown that thyroid disorders are unusually common in the relatives of schizophrenics.

There is little doubt of abnormal thyroid function in schizophrenia although this appears to change as the illness progresses. In the early acute stage, thyroxine (T4) levels are elevated but

there is some disagreement over whether, or not, the same can be said of triiodothyronine (T3). Roca and coworkers,<sup>9</sup> for example, took serial measurements of various thyroid hormone-related indices from 45 acute hospitalized psychiatric patients. These showed that thyroxine, the free thyroxine index, triiodothyronine, and the free triiodothyronine index are often elevated in psychiatric inpatients, especially early in hospitalization, and that the levels of thyroid hormones are strongly correlated with severity of psychiatric symptomatology. Simply put, elevated thyroid hormones are common amongst those recently hospitalized with acute psychiatric problems and the more elevated these hormones are, the worse the patients' symptoms. A similar study was conducted by Baumgartner and colleagues<sup>10</sup> on 63 schizophrenic patients, some of whom were in remission. These researchers concluded that the serum levels of thyroxine (T4) in acutely ill schizophrenic patients were elevated, but those of triiodothyronine (T3), reverse triiodothyronine (rT3), and thyrotrophin (TSH) were normal.

The situation in chronic schizophrenics, those "permanently" hospitalized, appears somewhat different. Othman and coworkers<sup>11</sup> examined the thyroid status of 249 chronic male and female schizophrenics who had been hospitalized for an average of 10 years. They discovered a wide range of abnormalities, including thyroid antibodies in 20 percent of such schizophrenics and elevated or depressed thyroid stimulating hormone (TSH) in 22 percent. Depressed triiodothyronine also occurred in 23 percent of those patients with normal levels of TSH. These data led Othman and colleagues to conclude that "there is a spectrum of thyroid function test abnormalities in chronic schizophrenia." These results seem to be consistent with the work of Turianitsa and colleagues<sup>12</sup> who carried out radioimmunoassays of the pituitary-thyroid systems of patients suffering from various types of schizophrenia, identifying an enhanced degregation of peripheral blood thyroxine and an excess of

metabolically active triiodothyronine. In a further study, Rao and coworkers<sup>13</sup> compared the basal serum amino acids, central monoamines, and hormone levels in 110 schizophrenic patients with those of 90 healthy controls. They found that in drug-free schizophrenics, dopamine levels were elevated and melatonin and thyroid hormones were depressed. They concluded it was dopaminergic overactivity in such schizophrenics that was lowering both melatonin and thyroid hormone levels.

## Niacin

Orthomolecular psychiatrists such as Abram Hoffer<sup>14</sup> have known since the early 1950s that schizophrenics typically are deficient in vitamin B3. Vitamin B3 refers to nicotinic acid and nicotinamide, more often called niacin and niacinamide by physicians. Both are precursors to nicotinamide adenine dinucleotide (NAD), an active coenzyme in the human body. Although niacin and niacinamide share similar properties, niacin is a vasodilator and niacinamide is not. This means that when a healthy person takes a medicinal dose of niacin (approximately 3 grams), they begin to flush strongly. This reddening is accompanied by sensations of both itching and heat because niacin opens the skin's capillaries and increases the blood flow.

The majority of schizophrenics receiving niacin do not flush. This may be because they are extremely niacin deficient or because their flushing mechanism is disabled. More recently, conventional physicians have begun to confirm that schizophrenics respond to niacin in a far more subdued way than individuals without a family history of mental illness. Ward and coworkers,<sup>15</sup> for example, tested the skin flushing of 38 schizophrenics and 22 normal controls, five minutes after the application of aqueous methyl nicotinate (AMN). It was found that 83 percent of the schizophrenics, but only 23 percent of

the controls, had little or no reaction to this solution. Several other researchers<sup>16-17</sup> have demonstrated such differences. As a result, the degree of skin redness after a niacin challenge is now the basis for a diagnostic patch test which has been developed by Horrobin.<sup>18</sup> When available to family physicians, this will allow them to diagnose acute schizophrenia with the accuracy now achieved by a team of highly trained psychiatrists.

### “Kryptopyrrole”

In 1960, the hallucinogenic drug LSD was being used to treat alcoholics.<sup>19</sup> Hoffer realized that this protocol was causing alcoholics to hallucinate in a manner similar to many schizophrenics. This coincidence led him to believe that LSD use might be triggering biochemical imbalances in alcoholics similar to those seen in schizophrenia. To test this hypothesis, urine samples were collected from alcoholic patients before and after receiving therapeutic doses of LSD.<sup>20</sup> Urine from the first of these patients showed a mauve staining spot on the paper chromatogram after development with Ehrlich’s reagent. Such a mauve spot did not appear in tests of the urine from alcoholics before they were given LSD, but it appeared in tests of the urine of many, but not all of them, after taking this drug. Schizophrenic patients’ urine was then tested in the same way. The characteristic mauve stain also appeared on the chromatogram paper for many, but again not all, of the samples from these patients. The mauve factor was structurally identified in 1969 by Irvine,<sup>21</sup> and is now thought to be 2-hydroxy-hemopyrrolene-5-one.<sup>22</sup> As it circulates in the body it “forms a stable Schiff’s base with pyridoxal (the aldehyde form of pyridoxine or vitamin B-6) and subsequently complexes with zinc, stripping the body of these two essential substances as it is excreted.”<sup>23</sup> As a result of these reactions, schizophrenics producing large quantities of it are simultaneously also very zinc and vitamin B-6 deficient.<sup>24</sup>

Just how common is elevated “kryptopyrrole” in schizophrenia? In 1965, O’Reilly and Hughes<sup>25</sup> claimed that it was present in 11 percent of healthy controls, 24 percent of disturbed children, 42 percent of psychiatric patients, and 52 percent of schizophrenics. Hoffer’s<sup>26</sup> experience after testing a much larger sample consisting of “thousands of patients at our four research centers” was somewhat different. Elevated “kryptopyrrole” was found in the urine of 75 percent of acute schizophrenics, 25 percent of all non-psychotic patients, and 5 percent of physically ill patients. It was absent from the urine of normal subjects and most interestingly was never found in the urine of recovered schizophrenics. The evidence suggests that although urinary “kryptopyrrole” (probably 2-hydroxy-hemopyrrolene-5-one) is not an absolute sign of schizophrenia, it occurs with much greater regularity in schizophrenics than in anyone else.

### Glutathione Peroxidase and Antioxidant Defence System

The brains of chronic schizophrenics often display enlarged fluid-filled spaces known as ventricles.<sup>27</sup> These are signs of brain atrophy and are highly suggestive of neuronal tissue damage. In 1987, Buckman and colleagues<sup>28</sup> published a paper that described using computed tomography scans to measure these ventricles and establish ventricle-brain ratios. Such ratios were then compared to the activity of the important antioxidant selenoenzyme glutathione peroxidase in blood samples taken from both chronic schizophrenics and age and sex-matched nonschizophrenic mental patients. Buckman and coworkers were able to show that in chronic schizophrenics, but not in patients suffering from other mental illnesses, there was a strong negative correlation between glutathione peroxidase activity in both isolated platelets and erythrocytes and computed tomography scan measures of brain atrophy and associated increased ventricle-brain ratios. In short, the less of the selenoenzyme glutathione peroxidase in the blood of a

chronic schizophrenic, the greater the brain damage suffered. These relationships were not found in the control group and suggested a unique relationship between levels of glutathione peroxidase (and hence one of its key components selenium), and the mechanism responsible for tissue damage in the brains of schizophrenics.

In the period since this paper was published, several other researchers have presented evidence to confirm that there is an impaired antioxidant defence system in schizophrenia that is associated with excessive lipid peroxidation and abnormal free radical pathology.<sup>29-34</sup> Mahadik and coworkers,<sup>35</sup> for example, have shown that elevated lipid peroxides, indicative of an abnormal antioxidant defence system, are characteristic of first episode, never-medicated schizophrenics. This analysis, involving 26 patients and 16 normal controls, demonstrates that the antioxidant defences of schizophrenics are in disarray as early as the appearance of the first significant symptoms. The work of Buckman and colleagues<sup>36-37</sup> has suggested that these inadequacies of the antioxidant defence system continue and ultimately result in serious brain damage in chronic schizophrenics.

While several studies have shown abnormal glutathione peroxidase activity in schizophrenics, problems with other antioxidant enzymes have also been reported, including abnormal catalase and superoxide dismutase activity.<sup>38-40</sup> Why schizophrenics suffer from the excess generation of free radicals, disrupted antioxidant defences, and associated brain damage is uncertain. Mahedik and Mukherjee<sup>41</sup> cautiously suggest that it may result from increased catecholamine turnover. In an interesting, comprehensive review of oxidative reactions and schizophrenia, Smythies agrees with the suggestion that some of this excessive lipid peroxidation is caused by excess adrenochrome.<sup>42</sup>

## Essential Fatty Acids

When phospholipids (highly complex lipids that are essential to brain function) were extracted from the plasma of schizophrenics and compared with those of controls, two abnormalities became apparent. The n-6 essential fatty acid levels were significantly reduced in schizophrenia, while those of the n-3 essential fatty acids were elevated.<sup>43</sup> More recently, membrane phospholipid abnormalities have been confirmed in the postmortem brains of schizophrenics using high-pressure liquid chromatography in conjunction with an evaporative light-scattering detector.<sup>44</sup> This technique showed that the membranes of schizophrenics contained depressed levels of phosphatidylcholine and phosphatidylethanolamine. In addition, levels of polyunsaturated fatty acid were determined utilizing capillary gas chromatography. These were found to be abnormally low in schizophrenic brains, relative to control brains. Particularly noticeable was a large decrease in arachidonic acid.

Interestingly, these abnormalities may be at least partially corrected by diet. Peet and coworkers,<sup>45</sup> for example, have shown that n-3 fatty acid supplements appear to improve schizophrenic symptoms. Similarly, on a larger scale, it has been demonstrated that eicosapentaenoic acid (EPA) supplements have a similar positive impact on these fatty acid abnormalities and, as a consequence, on patients suffering from schizophrenia.<sup>46-47</sup>

Horrobin,<sup>48</sup> who has been the major instigator of research into the role of abnormalities in fatty acid metabolism in schizophrenia, has recently described the current situation.

*We are still developing our understanding of the details of errors in biochemistry. But gradually a consensus is developing that there are two important*

*problems in phospholipid biochemistry in schizophrenia. One relates to a chronic overactivity of one or more of the phospholipase A<sub>2</sub> group of enzymes. This leads to a steady leak of AA [arachidonic acid] and other fatty acids from cell membranes, not leaving sufficient AA behind to mount a normal cell-signalling response to stimulation. The second relates to a failure to incorporate AA and related fatty acids back into phospholipids. The problem may be in one of a group of enzymes called FACL, the absence of one of which can lead to Alport syndrome. As a consequence of these two abnormalities, brain HUFAs [highly unsaturated fatty acids] are readily oxidized, and the breakdown products, which are volatile, are excreted in the breath.*

## Tryptophan and Serotonin

Tryptophan is the least abundant of the essential amino acids in food,<sup>49</sup> a characteristic that in the past has led to major mental health problems. Maize is deficient in tryptophan, and children eating a diet that was overly rich in it often developed pellagra. The symptoms of this disease were known as the four Ds, namely dermatitis, diarrhea, dementia, and ultimately, if not treated effectively, death.<sup>50</sup> Pellagra is thought to be due to a codeficiency of both tryptophan and its metabolite niacin.<sup>51</sup> As a result of eating too much maize, children became deficient in both of these nutrients and so could not produce adequate nicotinamide adenine dinucleotide, triggering the development of pellagra. Clearly then, inadequate dietary tryptophan can cause serious mental illness.

Tryptophan is also a necessary precursor of serotonin. Anyone with depressed levels of this essential amino acid, therefore, is always deficient in serotonin. As the author<sup>52</sup> has described in his book *What Really Causes AIDS*, whole blood serotonin levels are abnormally low in AIDS patients. This is

because HIV-1, as it is replicated, removes tryptophan from the human body. Interestingly, the lower the blood tryptophan and serotonin levels in AIDS victims, the worse their associated neuropsychiatric symptoms.<sup>53</sup>

There definitely appear to be tryptophan associated abnormalities in schizophrenia. Mileikovskii<sup>54</sup> found depressed serotonin levels in the urine of 30 Russian schizophrenics, while Ravikumar and coworkers<sup>55</sup> identified elevated tryptophan and its derivative serotonin in the plasma of Indian neuropsychiatric patients. Indeed, Lucca and colleagues<sup>56</sup> considered brain tryptophan in Italian schizophrenics to be so abnormal that it could be used to distinguish them from patients with severe depression.

At least two attempts<sup>57-58</sup> have been made to study the impact of depressed tryptophan and its derivatives niacin and serotonin in schizophrenics by deliberately reducing the levels of this amino acid in diet. The results suggest that low tryptophan diets cause a significant increase in the severity of negative symptoms in schizophrenia<sup>59</sup> that may be accompanied by a decline in cognition.<sup>60</sup>

These results are not too surprising due to the fact that the tryptophan derivative serotonin is a neurotransmitter associated with 5-HT receptors.<sup>61</sup> Abnormalities of such brain serotonin receptors have been discovered by post-mortem studies of unmedicated schizophrenics.<sup>62</sup> There is a decreased number of 5-HT<sub>2A</sub> receptors and an increased number of 5-HT<sub>1A</sub> receptors in the frontal cortex of brains of untreated schizophrenics. These abnormalities do not occur in young unmedicated patients, suggesting that they develop over a period of time as a consequence of serotonin abnormalities.<sup>63</sup> Interestingly, the hallucinogenic drug LSD has been found to be a 5-HT agonist, increasing its effects.<sup>64</sup>

## Histamine

According to Pfeiffer,<sup>65</sup> some 70 percent of all schizophrenics suffer from histamine imbalances. Fifty percent are thought to display an excess of copper and depressed blood histamine, while the remaining 20 percent have symptoms caused by a histamine excess and depressed blood copper levels. Such relationships appear to be biochemically logical. Histamine is a neurotransmitter and chemical modulator that is regulated by histaminase and ceruloplasmin, two copper-containing proteins. Pfeiffer and colleagues<sup>66</sup> argued that high levels of free copper in the body increases the activity of these two enzymes, causing excess degradation of histamine. This deficiency is, in turn, thought to be responsible for some of the psychiatric problems seen in a large subgroup of schizophrenics. Conversely, a copper deficiency reduces histaminase and ceruloplasmin levels and activity, creating an excess of histamine, which in itself has adverse psychiatric implications.

There is no doubt that histamine does have significant functions in the brain. It is associated with wakefulness, the suppression of seizures, hypothermia, and emesis.<sup>67</sup> It has been found that drugs that are antagonistic to it and so interfere with HI (histamine) receptors, modify eating and drinking patterns, alter endocrine secretions from the pituitary gland, and increase opioid-induced insensitivity to pain. Histamine also plays a role in cognition and arousal.<sup>68</sup>

There is mounting evidence that Pfeiffer<sup>69</sup> is correct in that many schizophrenics display histamine abnormalities. Lipman and Telias,<sup>70</sup> for example, tested the skin of long-term, hospitalized schizophrenics who had not responded favourably to conventional therapy with histamine. All of these chronic schizophrenics smoked or had been passively exposed to the smoke of others. Such patients were found to be very sensitive to the

histamine intracutaneous test. A healthy control group of non-smokers was not. Prell and coworkers<sup>71</sup> further analysed the levels of histamine metabolites in the cerebrospinal fluid of 36 chronic hospitalized schizophrenics and eight healthy controls. They found that the mean level of the key histamine metabolite tele-methylhistamine was 2.6-fold higher ( $p=0.006$ ) in schizophrenics than it was in controls. Twenty-six of such chronic psychiatric patients showed elevated levels of this metabolite that were higher than any seen in the control group. Such elevated histamine metabolite levels could not be attributed to medication, since they were very similar in schizophrenics taking and withdrawn from neuroleptic drugs. Prell and colleagues<sup>72</sup> also have shown that high levels of this primary histamine metabolite, an index of brain histaminergic activity, seems to be strongly associated with excess daily urine production, suggesting a role for histamine in fluid regulation.

The levels of the copper-containing enzyme histaminase, which is involved in the regulation of histamine, also has been measured in schizophrenics. Vieira and colleagues,<sup>73</sup> for example, analysed the activity of histaminase in the plasma of 23 schizophrenics and compared it with 32 healthy controls. They discovered that plasmatic histaminase was significantly higher in schizophrenics, especially in those they termed “non mentally deteriorated” and those with thymic symptoms.

## Glutamate

Glutamate imbalance may also play a role in schizophrenia. Faustman and coworkers,<sup>74</sup> for example, compared the levels of glutamate in the cerebrospinal fluid of 19 medication free male schizophrenics, or schizoaffective patients, with their clinical symptoms. Ratings of positive symptoms were significantly inversely related to glutamate levels, while hallucinatory behaviour was strongly positively linked to it. That is, higher

glutamate seemed related to more pronounced schizophrenia. Interestingly, kynurenic acid, an endogenous glutamate antagonist, is also highly elevated in the cerebrospinal fluid of schizophrenics.<sup>75</sup> This antagonist has a preferential action at the glycine-site of the N-methyl-D-aspartate receptor (a subtype of glutamate brain receptor).

Glutamate is essential but dangerous, a neurotransmitter that can be cytotoxic at high levels. It is clearly necessary for normal brain function since when healthy individuals are given its antagonists phencyclidine<sup>76</sup> or ketamine<sup>77</sup> they develop a psychosis that is very similar to schizophrenia. In contrast, the N-methyl-D-aspartate antagonist amantadine greatly improves the symptoms of catatonic schizophrenics. Viewed as a whole, the schizophrenia-glutamate biochemical evidence seems to suggest an excess of this excitatory amino acid neurotransmitter in this illness. This excess may be linked to a decrease in the non-N-methyl-D-aspartate subtypes of glutamate receptors in the medial temporal lobe.<sup>79</sup>

## Catecholamines

There are several reasons why schizophrenics are thought to be suffering the effects of too much dopamine. To illustrate, drugs that are designed to lower brain dopamine levels reduce some of the symptoms in schizophrenia. Others, like amphetamines that are known to increase brain dopamine, conversely worsen symptoms.<sup>80</sup> In addition, as previously discussed, there is considerable evidence of dopamine receptor abnormalities in schizophrenic brains.<sup>81</sup> One would expect, therefore, that the cerebrospinal fluid of schizophrenics would contain highly elevated levels of dopamine. Interestingly, this has been hard to establish. Issa and colleagues<sup>82</sup> simultaneously measured the levels of 20 biogenic amines, their metabolites and other compounds from 24 medication-free schizophrenics and 12 healthy

controls. This approach allowed the study of interactions between metabolites of each of the three major neurotransmitter pathways (serotonergic, noradrenergic, and dopaminergic). Statistical analysis (stepwise discriminant function analysis) comparing the cerebrospinal fluid of schizophrenics with that of healthy volunteers showed the major differences between these two groups involved levels of tryptophan (and its derivative tryptophol) and epinephrine but not dopamine.

Although there are studies<sup>83</sup> suggesting that the metabolite of dopamine, homovanillic acid, is elevated in the cerebrospinal fluid of schizophrenics, this may not be the case. Tuckwell and Koziol<sup>84</sup> conducted a meta-analysis of research results available in 1993 and concluded that “the data does not support the claim that the level of this dopamine catabolite is raised whereas some evidence strongly supports the claim that it is actually lowered.” In summary, as Yamamoto and colleagues<sup>85</sup> have pointed out: “In spite of extensive studies over the last two decades to find direct evidence in support of the dopamine hypothesis of schizophrenia, no undisputed experiential data has been obtained. In contrast, estimation of noradrenalin (another major catecholamine) and its metabolites in post-mortem brain and in the cerebrospinal fluid appears to be producing consistent results.”

## Homocysteine

The essential amino acid methionine is the indirect source of homocysteine. As methionine is metabolized by the body it produces homocysteine before either recycling it to methionine, or creating a final breakdown product, cystathionine. The former step requires vitamin B12 and folate and the latter requires vitamin B6.<sup>86</sup> Inadequacies of these key vitamins can slow homocysteine metabolism and allow abnormal levels of it to build up, creating a condition known as homocysteinemia,

associated with atherosclerosis,<sup>87</sup> strokes,<sup>88</sup> and cardiovascular disease.<sup>89</sup> Beyond this, it is well known that the oxidation product of homocysteine, homocysteic acid, exerts potent excitatory effects.<sup>90</sup>

As might be expected, therefore, evidence is growing that many schizophrenics suffer from elevated homocysteine levels.<sup>91-93</sup> Regland and coworkers<sup>94</sup> point out that numerous schizophrenics display high homocysteine levels that seem unrelated to psychopharmacological medication or to nutrient deficiency in folate or cobalamin. They believe, therefore, that this excess of homocysteine in schizophrenia must be related to an inherent methylation deficiency. It also seems linked to aggressive and antisocial behaviour.<sup>95</sup>

## SUMMARY

For centuries, the British aristocracy hunted for grouse and pheasants using cartridges filled with lead bird shot. This ammunition created an expanding circle of small pellets, each of which was capable of causing a fatal wound. Schizophrenia may be like this. It is possible, but unlikely, that each one, or most, of the biochemical abnormalities just described is linked to its own distinct genetic aberration or environmental trigger.

A display in the Guinness World Records Museum<sup>96</sup> shows that 60 Dutch students spent 7 weeks setting up 2.3 million dominoes at the Expo Centrum FEC in Leeuwarden. On August 28, 1998, the first domino was deliberately pushed over to trigger the fall of 1,605,757 more. This event was an extreme display of the domino effect. Schizophrenia may be another. It is possible that the numerous biochemical abnormalities just described may be linked in a chain of cause and effect. If this is the case, a single genetic aberration may result in one initial



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*Canst thou not minister to a mind diseased;  
Pluck from the memory a rooted sorrow;  
Raze out the written troubles of the brain;  
And, with some sweet oblivious antidote,  
Cleanse the stuffed bosom of that perilous stuff  
Which weighs upon the heart?*

William Shakespeare, *Macbeth*

*The most common diseases are the toughest to crack. Heart disease, cancer, diabetes, psychiatric illness: all of these are “complex” or “multi factorial” diseases, meaning that they cannot be ascribed to mutations in a single gene or to a single environmental factor. Rather they arise from the combined action of many genes, environmental factors, and risk-conferring behaviours. One of the greatest challenges facing biomedical researchers today is to sort out how these contributing factors interact in a way that translates into effective strategies for disease diagnosis, prevention, and therapy.*

P. Kiberstis and L. Roberts<sup>1</sup>

The very slow speed with which reproduction is able to modify the human genome ensures that epidemics cannot be driven by genetic change. Despite this, each of the five countries studied in detail by Torrey and Miller<sup>2</sup> had experienced steadily increasing schizophrenia prevalence rates for some two centuries or more. This slow but steady rise in the number of schizophrenics proves, beyond any reasonable doubt, that there must be more to this psychiatric illness than genetic mutation alone. However, identical twin studies<sup>3</sup> show that there has to be a very strong genetic dimension to schizophrenia. After all, the identical twin of a schizophrenic has roughly a 50-50 chance of developing this illness, even if reared apart from his or her sibling.<sup>4</sup> Nevertheless, it is just as true that these same statistics prove that half of the identical twins that “share” their genes

with a schizophrenic brother or sister never suffer from the illness. As Nicol and Gottesman<sup>5</sup> point out, the available evidence, therefore, shows that some members of the population must “have a genetic predisposition to the disorder but that this predisposition by itself is not sufficient for the development of schizophrenia.” Simply put, for genetic reasons some people have a higher than normal probability of becoming schizophrenics. Whether they do so, however, depends upon being exposed to some trigger or triggers. It is not yet agreed what such initiator(s) may be, but the steady increase in the prevalence of schizophrenia over the past 250 years<sup>6</sup> strongly suggests that exposure is becoming more common.

## GEOGRAPHICAL CONTRIBUTIONS—INTERNATIONAL

Numerous academic and clinical avenues have been used in attempts to identify what it is that triggers schizophrenia in genetically susceptible individuals. One of these approaches has been to study the genetic-trigger relationship geographically, since if the incidence and/or prevalence of schizophrenia can be shown to vary markedly from place to place, so too must their trigger(s).

A great deal can be learned about schizophrenia by studying its distribution patterns. This illness is still quite uncommon in parts of the Developing World, but as countries industrialize there is often a sharp accompanying increase in schizophrenia. Even so, prevalence rates still display at least an eight-fold difference among industrialized nations.<sup>7</sup> The highest number of schizophrenics per 100 population are found in Ireland, Scandinavia (especially parts of northern Sweden), and in Eastern Europe (particularly in Croatia). In parts of Western Ireland, for example, 4 out of 100 people will be afflicted with it during their lifetime. Intermediate prevalence rates for schizophrenia

can be found in England, Germany, Japan, and the USA. In the USA, for example, approximately 1 out of every 100 inhabitants will eventually develop this mental disorder. Southern Europe clearly has significantly lower prevalence rates but poor data collection makes it difficult to establish them accurately. This is also true of the Developing World although Field<sup>8</sup> identified 41 schizophrenics during a survey of 4,283 Ashanti people in southern Ghana. This would suggest a schizophrenia prevalence rate of about 4 per 1,000, roughly one-tenth that of the worst affected parts of Ireland.

There is growing evidence to suggest that such global spatial variations in numbers of schizophrenics in populations of similar size may be more of a reflection of rates of recovery than incidence. That is, there seems to be less variation in the incidence of schizophrenia than in its prevalence because patients from non-literate, rural societies recover from this illness far faster than those living in urban communities. Evidence supporting such rural-urban differences in the speed with which schizophrenics often recover has been reported in South Africa,<sup>9</sup> Nigeria,<sup>10</sup> Mauritius,<sup>11</sup> Sri Lanka,<sup>12</sup> and Taiwan.<sup>13</sup> It is not logical to argue that these differences are just a question of diagnosis. An *International Pilot Study of Schizophrenia*, coordinated by the World Health Organization, diagnosed patients using identical criteria in both developing nations (Columbia, India, and Nigeria) and developed countries (Denmark, England, the Soviet Union, Czechoslovakia, and the USA).<sup>14</sup> The initial 2-year follow-up of such schizophrenia patients showed considerably better outcomes in those from the Developing World. This negative relationship between schizophrenia and degree of industrial development was again confirmed by Jablensky and Sartorius.<sup>15</sup> There are many reasons why such a relationship may exist. Templer and Veleber,<sup>16</sup> for example, studied schizophrenia prevalence rates and diet in 18 countries, establishing quite marked product moment correlation coefficients

between this illness and the consumption of both wheat (0.38,  $O=0.06$ ) and milk (0.58,  $p=0.01$ ). Their research suggested that schizophrenia was more common in countries where wheat and milk formed a significant part of the diet. This concept was not new since Dohan<sup>17-18</sup> had been arguing for many years that allergies to milk and grains were involved in schizophrenia. This is interesting since Reading and Meillon<sup>19</sup> have proposed that susceptibility to milk and wheat allergies are inherited, a fact that could be used to account for the proneness of certain families to specific diseases, including schizophrenia.

### GEOGRAPHICAL CONTRIBUTIONS—NATIONAL

The most comprehensive national study of variables in the prevalence of schizophrenia was undertaken by this author<sup>20</sup> in the mid 1980s. Information was collected from the literature for 219 variables at the state scale for the conterminous United States. These variables included levels of 35 elements in soils and surface sediments and air and water pollutants, together with the frequencies of numerous social, industrial, commercial, and agricultural activities. Anyone interested in the original sources of this information is directed to two previous books on health and the environment published by the author.<sup>21-22</sup>

If the trigger(s) for schizophrenia is environmental, both it and the illness it promotes must vary spatially together. To explore this possibility, health data, collected during the same time period, for identical areas, was also needed. The best sources of information on the geographical distribution of schizophrenia in the USA are the annual surveys of *Patients in Mental Institutions*, conducted by the Biometry Branch of the Office of Program Planning and Evaluation, National Institute of Mental Health.<sup>23</sup> These volumes enumerate patients in state and county mental hospitals that provide psychiatric care. Since much of

the environmental information had been collected in the 1960s, it was decided to use medical data from 1965. Unfortunately, information from state and country mental institutions was not compatible with that from private and general hospitals. Whilst details of the number of patients being treated for schizophrenic reactions at the end of 1965 were given for 272 state and county mental hospitals, other institutions reported only admission and discharge rates for schizophrenics. Initial analysis, therefore, was restricted to schizophrenic patients in state and county mental facilities, many of these needing long term care. The data used to compare the prevalence of schizophrenia was obtained by dividing the number of patients recorded from each state by the total population of that state, as established by the 1960 census. Prevalence rates in 1965 were particularly high in the northeastern USA.

While each of the 219 geographical variables could have been mapped and visually compared with the USA prevalence of schizophrenia, this would have been a long, subjective, and tedious process. A statistical comparison, using Pearson correlation coefficients achieved the same goal both much more easily and accurately. It should be remembered that a high positive correlation between the 1965 USA distribution of schizophrenics and a particular variable, indicates that the two tend to rise and fall together from state to state. This suggests that the variable may be a trigger for the illness. Conversely, a strong negative correlation between schizophrenia prevalence and a geographical variable demonstrates that when one is common the other is not. This implies that a deficiency of this variable may trigger the illness.

Using this statistical approach it was found that the prevalence of schizophrenia in state and country mental hospitals in 1965 showed the strongest positive correlation with selenium deficient fodder crops ( $r=0.58497$ ,  $p=0.0001$ ). In contrast, the

highest negative correlation occurred between schizophrenia and sunlight ( $r=-0.57024$ ,  $p=0.0001$ ). What these results mean is that schizophrenia was found to be most common in those states in the USA where the agricultural soils were deficient in the trace element selenium but tended to be relatively uncommon in states receiving high levels of sunlight. A subsequent comparison of the prevalence means for the states with soils highest and lowest in selenium produced a relative risk of 1.77:1. This means that in selenium deficient states, schizophrenia in 1965 was almost twice as common as in those where soil levels of this element are elevated.<sup>24</sup>

There were also several strong positive correlations with evidence of industrial activity, namely the proportion of the population employed by manufacturing industries ( $r=0.55393$ ), industrial water withdrawal ( $r=0.54871$ ), population density of the state ( $r=0.53936$ ), the number of toxic waste sites per unit area ( $r=0.51000$ ,  $p=0.0003$ ), and the use of road salt ( $r=0.50225$ ,  $p=0.0004$ ) ( $p=0.0001$  unless otherwise stated). Also of significance appeared to be the reasonably strong negative correlations with soils that contained very high levels of calcium ( $r=-0.45784$ ,  $p=0.0014$ ) and were enriched in strontium ( $r=-0.43360$ ,  $p=0.0026$ ).

Correlations, such as these, do not *prove* cause and effect. What they do, however, is to stimulate hypotheses that can then be tested more rigorously. The proceeding study seems to suggest that in some way the triggering of schizophrenia in genetically susceptible individuals may involve deficiencies of selenium and /or calcium and/or sunlight and is most likely to occur in highly polluted urban areas. The evidence for and against these possibilities is reviewed later in detail.

Two subsequent studies have further supported the possibility that selenium deficiency may play a role in schizophrenia.

After the publication of my paper, Brown<sup>25</sup> decided to explore this idea and conducted a more detailed survey of the USA selenium-schizophrenia relationship. To do this, he used 2-by-2 contingency tables to compare prevalence data from the nine USA schizophrenia surveys that had been conducted between 1880 and 1963 with selenium deficiency in crops. This analysis provided further evidence of a significant correlation between schizophrenia and low environmental selenium ( $p < 0.0001$ ; Yates corrected chi-square). Simply put, for the entire time period for which reliable information has been available, schizophrenia has been most common in those states where the environment contains the lowest levels of the trace element selenium. This continuity suggests that the relationship between selenium deficiency and schizophrenia, first identified for the year 1965 in my own survey,<sup>26</sup> is not the result of any statistical quirk but rather reflects a long-term association. This does not, of course, prove a causal link, but it is certainly consistent with one.

In the book, *Reducing Cancer Mortality: A Geographical Perspective*,<sup>27</sup> I argued that global variations in deaths from cancers of the esophagus seemed to strongly reflect differences in environmental selenium and calcium. That is, mortality from cancers of the throat seems to be much more common in communities situated in regions where, for geological reasons, soil selenium and calcium levels are low. A similar relationship appears to occur between these two elements and schizophrenia.<sup>28</sup> If these suggestions are correct, it follows that rates of both these illnesses should rise and fall together, depending on the availability of selenium and calcium in the foodchain.<sup>29</sup> This may be the case. In 1990, Templer and his colleagues<sup>30</sup> correlated a series of medical and geographical variables with indicators of schizophrenia's frequency in both Italy and the USA. Only one of these variables, mortality from cancer of the esophagus, correlated positively and significantly in both countries. That is, only one of them, death from cancer of the esophagus, rose

and fell together with schizophrenia both in the districts of Italy and the states of the USA. This, of course, is what might be expected if there were some sort of link between a low intake of both selenium and calcium and the development of both schizophrenia and esophageal cancer.

In an attempt to explore this hypothesis further, I compared Arieti's map of first hospital admission rates for schizophrenia for Italian districts, for the period 1947 to 1949 with Dainelli's<sup>32</sup> geological map of that country. During that time period, the highest schizophrenic admission rates had occurred in districts located in the low calcium predominantly Paleozoic rocks of the north.<sup>33</sup> Examples include Emilia with 12.2, Lombardy with 11.8, and Venezia with 9.4 schizophrenic hospital admissions per 100,000 inhabitants, each year. In contrast, in Puglia, in Italy's "heel," where there are large outcrops of Cretaceous calcium-enriched chalk, the annual admission rate had been only 4.9 per 100, 000. However, the admission rates were also low in Sardinia, where the rocks are not of Mesozoic origin. Obviously, while the Italian evidence is not conclusive, it certainly seems consistent with the possibility that both high calcium environments and sunlight tend to reduce the incidence of schizophrenia.

Torrey and coworkers<sup>34</sup> have confirmed recently that schizophrenia is more common in urban than in rural areas. Using information from the Danish national case registry, these researchers divided the country into 217 regions which were used in a study of the geography of the birthplaces of 2,199 schizophrenics. Using log-linear Poisson regression, the data were analysed by age, gender, month of birth, genetic relatedness, and degree of urbanization. Torrey and colleagues concluded that the degree of urbanization of the place of birth could explain more of the clustering of schizophrenics, in Denmark, than any of the other variables examined.

Schizophrenia is an age specific disease that is usually first diagnosed in patients between the ages of 18 and 30. Geographical analysis, however, strongly suggests that it has its roots much earlier in life. It has been demonstrated, in every country in the northern hemisphere where the issue has been examined, that the birth dates of schizophrenics occur in higher numbers during the colder months of the year.<sup>35</sup> Hare and colleagues,<sup>36</sup> for example, have shown that in England and Wales a disproportionate number of schizophrenics have January, February, and March birthdays. This was also discovered to be the case in both Norway<sup>37</sup> and Denmark.<sup>38</sup> A fairly similar cold weather birth peak also has been identified in Sweden, Ireland, the USA, Japan, Germany, and the Philippines.<sup>39</sup> As Torrey<sup>40</sup> points out, "together these studies included over 125,000 schizophrenic patients and conclusively established the winter-spring seasonality of schizophrenic births in the Northern Hemisphere." The magnitude of this cold season excess of schizophrenic birthdays is generally between 6 and 10 percent. Although there is some evidence of seasonality in the birthdays of schizophrenic patients in the southern hemisphere, it is, as yet, not as convincing. However, when McGrath and colleagues<sup>41</sup> compared the birth dates of patients born in the northern and southern hemispheres, in a sample of 9,348 Australian schizophrenics, they identified a significant difference. Interestingly, in Singapore<sup>42</sup> where the birth dates of 9,655 schizophrenics were analysed, there appeared to be no such fluctuation. This is not surprising because in such equatorial areas there are no formal seasons of the year.

The seasonality of schizophrenia birth rates, therefore, shows on a global scale that the trigger(s) for schizophrenia varies in intensity with the seasons. While this fact seems to support the possibility of the involvement of sunlight intensity in the disorder, it should be remembered that a large number of other

geographical variables ranging from trace element levels in drinking water and food to viral infection also tend to fluctuate with the seasons.

## GEOGRAPHICAL CONTRIBUTIONS—LOCAL

As early as 1939, Faris and Dunhan<sup>43</sup> demonstrated that in Chicago schizophrenics tended to live on the fringes of the central business district in what is often called the 'Zone of Transition' by geographers. A similar distribution pattern was later recognized in English cities, in Nottingham,<sup>44</sup> Plymouth,<sup>45</sup> and Brighton.<sup>46</sup> Two basic theories have been put forward in efforts to explain this clustering phenomenon.<sup>47</sup> The breeder theory argues that it is the social and/or physical characteristics of the environment in these particular high prevalence zones that cause mental illness in abnormally high numbers of their population. That is, the trigger(s) that promote the development of schizophrenia in genetically predisposed individuals are especially common surrounding the central business districts of large cities. The drift theory,<sup>48</sup> in contrast, suggests that the alienation, loss of confidence and economic loss that accompanies the symptoms of schizophrenia causes a decline in status that often forces those with this mental illness to relocate in poor quality, older housing on the fringes of the prosperous central business district.

Beyond its spatial dimensions, schizophrenia displays a socio-economic dimension. The illness occurs most often amongst the poor in England, Ireland, Norway, Iceland, the USA, and Japan, but in India, and possibly Italy, it is more prevalent amongst the rich.<sup>49</sup>

## SUMMARY

Infants destined to become schizophrenics are most often born in the coldest season of the year, to lower class mothers who live in the urban centres of temperate industrialized nations. Symptoms of their mental illness begin to become apparent in early adulthood. If not institutionalized, schizophrenics often congregate in the 'Zone of Transition,' that is in the older, dilapidated properties that ring the central business districts of urban cores. Their diets tend to include milk and wheat from agricultural areas where soils are calcium and selenium deficient. Clearly, this is a stereotype but it is based on some 50 geographical studies that together ought to be of value in identifying the trigger(s) that cause the development of schizophrenia in the genetically susceptible.

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*Inspector Gregory: "Is there any other point to which you would wish to draw my attention?"*

*Holmes: "To the curious incident of the dog in the night-time."*

*"The dog did nothing in the night-time."*

*"That was the curious incident," remarked Sherlock Holmes.*

*The Adventure of Silver Blaze,  
Arthur Conan Doyle (1892)*

As Arthur Conan Doyle so clearly showed in *The Adventure of Silver Blaze*,<sup>1</sup> sometimes what does not happen can be the key to solving a mystery. The dog had seen no reason to bark because it knew and trusted the criminal, greatly reducing the length of Sherlock Holmes' list of suspects.

## CANCER

Schizophrenics typically are heavy smokers, but very rarely do they develop lung cancer. Together with Abram Hoffer, I have argued that this medical anomaly may eventually provide new treatments for both disorders.<sup>2</sup> About 33 percent of Americans smoke, but this figure rises to 90 percent amongst USA schizophrenics.<sup>3-4</sup> Similarly, in Ireland about 49 percent of males and 36 percent of females smoke, compared to 92 percent of chronic

male and 82 percent of chronic female schizophrenics.<sup>5</sup> Indeed, every available study confirms that schizophrenics are much more likely to smoke than are the general population. Not only that, but, as already pointed out in the previous chapter, they tend to live in selenium deficient regions and their serum displays depressed levels of the enzyme glutathione peroxidase. This is significant because this selenoenzyme plays a major role in the body's defence against the free radical damage caused by smoking. Schizophrenics then are exceptionally heavy smokers who lack a key enzyme which protects against cancer.

It follows that lung cancer must be rampant amongst schizophrenics. Strangely it is not. Indeed, the available evidence suggests it is rare. As early as 1893, Snow<sup>6</sup> suggested psychiatric patients never developed cancer. This is an exaggeration today, but the evidence is good that they are very unlikely to die of it, especially of cancer of the lung. In 1979, Rice<sup>7</sup> claimed that there had never been a recorded case of bronchogenic carcinoma in a hospitalized chronic schizophrenic, despite that group's abnormally high tobacco use. Craig and Lin<sup>8</sup> also documented a depressed incidence of lung cancer in chronic schizophrenic smokers. Probably, the most comprehensive study of the occurrence of cancer amongst schizophrenics was conducted by Gulbinat and colleagues.<sup>9</sup> They also established very low relative risks of lung cancer, during the period 1957 to 1980, amongst Dutch male (rr = 0.38) and female (rr = 0.33) schizophrenics. Similarly, in Canada, Hoffer<sup>10</sup> has treated some 4,000 schizophrenics since 1952. There have been only five cases of cancer amongst them; lymphoma, thyroid cancer, and three examples of breast cancer. In every case, the patient responded well to treatment and is still alive.

All the available evidence then suggests that schizophrenics are very heavy smokers who, nevertheless, die far less frequently of lung cancer than the general public. This low lung

cancer incidence has been recorded amongst the patients of both conventional and unconventional physicians over a long time period. It appears very likely, therefore, that it cannot be due to treatment but must be related to the biochemistry of the mental illness itself.

## RHEUMATOID ARTHRITIS

Lung cancer is not the only illness that appears to be less common than normal in schizophrenics. As early as 1936, Nissen and Spencer<sup>11</sup> noted that patients with arthritis rarely suffered from psychotic disorders. Conversely, schizophrenics developed arthritis less often than might be expected. Oken and Schulzer<sup>12</sup> conducted a meta-analysis of this negative relationship in 1999. These researchers combined their own data with that from 14 earlier studies, 12 of which had confirmed this lack of comorbidity. In total, rheumatoid arthritis was discovered to have occurred in only 31 of 28,953 schizophrenics, a mean frequency of 0.107 percent—well below the expected range of 1 percent. This evidence strongly suggests that rheumatoid arthritis is, indeed, relatively uncommon in schizophrenics.

As Torrey and Yolken<sup>13</sup> point out, schizophrenia and rheumatoid arthritis share many similarities. Both are chronic, relapsing diseases of unknown etiology. Both became prominent early in the 19<sup>th</sup> century and affect approximately 1 percent of the European and North American populations. Both run in families and have a high pair wise concordance among identical twins, so that if one such twin has rheumatoid arthritis there is about a 30 percent chance of it developing in the other. Both schizophrenia and rheumatoid arthritis are more common in urban than rural areas. Nevertheless, having one appears to reduce the chance of suffering from the other.

## PAIN THRESHOLD

There is extensive literature indicating that schizophrenics are insensitive to pain, especially during psychotic episodes. This is as true of physical pain associated with illness or injury as it is of deliberately inflicted experimental pain.<sup>14</sup> The strong evidence for this phenomenon has been summarized by Dworkin<sup>15</sup> in *The Schizophrenia Bulletin* and there are numerous case histories to support it. Horrobin<sup>16</sup> recalls a patient who jumped from a high window, picked himself up, and walked a mile to the nearest bus stop. Later that day he was found behaving distractedly in the local town centre and was returned to the hospital. He had no complaints, but a routine medical examination discovered two broken ankle bones. In a healthy person such breaks would have caused agony, but the patient had walked around for half a day without feeling the pain. Another example of such pain insensitivity was that of a hospitalized schizophrenic patient who seemed unwell to the nurse on duty, despite claiming to be in good health.<sup>17</sup> Although the individual did not complain of any problems, the nurse eventually called for the doctor. A clinical examination suggested a ruptured appendix, later confirmed by operation. This condition is normally exceptionally painful but the patient felt nothing to complain about.

## MALARIA

In 1927, the Austrian psychiatrist, Julius Wagner-Jauregg won a Nobel Prize for treating psychosis with malaria.<sup>18</sup> He had discovered that the fevers and high temperatures caused by malaria could kill the spirochaete bacterium, *Treponema pallidum*, that caused syphilis. This bacterium is very sensitive to temperature and a rise of a few degrees will kill it. Patients and doctors were happy to exchange malaria for syphilis and

so avoid the dementia eventually caused by the latter. Malaria therapy continued to be widely used until the 1950s, when penicillin became the accepted treatment for cerebral syphilis. Naturally, Wagner-Jauregg also wanted to see what effect malaria would have on the other large group of patients in mental hospitals, schizophrenics. The impact of deliberately giving malaria to schizophrenics was even more unexpected. To quote Horrobin:<sup>19</sup>

*As the first fever took hold, a few days after the deliberate infection, the schizophrenic patients seemed to lose their psychosis. But sadly, when the fever came down, the psychosis returned. In contrast to the situation with syphilis, there was no long-term improvement and certainly no cure.*

Nevertheless, elevated temperatures or other fever-related changes must somehow depress one or more of the biochemical processes causing schizophrenic psychosis.

## HERPES

The experimental infection of the rat neonatal brain with herpes simplex virus type 1 (HSV-1) has been shown to delay the development of prepulse inhibition of acoustic startle.<sup>20</sup> This brain function is also known to be diminished in schizophrenia. The question arises then, "Is there evidence that maternal herpes infection can increase the probability of the development of schizophrenia in her offspring?" The answer to this question appears to be yes.

Pandurangi and coworkers<sup>21</sup> discovered that schizophrenics with abnormally high serum levels of antibodies to the herpes virus had more extensive cortical atrophy, a smaller left frontal brain area, and a larger second quadrant of the corpus

callosum. In short, schizophrenics that had been infected, at some time, with herpes displayed more obvious brain anomalies than those who had not. It appears that many such schizophrenics were exposed to herpes in the womb. Buka and colleagues<sup>22</sup> conducted a nested case-control study of 27 schizophrenics and 54 matched volunteers. Stored blood samples, taken from their mothers at the end of pregnancy, were analysed for specific antibodies. This research showed that the children of mothers whose blood contained elevated antibodies to herpes simplex virus type 2 were at increased risk of developing schizophrenia and other psychotic illnesses later in life.

## CELIAC DISEASE AND OTHER ALLERGIES

Patients with celiac disease are unable to adequately absorb fats, certain starches, and some sugars. This digestive tract disorder has been connected with an allergy to gluten, a grain protein.<sup>23</sup> As a consequence of this maldigestion, celiacs often become deficient in a wide variety of nutrients including fats, folic acid, vitamins A, B<sub>12</sub>, D, E, K, copper, iron, and selenium.<sup>24</sup> Interestingly, many schizophrenics test positive for celiac disease.<sup>25</sup> Conversely, relatives of celiacs tend to develop schizophrenia more often than normal.<sup>26-27</sup> There is conflicting evidence on whether or not schizophrenics have abnormal intestinal absorption.<sup>28-29</sup> This tendency may be a consequence of their medications. Nevertheless, some schizophrenics certainly improve on gluten-free diets.<sup>30</sup>

The conventional viewpoint is that schizophrenics are rarely allergic.<sup>31</sup> Conversely, many alternative physicians consider brain allergies to be the root cause of schizophrenia and base their treatments around this belief.<sup>32</sup> Why this disagreement may be occurring is discussed in detail in a later chapter.

## TICK-BORNE ENCEPHALITIS

Brown<sup>33</sup> has shown that there is a strong positive geographical association between schizophrenia prevalence in the USA and the distribution of Lyme disease together with its primary vectors, Ixodid ticks. Such Ixodid ticks are responsible, in North America and throughout the world, for the spread of encephalitis. Interestingly, tick-borne encephalitis occurs most often in countries, including Croatia, Norway, Finland, Germany, and Ireland, where the highest rates of schizophrenia also are found.<sup>34</sup> Recently, Fritzche and Schmidli<sup>35</sup> have argued that the dual seasonality of schizophrenic births in Switzerland “mirrors the seasonal concentration of ticks (*Ixodes ricinus*) nine months earlier, with a major peak in spring and a minor peak in autumn separated by a decrease in humidity in the summer.” These authors believe that maternal infection by *Borrelia burgdorferi* through tick bites is an environmental determinant of schizophrenia. This is an interesting hypothesis that deserves further examination.

## SUMMARY

The evidence just presented suggests that maternal infections during pregnancy, such as herpes simplex virus type 2 (HSV-2) and tick-borne encephalitis, may increase the future risk of schizophrenia in offspring. The biochemical abnormalities associated with schizophrenia may also help to prevent lung cancer and rheumatoid arthritis. A final group of anomalies, such as an insensitivity to pain, a decline of symptoms with increasing body temperature, and susceptibility to celiac disease, provide direct insights into the biochemistry of schizophrenia itself.

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*The way of the world is to praise dead saints, and persecute living ones.*

Nathaniel Howe<sup>1</sup>

Thomas Alva Edison (1847-1931) was probably the greatest and most prolific inventor the world has ever known.<sup>2</sup> He started inventing at an early age, continuing until his death, and was granted a total of over 1,000 patents, including those for the electric light, phonograph, and motion-picture camera. These inventions in turn permitted the development of several enormous industries, including the electric utilities and the recording and motion picture industries. How could one man be so prolifically creative?

After patenting his phonograph, Edison began attempting to develop an electric light bulb that would be suitable for the home. He wanted to use a glowing wire or filament, made out of a substance that was able to endure very high temperatures, yet did not burn out, melt or fuse. Edison and his staff tried hundreds of possible filaments, quickly discarding those that did not meet these criteria. After more than a year of hard work, Edison developed a high-resistance carbon-thread that burned steadily for over 40 hours. This became the first effective incandescent electric light because it lasted a long time and used a small current. Edison, therefore, produced some of the most influential inventions of the 19th and 20th century

by trial and error. He experimented to see whether or not something was effective. If it was not, he abandoned it and quickly moved on. If it was effective, he rapidly put it to practical use.<sup>3</sup> This is the approach that has been taken by several unorthodox physicians who have developed their own treatments for schizophrenia. I know some of them personally and have met former schizophrenics who have been treated by them and now appear completely normal. Others, I am simply aware of through the published alternative literature and am impressed by their results. This chapter describes what I consider to be the five most effective unconventional approaches to the treatment of schizophrenia and the innovators who were behind their development.

## CONTROLLED FASTING

The Moscow Psychiatric Institute, a huge 3,000-bed research centre, contained a 77 patient unit headed by Dr. Uri Nickolayev that, for over 20 years, treated schizophrenics with 20 to 30 day fasts.<sup>4</sup> The large majority of patients had requested admission to this unit, but a few were transferred to it after all conventional treatments had failed.

Throughout the fasts, patients were obliged to drink a minimum of one litre of water each day. Most drank much more. They were also expected to exercise for at least 3 hours daily, participating in outdoor walks, deep breathing classes, and other physical exertions. There was also a regimen of daily cleansing enemas, baths, showers, and massage. During a typical 28-day fast, patients lost 15-16 percent of their total body weight, but their skin colour remained good and muscle tone healthy. At the conclusion of their fasts, patients stayed in the hospital where they were fed a salt-free, fruit, vegetable, and milk diet. The amounts of food and its caloric value were

gradually increased. Meat, eggs, and fish were excluded from the diet and bread was not eaten until the sixth or seventh day. Patients were normally discharged after they had been eating for a length of time equivalent to that spent fasting. They were advised to continue taking regular prophylactic fasts of some 3 to 5 days in length but were told not to abstain from eating for more than 10 days in any one month. Fasting stopped when a patient's appetite was fully restored, tongue became clean, and symptoms had been alleviated. Anyone thinking of using fasts to treat mental illness should read Cott's article in *Schizophrenia* which provides far more detail, including the risks involved. Contraindications for the use of Dr. Nickolayev's fasting treatment, for example, are heart problems (such as history of cardiac arrhythmias or of thrombosis), tumours, ulcers, and pulmonary disease.

Such fasting seemed to work well. Symptoms greatly improved in 64 percent of all chronic schizophrenics completing the Soviet program. Effects were most obvious 2 or 3 months after recovery began, provided the prescribed diet had been faithfully followed. Unfortunately, although paranoid schizophrenics showed marked improvement while fasting, this diminished after they began eating once again. Other types of schizophrenics tended to continue to improve provided they ate only the suggested diet.

Dr. Juli Shapiro studied many of the schizophrenic patients undergoing this fasting/diet regime, discovering that fasting had a major impact on histamine levels.<sup>5</sup> This was because during the time patients abstained from eating, large quantities of heparin formed in tissue surrounding blood vessels. This lowered histamine levels. It was discovered also that catecholamines were depressed in the urine of schizophrenics, prior to fasting. During fasts, their urine catecholamines normalized and then in the early part of the recovery period rose

above levels seen in controls. Eventually, they stabilized at levels seen in normal, healthy individuals. The elevated levels of serotonin seen in schizophrenics before fasting also dropped to an optimum during the fast, but tended to rise again later. It is clear from Shapiro's work that fasting and associated restrictive diets normalized some of the biochemical irregularities previously described in schizophrenics. Significant changes were also noted in transaminase, cholesterol, bilirubin, and glucose levels during this program.<sup>6</sup>

In Canada, Dr. Abram Hoffer used a modified fast to treat those of his schizophrenic patients who had not responded well to his usual orthomolecular treatment.<sup>7</sup> Two hundred such patients were asked to drink only water while fasting for 4 days. On the fifth day they proceeded to reintroduce foods, one at a time. When eating a food to which they were allergic, schizophrenic symptoms often quickly reappeared, although this might take several days in the case of certain grains. In numerous patients, cow's milk acted as a hallucinogen. In total, 60 percent of the 200 "problem" patients tested in this way responded well to the fast and, when placed on permanent diets that eliminated the offending foods, experienced significant permanent improvements in their mental health.

## HISTAMINE THERAPY

Many triggers can induce psychotic states. They include inadequate atmospheric oxygen, organic causes of deficient blood oxygenation, impaired cerebral blood flow, improper cerebral oxygen exchange, or disturbed cerebral cellular chemistry. The fact that so many of these triggers had a common denominator (interference with cerebral oxidative processes) stimulated Sackler and colleagues<sup>8</sup> to experiment in 1949 with histamine,

a vasodilating agent. This they believed might improve oxygen flow in the brains of hospitalized psychotics. Their treatment protocol was described in detail in two articles<sup>9-10</sup> published in the *Journal of Nervous and Mental Disease*. It consisted of an average of fourteen, 1 to 3 mg histamine injections given once or twice daily. Twenty one catatonic schizophrenics were treated in this way with histamine. Nine of these improved, one sufficiently to be discharged. Similarly, two of the nine paranoid schizophrenics given histamine were sufficiently well enough to be sent home.

In 1955, Hoffer and Parsons<sup>11</sup> repeated Sackler and coworkers<sup>12</sup> treatment protocol on 12 acute Canadian schizophrenics. Nine of these were improved and discharged, with four of them still being in good health 1 to 2 years later, despite the fact they had been given no further histamine after leaving the hospital. It would seem from these three studies that injection with high doses of the vasodilator histamine is of lasting benefit to roughly a third of schizophrenics.

## THYROID HORMONE THERAPY

Thyroid hormone appears to be the most successful of all unconventional treatments for schizophrenia. Between 1946 and 1956, Danziger prescribed desiccated thyroid for 120 schizophrenics.<sup>13</sup> Daily dosages ranged from 120 to 1,200 milligrams, although only 10 patients required over 600 milligrams. Many of those given thyroid hormones had received and failed to respond positively to a wide variety of other therapies, including ECT, psychotherapy, and psychoanalysis. Thyroid medication was taken for at least 100 days, since for many, recovery was slow. According to Hoffer,<sup>14</sup> 45 percent of the chronic schizophrenics recovered, becoming normal in every way. Even more surprising, every one of the 80 schizophrenics who had been

ill for 6 months or less, and who completed the treatment, recovered, suffering relapses only if they later discontinued their own home thyroid medication.

In 1963, Lochner and coworkers<sup>15</sup> conducted a double blind controlled comparison study on 30 chronic schizophrenics who had been hospitalized for at least 4 years and who had a history of mental illness that had lasted 8 years or longer. Half of this group received 200 micrograms of triiodothyronine, while the remainder were given a placebo. Twelve of the group receiving the hormone improved, becoming more active, sociable, interested in their environment and willing to work. One, who for years had proved unresponsive to all other medications, recovered to the point he was able to work in the hospital kitchen. None of the placebo group improved, but two became more active.

Danziger and Lochner and coworkers<sup>16</sup> have demonstrated that desiccated thyroid and triiodothyronine are very effective treatments for many types of schizophrenia. The required doses are very high and seem most effective in the early, acute stages of mental illness. However, thyroid hormone treatment is still valuable for chronic schizophrenics, although improvement is usually less dramatic and may take longer to achieve.

## DR. CARL PFEIFFER'S PROTOCOLS

The Princeton Brain Bio Center was established in New Jersey in 1971. It was headed for many years by Dr. Carl Pfeiffer. By the time of publication of his book *Nutrition and Mental Illness*<sup>17</sup> it had treated over 5,000 schizophrenic patients using its own unique protocols. Pfeiffer was a biochemist who believed that 95 percent of all schizophrenics belonged to one of five biotypes. In histapenia, the most common, the patient suffered

from depressed blood histamine and an excess of copper. The daily treatment given at the Brain Bio Center to the 50 percent of schizophrenics with these characteristics was 100 mg of niacin and 250-500 mg of niacinamide, 1-3 mg of folic acid, 10-30 mg of zinc and 5-50 mg of manganese (both as gluconates). In addition, the patients were expected to eat a high protein diet and to take 2 grams of vitamin C a day to help excrete copper. Histadelia was diagnosed in 20 percent of the Center's schizophrenic patients. This was characterized by high blood histamine and low copper. Its treatment consisted of 500 mg of calcium gluconate taken twice a day (in the morning and evening) to release histamine and 500 mg of methionine, taken at the same times to help excrete it. In addition, histadelics were given 10-30 mg of zinc and 5-50 mg of manganese daily to increase their basophils (white blood cells that contain the majority of the body's histamine). Thirty percent of the 5,000 schizophrenics examined at the Princeton Brain Bio Center, 30 percent also were considered to suffer from pyroluria, caused by a double deficiency of both zinc and vitamin B<sub>6</sub>. The treatment for this illness is fairly obvious and included vitamin B<sub>6</sub> (at a daily dose sufficient to allow dream recall but never beyond 2 grams), and 30 mg of zinc gluconate taken both in the morning and again in the evening. Manganese gluconate also was prescribed twice daily, at doses of 10 mg. Care was taken to avoid numbness of fingers and toes from these high levels of vitamin B<sub>6</sub>. If such symptoms appeared, the patient stopped taking this vitamin but replaced it with pyridoxal phosphate at one-tenth the normal vitamin B<sub>6</sub> dose.<sup>18</sup>

Ten percent of schizophrenics who attended the Princeton Brain Bio Center out-patient clinic were considered to be suffering from cerebral allergy (often caused by wheat gluten), and a further 20 percent from nutritional hypoglycemia. The former were treated with supplements, similar to those given to histadelics, with the addition of vitamin B<sub>6</sub> and vitamin C. Where the latter

avoided sugar and alcohol, while taking magnesium gluconate, zinc, chromium, vitamin B<sub>3</sub>, and a multivitamin that did not contain copper.<sup>19</sup>

The percentages of each of the five types of schizophrenia, given in the preceding discussion of treatment at the Princeton Brain Bio Center, do not add up to 100 percent. This is because many of Pfeiffer's patients were found to be simultaneously suffering from more than one type. How effective were Pfeiffer's protocols for the treatment of schizophrenia? He writes, "When the exact biotype guides the appropriate treatment, 90 percent of these patients will attain social rehabilitation."<sup>20</sup> Dr. Carl C. Pfeiffer was a prolific author. Anyone needing more detailed information on his approach is directed towards his books.<sup>21-23</sup> These include *The Schizophrenias: Ours to Conquer*; *Nutrition and Mental Illness*; and *Mental Illness: The Nutritional Connection*.

## DR. ABRAM HOFFER'S PROTOCOL

In the early 1950s, Osmond and Smythies realized that pink (that is deteriorated) adrenaline sprays were making some asthmatics psychotic, causing them to hallucinate.<sup>24</sup> Hoffer<sup>25</sup> knew that similar side effects accompanied the use of mescaline and made a list of all identified compounds that caused hallucinations in those who were awake. The list is short. It included harmaline, mescaline, ibogaine, d-lysergic acid diethylamide (d-LSD-25), and deteriorated adrenaline. Hoffer was delighted to realize all were indoles (LSD, harmaline, ibogaine) or could become indoles (mescaline). It was not known what pink adrenaline was, however, until 1952 when Hutcheon<sup>26</sup> described how the oxidation of adrenaline created the indole adrenochrome. Hoffer then experimented by taking this substance himself, finding it made him paranoid.

It seemed logical, therefore, to design a treatment for schizophrenia that was directed at reducing the patient's exposure to adrenochrome.<sup>27</sup> In the body, noradrenalin is converted to adrenaline and then to adrenochrome. Hoffer and coworkers knew the conversion of noradrenalin to adrenaline requires methyl groups, which are provided by methyl donors.<sup>28</sup> Noradrenalin is a methyl acceptor that adds one methyl group to become adrenaline. They argued that if they could prevent the addition of this methyl group to noradrenalin, there should be a corresponding reduction in the amount of adrenaline available for conversion to adrenochrome. As a result, they decided to use high doses of another natural methyl acceptor, niacin (vitamin B3), to reduce the conversion rate of noradrenalin to adrenaline and then to adrenochrome. Double-blind controlled experiments on acute schizophrenics conducted in Saskatchewan with high doses of niacin (usually 3 to 6 grams daily) were very successful, outperforming the then conventional treatments and reducing suicide rates.<sup>29</sup>

Dr. Hoffer was involved with these trials in the 1950s, but is still an active physician. His treatment of schizophrenia has not remained static. Rather it has evolved as additional evidence of the links between schizophrenia and nutrition has become available. His patients are now initially put on an elimination diet to identify foods to which they are allergic or sensitive. They are also encouraged to stop consuming any processed or prepared foods to which refined sugar has been added. This reduces their exposure to many other food additives which are very common in such "junk" foods.<sup>30</sup>

Beyond this, patients are given the following supplements: vitamin B<sub>3</sub> (niacin or niacinamide), 0.5 to 2 grams 3 times daily; vitamin B<sub>6</sub>, 250-500 mg daily (in most cases); B vitamin complex; vitamin C, 3 or more grams daily; zinc gluconate or zinc citrate, 50 mg daily. If there is danger of tardive dyskinesia

from prescription drugs, 15-30 mg of manganese is added each day to prevent it. Patients are also given selenium and omega 3 essential fatty acids that are rich in EPA (Eicosapentaenoic acid), but not in DHA (Docosahexaenoic acid).<sup>31</sup> The best preparation, Kirunal, has a ratio of some 3:1. Four large capsules are taken twice daily by the patient.

Based on six prospective double-blind studies, the personal treatment of over 4,000 patients, studies conducted by other molecular physicians, and letters from schizophrenics who have tried his treatment program after reading his books, Hoffer provides these statistics. Ninety percent of patients who are ill for the first time, or who are suffering their second or third schizophrenic episode and who follow the regime just cited will become well within 2 years. No patients will be worse than they were when they started the treatment protocol and none will have tardive dyskinesia (drug-related involuntary muscular movements). All such patients continue to have the best results if they stay on the regimen indefinitely. Approximately 50 percent of chronic schizophrenics, including those mentally disturbed for several years, will show improvement on this treatment after 10 years. Only some of them will be able to return to work. Hoffer does not include “the chronic patients seen in the back wards of mental hospitals” in this latter group.<sup>32</sup>

## SUMMARY

Relative alternative medicine cure rates for different protocols provide insights into the origins of schizophrenia. Most impressive are the extremely high recovery rates observed in acute schizophrenics treated early with elevated triiodothyronine or desiccated thyroid.<sup>33</sup> These results imply that a deficiency of triiodothyronine occurs at or very near the top of schizophrenia’s causal chain. Similarly, the frequent success

achieved by Pfeiffer's<sup>34</sup> regime for reducing histamine and by Hoffer's<sup>35</sup> orthomolecular treatment designed to lower adrenochrome suggest that excesses of both of these compounds occur early in schizophrenia's development. Similarly, the Soviet<sup>36</sup> recoveries achieved by fasting imply that various foods may trigger schizophrenia through allergic reactions. In addition, the lower but still impressive cure rates<sup>37</sup> caused by elevating histamine support Pfeiffer's<sup>38</sup> contention that there is a subgroup of schizophrenics whose members suffer from a deficiency of that substance.

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## CONVENTIONAL TREATMENT

*Nothing will ever be attempted if all possible objections must first be overcome.*

Samuel Johnson<sup>1</sup>

Over the past 30 or 40 years, consumer confidence in conventional medicine has been in serious decline.<sup>2</sup> There have been many reasons for this, including drug side-effects, the emergence of resistant bacteria, and failure to make much progress in curing chronic illnesses, such as arthritis, cancer, cardiovascular disease, and schizophrenia. Simultaneously, there has been a general questioning of authority, driven by the civil rights, consumer, and women's movements. One of medicine's harshest critics has been Horrobin,<sup>3</sup> who has argued that medical progress has been "pathetic" over the last 30 to 40 years. He suggests that something has gone seriously wrong with the process of drug discovery in the pharmaceutical industry, but because of the astronomical cost of developing innovative drugs, they are unlikely to come from anywhere else. To quote Horrobin<sup>4</sup> directly:

*We have taken drug discovery procedures from patient-orientated clinicians and handed them over to large bureaucracies who will work only with patent-protected products that give an adequate financial return. No wonder that real progress is so slow.*

This chapter sets out both to see whether this criticism is valid for the treatment of schizophrenia, and to collect clues from conventional medicine that may be of value in understanding the etiology of the disorder.

## INSULIN COMA THERAPY

The discovery of insulin led to the realization that in small doses it could improve the appetite and mental state of patients with anorexia.<sup>5</sup> Sakel<sup>6</sup> then discovered that deliberately causing insulin hypoglycemia countered the symptoms of withdrawal in morphine addiction. Prior to this, clinical hypoglycemia had been considered dangerous, but Sakel<sup>7</sup> showed that it could be controlled by the administration of glucose. He then began to use the technique to treat schizophrenia. Trials were carried out in most of the Developed World, nearly all of them reporting favourable results. In a series of over 400 Swiss patients treated before 1937, 59 percent reached either the complete or social remission of schizophrenia.<sup>8</sup> In over one thousand schizophrenics given insulin coma therapy, 11.1 percent recovered, 26.5 percent greatly improved, and a further 26 percent showed some benefit. The figures from an untreated control group of patients were 3.5 percent, 11.2 percent, and 7.4 percent respectively. In contrast, a comparable number of schizophrenics who received cardiazol convulsion therapy did not even match the recovery rates seen in the control group.

Three aspects of insulin coma therapy soon became obvious. Firstly, the treatment greatly shortened the duration of the illness. In one Pennsylvania hospital, for example, 95 percent of schizophrenics who were treated and recovered were discharged within a month.<sup>9</sup> Untreated patients who made spontaneous remissions took 1 to 3 years to reach a similar stage of improvement. Secondly, only 38 percent of patients treated with insulin coma therapy remitted. In contrast, only 10 percent of those untreated with insulin showed such a recovery. Thirdly, results were much more impressive if treatment was given early in the illness. Figures from New York<sup>10</sup> showed that only 27 percent of schizophrenics treated within 6 months

of the first appearance of their symptoms failed to improve. If insulin coma therapy was given to patients who had been schizophrenic for 5 years or longer, the percentage of those failing to respond increased to 66 percent. Bond<sup>11</sup> discovered that 67 percent of patients who had displayed schizophrenic symptoms for less than 18 months fully recovered or showed great improvement after insulin coma therapy. In contrast, only 30 percent of those treated 18 months or more after onset showed similar improvement. Many of the recoveries were long lasting. In New York State, for example, 60 percent of insulin coma treated patients were still living in the community, in a recovered or improved condition, 2 years later.

Although the use of insulin to treat schizophrenia showed impressive early results, further controlled studies demonstrated that most improvements were temporary. Nevertheless, since Sakel's treatment was gentler and carried fewer side effects than many other techniques, it was still in use in many countries until fairly recently.<sup>12</sup> Why did it achieve the beneficial results seen from the quoted statistics? Some clues appear obvious from the research of Baumann and MGaillard,<sup>13</sup> who showed that the injection of insulin in schizophrenia decreased the levels of free and total tryptophan and tyrosine in plasma, enhancing the tryptophan to tyrosine ratio. Conversely, the administration of glucose to reverse insulin's effects increased plasma tryptophan. They argued that the reason that insulin coma therapy was beneficial to schizophrenics was probably because it increased tryptophan uptake by the brain and so enhanced cerebral serotonin synthesis.<sup>14</sup> One might add that it may also have increased the availability of another tryptophan derivative, niacin. Interestingly, insulin potentiation therapy, a non-diabetic use of the hormone, is claimed to dramatically improve the effectiveness and delivery of a wide range of drugs. It has been used in the treatment of cancer, arthritis, cardiovascular, and various neurological diseases.<sup>15</sup>

## ELECTROCONVULSIVE TREATMENT (ECT)

The first experiments with electroconvulsive treatment (ECT) were made by Cerletti more than 50 years ago.<sup>16</sup> It became a widely used therapy until the 1970s, when strong opposition was voiced against it.<sup>17</sup> According to Hoffer<sup>18</sup>

*There is a loud, hostile, anti-ECT group, consisting of ex-ECT patients and a small number of physicians, who are violently opposed to its use. Their reasoning is entirely out of context, and much of their argument is driven by the word "shock" not by the treatment itself. ECT, like any medical or surgical procedure, must be used carefully. When it is so used, it is a very effective treatment for a very small proportion of patients with severe depression and/or schizophrenia.*

Since the mid 1980s, there has been a renewal of electroconvulsive treatment on patients under general anaesthesia.<sup>19</sup> The major objection to this therapy by former patients is that it causes serious memory losses that are considered to outweigh any decline in symptoms associated with this therapy. Interestingly, Hoffer<sup>20</sup> has shown that high doses of niacin, given for a few weeks prior to electroconvulsive treatment, prevents such memory loss.

It is unusual to find both conventional and unconventional physicians supporting the same therapy. However, as Hoffer<sup>21</sup> has pointed out:

*Critics have complained about the use of ECT by orthomolecular physicians [such as himself] because they declare ECT is not orthomolecular. Of course, since no one knows why ECT is effective, they may be wrong. It certainly does correct some biochemical abnormality because patients are improved or cured. All we need to assume is that the presence of symptoms is a measure of metabolic abnormality.*

While I agree entirely with Hoffer's sentiments expressed above, I believe that there is considerable evidence to show *why* electroconvulsive shock can benefit schizophrenics. 3-methoxy-4-hydroxyphenylglycol (MHPG) is a major metabolite of noradrenaline.<sup>22</sup> Researchers have shown that electroconvulsive shock treatment lowers plasma MHPG in schizophrenics and depressed patients,<sup>23-24</sup> suggesting that it slows the conversion of noradrenalin to MHPG and possibly to adrenaline and hence to adrenochrome.

## DRUG THERAPY

The discovery of the beneficial effects of chlorpromazine (thorazine) in the early 1950s began the drug era in the treatment of schizophrenia.<sup>25</sup> This tranquillizer calmed down hyperactive patients and ameliorated some of their "hot" or "positive" symptoms, such as agitation and restlessness. Chlorpromazine and its successor drugs, such as haloperidol (haldol), thioridazine (mellaril), fluphenazine (prolixin), and trifluoperazine (stelazine), are known as conventional antipsychotics, or "neuroleptics." The latter term is derived from the Greek and means "to clasp the neuron."<sup>26</sup> This designation stems from the work of Delay and Deniker,<sup>27</sup> who discovered that the best dose of chlorpromazine varied enormously from patient to patient, but that the drug seemed most effective when given at levels close to those causing neurologic side effects, like those seen in Parkinson's disease. This might be expected since Parkinson's disease patients are deficient in dopamine and neuroleptics block the D2 subtype of dopamine receptor.<sup>28</sup> Conversely, amphetamines<sup>29</sup> have been found to release dopamine and to exacerbate schizophrenia's positive symptoms. These contrasting drug effects gave rise to the "dopamine hypothesis," which rests on the belief that excess dopamine accentuates and decreased dopamine reduces the positive or hot symptoms of schizophrenia.

More recently, several “atypical” neuroleptics have been developed that carry lower incidences of neurologic side effects than older conventional antipsychotics, such as chlorpromazine.<sup>30</sup> The most effective of these new drugs appears to be clozapine (clozaril), which, as well as blocking dopamine receptors, also impacts at the 5-HT<sub>2</sub> subtype of serotonin receptor.<sup>31</sup> Indeed, many “atypical” neuroleptics have been designed to exert greater potency at 5-HT<sub>2</sub> serotonin receptors than at dopamine D<sub>2</sub> receptors. Drugs that block these specific serotonin receptors include olanzapine (zyprexa), quetiapine (Seroquel), and risperidone (risperdal).<sup>32</sup> Even more recently, certain antipsychotics have begun to target a subtype of glutamate receptor.<sup>33</sup>

How effective are such drug treatments for the average schizophrenic? In 2000, Geddes and coworkers<sup>34-35</sup> published a meta-regression analysis based on pooled data from 52 controlled studies. Together, these studies had compared the newer atypical antipsychotics against the traditional typical antipsychotics in the treatment of 12,649 patients. Geddes and colleagues could find no clinical evidence of greater efficacy or tolerability in the newer drugs. In short, Horrobin<sup>36</sup> was correct when he wrote:

*Almost fifty years after the first anti-schizophrenic drug, chlorpromazine, was produced we have made virtually no further progress in controlling schizophrenic symptoms. Drugs, on average, still improve symptoms by only 15-25 percent, leaving 75-85 percent of symptoms unresolved. The side-effects of Parkinsonism, TD [tardive dyskinesia] and agranulocytosis have been drastically reduced, but new side effects of weight gain, sedation, diabetes and cardiac problems are still there and may have worsened. There has not been much change in tax paying, nor in employment at levels commensurate with the underlying abilities of the patient. Despite billions of dollars of expenditure, we have not made that much progress.*

Naturally, such frank assessments have not been well received in psychiatry.<sup>37</sup> Nor was the profession comforted by the recent Cochrane Review<sup>38</sup> of beta-blocker supplementation, the adjunct use of beta-adrenergic receptor antagonists. This review, written by Cheine and coworkers,<sup>39</sup> examined all published randomized control trials using these drugs and concluded that “there is no evidence of any effect of beta-blockers as an adjunct to conventional antipsychotic medication.” In short, there is no evidence that beta-blockers work. For a detailed discussion of many of the adverse side-effects of psychiatric drugs the reader is directed to Peter R. Breggin’s website.<sup>40</sup>

## SUMMARY

The meta-regression analysis conducted by Geddes and colleagues<sup>41</sup> and the Cochrane Review of beta-blockers<sup>42</sup> both imply that conventional medicine has made little, if any, progress in the treatment of schizophrenia in the last 40 years. Indeed, the recovery records hint that both insulin coma and electroconvulsive (with niacin) therapies may have been more effective than current drug regimes. If this is the case, then dopamine excess cannot be the key to schizophrenia. If it indeed exists, elevated dopamine in schizophrenics must be of relatively minor significance, given the small decline in symptoms achieved by drugs designed to correct it. The results obtained by the use of insulin coma and electroconvulsive therapies suggest that an excess of dopamine is less important in schizophrenia than either the conversion of tryptophan to serotonin and niacin, or the metabolism of noradrenaline to MHPG.

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*We should be paying more attention to the exceptional patients, those who get well unexpectedly, instead of staring bleakly at all those who die in the usual pattern. In the words of René Dubos, "Sometimes the most measurable drives out the most important."*

B.S. Siegel (1986)<sup>1</sup>

I first used this quotation from *Love, Medicine and Miracles* in 1988 in "Lifestyle changes and the 'spontaneous' regression of cancer: An initial computer analysis."<sup>2</sup> That article was designed to shed new light on the strange, unexpected cancer recoveries that occasionally delight those affected by them, while perplexing the medical profession. The idea behind the paper was simple. A questionnaire was used to collect information from published accounts that included patients' treatment(s), dietary and lifestyle changes, mineral, vitamin, and herbal supplements, and detoxification procedures. This approach generated a great deal of useful new information, while stimulating hypotheses that may eventually help to explain such 'spontaneous' regressions. As a result of this modest success, the same basic technique was used to write this chapter, a discussion of information collected from the testimonies of 50 recovered schizophrenics. *The Schizophrenia Bulletin* regularly publishes such accounts. Many former schizophrenics have written or contributed to books or articles. Some have described their experiences on the Internet. *Masks of Madness: Science of Healing*,<sup>3</sup> a documentary hosted by Margot Kidder

and sponsored by *The Canadian Schizophrenia Foundation*, was another useful source. Obviously, since material was simply abstracted from the first 50 cases encountered, no claims can be made that the sample was necessarily random or representative. Nevertheless, the exercise provided some interesting insights into the causes of and cures for schizophrenia.

Since the publication of *A Beautiful Mind*<sup>4</sup> and the release of the movie based upon it, recovered schizophrenics have been receiving more public attention than usual. John Nash was a prodigy, an outstanding member of Princeton and MIT mathematics departments in the 1950s until, at 30, he had a schizophrenic breakdown. Eventually, thanks in part to his wife's selflessness and support from the mathematics community, Nash emerged from the world of mental hospitals and psychosis to win a Nobel Prize for his early work on game theory that had revolutionized economics.<sup>5</sup> Dr. Nash, however, is not unique. Many recovered schizophrenics are extremely intelligent. Dr. Fred Frese,<sup>6</sup> for example, is the director of a large mental health clinic in Ohio, a trained psychologist, and a diagnosed schizophrenic. Indeed, Hoffer<sup>7</sup> in his *Editorial: The Future of Psychiatry* writes "I know of 17 young men and women who became schizophrenics in their teens, were treated properly, recovered, went to college, became doctors and psychiatrists and are practising." What, then, can we learn from such schizophrenics who are once again fully functional?

## CONVENTIONAL TREATMENT

### Drugs

Few (12 percent) recovered schizophrenics consider the drugs they received while hospitalized to have been of much benefit. More typical are the views of a former patient who, when writing, worked as a mental health professional employed by the

US National Institutes of Health. Philosophically, she considered her stay at the “funny farm” the very best training she could have had as a mental health professional.<sup>8</sup> To quote her directly:

*I don't need to read a textbook to understand the meaning of psychosis and neurosis. I know how it feels to be a guinea pig; to shuffle under the influence of Haldol; to sleep under the influence of Dalmane; to lose my hair under the influence of Lithium. I know the joy of insanity and the hell of an insane asylum.*

Prior to her illness, the same author had seen the movie *One Flew Over the Cuckoo's Nest*.<sup>9</sup> She recalls laughing at the patients' antics and silently applauding their ability to survive in a world of silent suffering and sadness. However, the nature of her own mental hospital stay contrasted markedly with the virtual reality of Hollywood.

*Later, as a cuckoo in the nest, I found the experience of hospitalization much less amusing. Medication upon medication made my thoughts return to reality, but my body seemed suspended in time and space. There was no laughter; there were no tears; there was only existence. The poignantly painful ending of the movie reappeared as my own personal pain. I, too, had been symbolically suffocated in the name of caring and love. The major difference between me and the movie character was that I had survived.*

In a similar vein, John Hammell,<sup>10</sup> the founder of International Advocates for Health Freedom writes:

*On the back wards, where the sun doesn't shine, time is measured in the burning of cigarettes. Drugged zombies pace listlessly past the peering eyes of hospital staff who observe the pathetic scene from the other side of the nurses' station window, like people peering into an aquarium.*

*Locked naked behind a two inch thick steel door, I felt sealed in a tomb of hopelessness. I lay on the rubber mat in the corner, with muscles turned to jello by an injection of a highly toxic neuroleptic drug called thiorazine. On the walls were obscenities scrawled in blood and excrement from past prisoners in the seclusion room, and the fetid stench of stale urine filled the air.*

Hammell fortunately managed to encourage his mother to take him, on a pass, to see Carl C. Pfeiffer:

*Armed with the proper nutrients, I smuggled them back in to the last hospital I was in, and took them on the sly while mouthing my medication, and spitting it down a toilet. I had to hide my vitamins in a cavity gouged out from the underside of a foam mattress because they did room searches for contraband – and if they’d found my vitamins, they would have confiscated them as if they were cocaine or marijuana, having been brainwashed into believing that any amount over the RDA merely gives us “expensive urine.”*

*After just three weeks of taking my supplements, I was doing so much better that I was given a full medical discharge, with the doctors scratching their heads, wondering which of their drugs had been helping me, but none of them had been – I was spitting them all down the toilet where the toxic substances belonged. That was 23 years ago.*

## Accommodation and Support

Housing, work and respect are crucial dimensions of recovery. One patient, Ronald Peterson,<sup>11</sup> wrote about the benefits of *Fountain House*, a clubhouse model program, run by its members and staff. Its major goal was to provide practical and emotional support to patients so that they could become part of the wider community. The author recalls comments by chronic patients about their need to have a special place to relate to:

*Here you are really needed.... This is the only place in the city that can use me.... I'm expected here every day and that's what is important to all of us.*

As another patient related:

*I've got a lot of work to do here every day and this makes me feel worthwhile.... Here there's no busy work - everything we do is something that has to be done.*

Patients also need to believe that the future will be better than the past.

*It's really something to feel you are back in the world today.... I feel more adjusted to the outside world.... For the first time, I'm looking forward to the future.... What you get here most is hope for the future.... Here we have the outlook that all of us can make it on our own some day.... I'm 30, and it's about time to get away and be on my own, to live my own life.*

## UNCONVENTIONAL TREATMENT

### Diet

Interestingly, 22 percent of the recovered schizophrenics believed that much of their improvement could be traced to dietary change. To quote directly from J.F. Donald<sup>12</sup> of New York:

*As a schizophrenic, I have also learned that avoiding certain foods is necessary - namely, cheese (except cottage cheese and cream), caffeine and cigarettes. These all contain taraxacin which is toxic to the schizophrenic. Another thing of interest is that over fifty percent of schizophrenics suffer from hypoglycemia, or low blood sugar. It is extremely important that these people avoid anything with a high content of sugar, as well as the things named above (cheese, caffeine, and cigarettes). It is also important that these people eat*

*often, or their blood sugar level will drop and they will experience uncomfortable psychological symptoms, such as depression or lightness of the head.*

*I will now attempt to give a fairly complete list of the things which a person with hypoglycemia should avoid: cheese, anything made with sugar, potatoes, rice, cereals, spaghetti, macaroni, noodles, wines, cordials, cocktails, and beer.*

## VITAMINS AND MINERALS

Many recovered schizophrenics believe that their improved health is due largely to high doses of vitamin and mineral supplements. The most commonly taken nutrients are niacin, niacinamide, and vitamin C, used by 28, 8, and 14 percent of former patients respectively. Most of these nutrients are taken at levels way beyond Recommended Daily Allowances. The largest daily dose I encountered was 25 grams of niacin.<sup>13</sup> One of the most spectacular recoveries related to this vitamin involved a young schizophrenic known simply as S from New York.<sup>14</sup> Her history was described by her mother but had been verified by *Schizophrenics Anonymous*.

*Our daughter's illness was rapidly coming to a climax when she slashed her wrists, which landed her in the psychiatric ward of one of our hospitals. She was delirious and escaped from the ward, climbed out an open window, and jumped seventy-two feet to the ground. When found, she was in a coma and for the next two months she had continuous hallucinations. I was told she would have to be sent to a state hospital and that she was incurably insane.*

The mother then read of Dr. Hoffer's program in a national magazine and sought out a local psychiatrist who was sceptical but willing to try the regime on her daughter. Here is how S's mother<sup>15</sup> described the results:

*After a month on niacin, ascorbic acid, other vitamins, and minerals, my daughter appeared to have made remarkable progress. Then she had a relapse. The psychiatrist had only been giving her the dosage for acute cases, so, at my insistence, he prescribed the double dosage needed for chronic cases.*

*After nine months, she is a different person! She is in excellent health, pink cheeks, clear skin, firm face, and bright eyes. Before she was hospitalized, she was always tired and despondent, pale, with skin rashes. Her medication is not to be changed for five years.*

Another parent wrote<sup>16</sup> about the experiences of their son who unwittingly verified the value of niacin in schizophrenia's treatment by starting, stopping, and then restarting a supplementation program. This boy was first diagnosed as a schizophrenic at age 16, after 3 years of antisocial activity and withdrawal. By this time, he hardly spoke and his behaviour was bizarre and inappropriate. A year later, he began to take 3 grams of niacin and 1 gram of vitamin C each day. He was on no other medication and had never taken tranquilizers.

*The change was obvious within a few weeks. He began functioning again as a human being, slowly emerging from the cocoon of silence and withdrawal in which he had wrapped himself. His school grades shot up amazingly.*

For a year he took his vitamins faithfully, never missing a day. His grades became so good that he was then accepted by a nearby university. Feeling that he had been cured largely by his own "will to get well," he stopped taking any vitamins. He did reasonably well during his first year on campus but "during the second he gradually slid back into a milder form of the old apathy and lethargy." After 3½ years without niacin and vitamin C "the depression, extreme fatigue, irritability, mental confusion had all come back." He then returned home and restarted his alternative treatment, but replacing niacin with

niacinamide to avoid flushing. He also went on an antihypoglycemic diet and added other vitamins to the regime. “Again he responded in a completely positive way to this therapy.” Eventually he became an excellent driver, found a job as a landscape architect and, for the first time in his life, a girl friend. In short, he was “well and a functioning, self-supporting member of society” by the time his father contributed to *The Schizophrenia Bulletin*.<sup>17</sup>

Perhaps the last word on niacin is best left to Irene<sup>18</sup> from British Columbia:

*I started on vitamin B-3 a year and a half ago, and it has truly given me a kind of life I've never experienced. Until then I was on a medication that did keep my nerves under control but, unfortunately for me, kept me in a state of complete fatigue.*

*The B-3 seems to put the vitality in my constitution that I feel the other medication must have stifled. It has helped me to concentrate and think clearly. Because of this, I started to get my self-confidence back and then I started 'feeling' things again. Like my emotions began to work again. I started to feel friendly with people. I was able to share an experience and relate to people and really started to live again.*

Niacin, niacinamide, and vitamin C are not the only apparently beneficial orthomolecular treatments. Other patients appear to have been cured by high doses of desiccated thyroid. Shirley Christina,<sup>19</sup> treated for 3 years with this protocol, wrote “since I can remember, I was, for the lack of a better word, screwy.” Ms. Christina had formerly suffered from serious emotional problems and had been suicidal. “[Thyroid medication] has changed my life. I can hold down a job. I was so suicidal when I met him [Dr. David Derry, the physician prescribing thyroid medication], I don't think I'd be alive today [without his prescribed treatment].”

Also of considerable interest is the dramatic recovery of a catatonic schizophrenic,<sup>20</sup> Mrs. J., after she was given intravenous glutathione and injections of vitamin B<sub>12</sub>, together with various other oral nutrients, including lipoic acid.

*The first evening after treatment there was no apparent change. But the following day it was quite apparent that something had happened, and by evening the changes became dramatic. After several months of not speaking to anyone, she began singing Christmas carols that afternoon. In the evening, she had a telephone conversation lasting over an hour, then had a half-hour conversation with me. For days, a persistent smile frequently graced her face, and on several occasions she spontaneously began dancing about the house and thoroughly enjoying the music playing.*

*The IV treatments were continued twice weekly for two more weeks, then cut back to once per week for three weeks, and are now being given once every two weeks. The overall elapsed time of recovery was about six weeks from the start of the first treatment, though it would have been about four weeks if treatment had been started with twice-weekly IVs and lipoic acid from the beginning.*

*She has completely recovered and shows no lingering trace of her former mental state. Her condition would now be considered to be completely normal (or above) under any competent examination.*

## SUMMARY

The views of the 50 recovered schizophrenics discussed in this chapter do not represent a statistically valid sample. These case histories were chosen because they appeared in publications in the University of Victoria McPherson Library, in my own book and tape collection, or on the Internet. Nevertheless, the analysis does provide “food for thought.” Relatively

few former schizophrenics consider that they owe their current better health to the conventional drug treatments that they received in mental institutions. Indeed, most feel they were abused by their hospital experiences. There is far greater support amongst them for the orthomolecular treatments of schizophrenia, especially the use of very high doses of niacin. Perhaps more surprising is the widespread belief amongst recovered schizophrenics that dietary change played a major role in their recoveries. Many of them claim to have suffered from hypoglycemia and to have regained their health only after avoiding sugar, cokes, cheese, cereals, spaghetti, and other foods that greatly influence the body's production of insulin. A link between diet and the mind is hardly news.<sup>21-22</sup> However, recently it has been confirmed by an experiential double-blind, placebo-controlled, randomized trial of the effects of nutritional supplements on 231 young adult prisoners in the custody of HM Prison Service.<sup>23</sup> Prisoners receiving vitamin, mineral, and omega-6 and omega-3 essential fatty acid supplements, for a minimum of 2 weeks, committed an average of 26.3 percent fewer disciplinary offences than controls during the trial. In short, nutritional supplements reduce violence in young prisoners, some of whom are almost certainly schizophrenic. This overview also highlights the strong need that schizophrenics, like everyone else, have for decent shelter, jobs, and respect. That is, they have a need for a reduction of stress in their lives, something that unfortunately is a rarity both in hospitals and on the streets.

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## A TALE OF TWO HYPOTHESES

*Science does not progress by traditional beliefs, but rather by radical new ideas of single, imaginative minds.*

Philip S. Callahan<sup>1</sup>

Jigsaw puzzles must be challenging yet possible to solve. This balance is achieved by cutting an attractive picture into myriad complex shapes, while also providing a photograph proving they can be correctly reassembled. The best way to recreate the picture is to begin by sorting pieces into piles with common characteristics. Eventually, after a little trial and error, the green, black, and white fragments may begin to form a herd of grazing cattle. The brown, grey, and white pieces may then create a windmill. Finally the complete scene becomes clear.

Unfortunately, disease jigsaws do not have pictures on their boxes. We do not know ahead of time what the illustration on schizophrenia's container looks like, although the proceeding 10 chapters have provided us with numerous pieces of the puzzle. These now have to be sorted into groups, unified by common themes. Clearly, for example, Skoliarova's autopsy observations of thyroid damage in schizophrenics<sup>2</sup> belongs together with Danziger's very successful desiccated thyroid treatment regime<sup>3</sup> and Roca and colleagues' observation that the severity of schizophrenic symptoms in early hospitalization reflect thyroxine and triiodothyronine imbalances.<sup>4</sup>

How difficult is the schizophrenia jigsaw? How complex is the puzzle? In *The Madness of Adam and Eve*, Horrobin<sup>5</sup> points out that:

*While in familial and personality terms the problem is devastating, in biochemical terms the problem cannot be very serious. After all, the young person functioned near normally for fifteen, twenty-five or thirty-five years before becoming ill. Moreover, all schizophrenic patients vary in the severity of their illness, often, as documented earlier, becoming near normal while the body temperature is elevated. The fundamental biochemical problem, therefore, cannot be too serious and must be reversible.*

This is an extremely intelligent and encouraging characterization. It seems fair to ask, however, if the problem is so biochemically simple, why have thousands of scientists spent billions of dollars, over more than 100 years, in endless unsuccessful attempts to discover the etiology of schizophrenia? During the past 30 years knowledge and equipment has greatly improved yet, at best, the cure rates for schizophrenics have remained static.

As a child, I would occasionally have trouble completing a jigsaw puzzle. In frustration, I would take a piece that looked as it might fit, but did not, and force it into a vacant spot. At the same time, I would probably be complaining about the poor quality of the puzzle's manufacture. Driving a round piece into a square hole was, of course, the easiest way to guarantee failure. I will begin this attempt to put together the pieces of the schizophrenia jigsaw by showing that the main reason conventional medicine has made so little progress in understanding the etiology of the disease is because several critical pieces of the puzzle have been hammered into the wrong holes.

## DOPAMINE HYPOTHESIS

The current conventional treatment for schizophrenia rests largely upon the belief that there is an excess of dopamine involved in the disorder. This suggests that schizophrenia is somewhat like the mirror image of Parkinson's disease which involves a deficiency of the same neurotransmitter.<sup>6</sup> The evidence for the dopamine hypothesis in schizophrenia is shaky at best. It includes the fact that drugs designed to reduce dopamine's effect, such as haloperidol and chlorpromazine, act by blocking dopamine receptors in the brain. However, as previously discussed, this only tends to reduce the symptoms of schizophrenia by some 15 to 25 percent.<sup>7</sup> Interestingly, such drugs have Parkinsonism as a side effect, suggesting that in reality they may be causing a deficiency of brain dopamine.<sup>8</sup>

Other evidence used to support the dopamine hypothesis comes from the fact that high doses of amphetamines produce schizophrenia-like symptoms known as "amphetamine psychosis." This is thought to be because amphetamines work by making the brain upregulate its dopamine D2-like receptors, while causing a persistent decline in striatal dopamine levels.<sup>9</sup> However, amphetamines only mimic the positive symptoms of schizophrenia. There is no evidence that they cause negative symptoms, such as lack of emotion, action, or speech. Beyond this, children at risk for schizophrenia have brain wave patterns similar to those seen in schizophrenics. These childhood symptoms can be reduced by drugs that block dopamine receptors.<sup>10</sup>

While it cannot be denied that there are abnormally high numbers of dopamine D2- and D4-like receptors in the schizophrenic brain,<sup>11-12</sup> there are many good reasons to believe that the dopamine hypothesis is, at best, incomplete and, at worst, in error. Amphetamines do more than increase dopamine levels in the brain, they also alter other neurotransmitter levels.<sup>13</sup>

It is possible, therefore, that some of the symptoms of “amphetamine psychosis” are associated with these other affects. Furthermore, drugs that block dopamine receptors do so quickly, and yet it sometimes takes days before their effects on schizophrenics become obvious.<sup>14</sup> This suggests that they are having an impact further down the “catecholamine chain,” perhaps by reducing one or more of dopamine’s derivatives. Alternatively, the effects of dopamine blockers may be even more indirect. Such drugs may be influencing other systems that have a more direct impact on schizophrenia. Newer drugs, such as clozapine, block both dopamine and serotonin<sup>15</sup> receptors, but as discussed earlier, they appear to be no more effective than the traditional neuroleptics that impact on dopamine alone.<sup>16</sup>

The best evidence against the dopamine hypothesis, however, seems to come from experimental biology and biochemistry. The great driving force behind the hypothesis is the belief that extra dopamine receptors in the brain must result from an excess of dopamine. This belief is an error, since there is good evidence that it may be a malfunction of the thyroid system that is responsible for such abnormalities. Overstreet and colleagues<sup>17</sup> have demonstrated that male rats, raised on iodine-deficient diets, develop an abnormally high (28 percent increase) number of dopamine receptors in the striatum. Gilbert<sup>18</sup> has argued also that long exposure to a lack of iodine, seen, for example, in many Africans and Chinese, results in a crucial dopamine-thyroid action that slows cell timing mechanisms. Interestingly, in women suffering from multiple sclerosis, the rate of relapse declines during pregnancy as dopamine levels increase.<sup>19</sup> In contrast, pregnancy is often associated with a depressed thyroid function, which in some cases culminates in goiter.<sup>20-21</sup> Certainly, there is a link between dopamine and the thyroid because Kaptein and colleagues<sup>22</sup> have shown that dopamine reduces serum TSH and aggravates low thyroxine

levels in patients for whom it is prescribed. It is quite likely, therefore, that the dopamine receptor anomalies seen in schizophrenics are caused not by an excess of dopamine but by a depression of thyroid hormones.

If there were an excess of dopamine in schizophrenia one would expect that biochemists would easily be able to identify it. This has not been the case. Indeed, when Tuckwell and Koziol<sup>23</sup> conducted a meta-analysis of research results on the topic, examining all the literature available to them in 1993, they found no evidence of high levels of homovanillic acid, the dopamine catabolite, in schizophrenics. This lack suggests that there is not an excess of dopamine in schizophrenia. Beyond this, these researchers<sup>24</sup> concluded that homovanillic acid levels were, if anything, perhaps below normal. Yamamoto and colleagues<sup>25</sup> also pointed out that extensive biochemical studies, spread over two decades, had failed to provide any conclusive evidence of undisputed dopamine excess in schizophrenia. They further noted that this was not true for noradrenalin and its metabolites, which appeared to be elevated in the cerebrospinal fluids and postmortem brains of schizophrenics.<sup>26</sup> The most logical conclusion to be drawn from the biological and biochemical evidence is that for some 50 years the pharmaceutical industry and its researchers have been trying to push a round jigsaw puzzle piece into a square hole. This explains why, as Horrobin<sup>27</sup> has pointed out, their clinical results have been so poor and their drugs so ineffective in treating the disorder.

## ADRENOCHROME HYPOTHESIS

In the 1950s a few asthmatics using out-of-date adrenaline sprays became psychotic.<sup>28</sup> It was later discovered that the pink or deteriorated adrenaline such sprays contained had

been oxidized to adrenochrome and to other indoles. In an effort to discover what was causing the psychological problems, Drs. Hoffer and Osmond began to experiment on themselves. In one such trial, Osmond<sup>29</sup> was administered 300 milligrams of spray containing adrenochrome. Within 11 minutes his ears felt plugged and his vision became abnormal. Rapidly swinging one arm back and forward caused him to see it as a series of stationary arms. Within an hour, he decided to cycle home from the hospital and noticed that the roadside trees were expanding as if being pumped up with air. Clearly, he was hallucinating. Arriving home earlier than usual he found his wife was out and became very depressed, deciding that she must have left him and returned to her mother in a distant city. He counted all the suitcases. One was missing, increasing his certainty that she had gone. Finding a pile of clothes he concluded his wife had been packing to leave and had decided to go out to purchase her airline ticket. His depression increased. Remembering the experiment, he became very angry with the person who had forced him to take adrenochrome. [He had, in fact, been a very willing participant in the experiment.] Clearly, he was becoming paranoid. Hoffer<sup>30</sup> describes similar experiences, including adrenochrome induced paranoia. This evidence suggests that intelligent, highly educated individuals can be made to display many of the symptoms of acute schizophrenia very quickly, simply by exposing them to excess adrenochrome.

What, then, is the chance that elevated adrenochrome is the key to most schizophrenia? Four significant genetic aberrations have been recognized in this disorder. Many patients suffering from it have a low enzyme activity variant of the catechol-O-methyltransferase (COMT) gene in which valine has been replaced by methionine.<sup>31</sup> This methionine type of the enzyme has only 25 percent of the activity of the valine form. Since catechol-O-methyltransferase metabolizes epinephrine

to the inactive metabolite metanephrine, this means that schizophrenics with this variant produce far less metanephrine than normal, leaving more epinephrine for possible oxidation to adrenochrome.<sup>32</sup> As might be expected, therefore, five recent studies<sup>33-37</sup> from countries as diverse as the USA, Finland, Wales, and Israel have reported that this low enzyme activity variant of the catechol-O-methyltransferase (COMT) gene is associated with aggression, homicides and violent suicides in schizophrenics.

In contrast, other schizophrenics seem to carry an abnormal form of the GSTM1 gene, known as the GSTM1\*0 allele.<sup>38</sup> The GSTM1 gene catalyses a glutathione conjugate of catecholamine-O-quinones, that includes dopachrome, adrenochrome, and noradrenochrome. There are five classes of GST but the GSTM1 gene is much more effective than the other four classes as a catalyst of adrenochrome.<sup>39</sup> What this means is that schizophrenics carrying the GSTM1\*0 allele probably produce higher than normal levels of adrenochrome.

Two of the known genetic aberrations in schizophrenia, consequently, by different mechanisms, increase brain exposure to adrenochrome, an indole that has been demonstrated experientially to produce hallucinations and paranoia. This is because the abnormal form of the catechol-O-methyltransferase gene, found in many schizophrenics, increases the amount of epinephrine that is available for oxidation to adrenochrome. In contrast, the abnormal type of glutathione S-transferase gene, also common in schizophrenics, is very effective in catalysing adrenochrome. As a consequence, either genetic variant will result in an abnormal exposure to this paranoia-producing indole.

The biochemical impact of the third genetic aberration, identified in a subgroup of schizophrenics,<sup>40</sup> is less obvious.

Certainly, the C677T allele of the gene coding for methylenetetrahydrofolate (MTHFR) reduces the availability of methionine, while simultaneously increasing homocysteine.<sup>41</sup> That is, this allele, apparently fairly common in schizophrenics, disrupts the normal remethylation of homocysteine to methionine. The implications of this are not so clear.

Miller and Kelly<sup>42</sup> have published an interesting overview of the known and anticipated biochemical impacts of elevated levels of homocysteine. It is obvious that these are extremely complex. Specifically, homocysteine:

*is an intermediate metabolite of methionine metabolism and is itself metabolized by two pathways: the re-methylation pathway, which regenerates methionine, and the trans-sulfuration pathway, which degrades homocysteine into cysteine and then taurine. Because homocysteine is located at this metabolic crossroad, it impacts all methyl- and sulfur-group metabolism occurring in the body. Consequently, elevated levels of homocysteine would be expected to negatively impact the biosynthesis of all of the following: S-adenosyl-methionine, carnitine, chondroitin sulfates, coenzyme A, coenzyme Q10, creatine, cysteine, dimethylglycine, epinephrine, glucosamine sulfate, glutathione, glycine, melatonin, pantethine, phosphatidylcholine, phosphatidylserine, serine and taurine.*

What, then, is the impact of elevated homocysteine and depressed methionine on the adrenochrome levels in the brain? The Hoffer protocol for the treatment of schizophrenia seeks to alter remethylation by providing high doses of niacin (vitamin B3), a natural methyl acceptor, that is used to reduce the methylation of noradrenalin to adrenaline and then to adrenochrome.<sup>43</sup> Since methylation is so important to the formation of adrenochrome, it is clear that the C677T allele must have an impact on brain levels of this metabolite of adrenaline.

The literature seems unclear, however, on whether high levels of homocysteine and/or low levels of methionine and cystathionine will elevate or depress adrenochrome production. Axelrod,<sup>42</sup> for example, has shown that in the rat liver a shortage of methionine reduced the metabolism of adrenaline to adrenochrome. On the other hand, Fonlupt and coworkers<sup>45-46</sup> have shown that elevated S-adenosylhomocysteine increased norepinephrine synthesis in the rat brain. This, of course, is likely to increase adrenochrome levels. Similarly, Brown and colleagues,<sup>47</sup> in a paper entitled “Unexpected increase in catecholamines in adrenals of rats treated with 3-deazaadenosine,” describe how this methylation inhibitor caused a doubling of both norepinephrine and epinephrine in rat adrenals. Beyond this, Yoshida and coworkers<sup>48</sup> have described how supplementing rat diets with methionine caused a decline, not an increase, in brain levels of norepinephrine (and one would assume adrenochrome). If methionine does, in fact, decrease brain adrenochrome, then it follows that the activity of the C677T allele will increase it. All that seems clear at the moment is that this genetic aberration alters brain adrenochrome levels in schizophrenics. It is also known that elevated homocysteine is associated with aggression and rage in both men and women,<sup>49</sup> characteristics that are much more likely to be linked to a rise than a fall in brain adrenochrome.<sup>50</sup>

The fourth genetic aberration that has been linked to schizophrenia is an unusual Nogo variant gene that seems likely to overproduce proteins that reduce the number of nerve endings in the regions of the brain associated with schizophrenia.<sup>51</sup> If this is the case, this aberration probably makes those affected by it more likely to be adversely impacted by neurotoxins such as adrenochrome.

## SUMMARY

Why has the role of adrenochrome in schizophrenia been so neglected by mainstream medicine? Unfortunately, soon after the initial studies by Osmond, Smythies, and Hoffer, Rinkel published a report claiming that adrenochrome was not an hallucinogen.<sup>52</sup> This quickly killed off the interest of psychiatrists in the substance. However, as Hoffer<sup>53</sup> has pointed out, Rinkel:

*obtained a supply of adrenochrome semicarbazide, known commercially as stable adrenochrome. It was used by surgeons to decrease bleeding. Rinkel gave this inert material to a few subjects and found no hallucinogenic activity. He was unaware this substance is not hydrolyzed in the body, does not release adrenochrome and has different properties. Adrenochrome critics apparently never read Rinkel's subsequent report where he acknowledged his error.*

As a consequence of this mistake by Rinkel, the dopamine hypothesis has been dominant in psychiatry for half a century.

Chamberlin<sup>54</sup> noted in his discussion of the multiple working hypotheses concept that the originators of a new theory tend to have a maternal or paternal relationship to it. As a result, they tend to continue to defend it long after it becomes obvious that it is incorrect. The pharmaceutical industry has made billions of dollars selling drugs to combat an excess of nonexistent dopamine in schizophrenia. Countless psychiatrists have built reputations and businesses on treatments that depend upon it. However, despite all the vested special interests intent on propping up this hypothesis, it is clear that there is no dopamine excess in schizophrenia. While the experimental, clinical, genetic, and biological evidence does strongly support an excess of a catecholamine in schizophrenia, it is adrenochrome

not dopamine. The remainder of this book demonstrates that, while it is impossible to complete a jigsaw puzzle if one believes that dopamine is the key to schizophrenia, it is a relatively simple task to do so on the assumption that adrenochrome plays that role.

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*First they ignore you, then they laugh at you, then they fight you, then you win.*

Mahatma Gandhi

*I know that most men, including those at ease with problems of the greatest complexity, can seldom accept even the simplest and most obvious truth, if it be such as would oblige them to admit the falsity of conclusions which they have delighted in explaining to colleagues, which they have proudly taught to others, and which they have woven thread by thread into the fabric of their lives.*

Leo Tolstoy (1828-1910)

Genetic inheritance plays a significant role in determining who becomes a schizophrenic and who does not. This, of course, is why schizophrenia tends to run in families<sup>1</sup> and why roughly 50 percent of identical twins will eventually become a schizophrenic, if their counterpart already is one.<sup>2</sup> Nevertheless, if genes were destiny, all such identical twins would develop the disorder, once their sibling had been affected. Bishop and Waldholz,<sup>3</sup> in their book *Genome*, explain such relationships, pointing out that “aberrant genes do not, in and of themselves, cause disease. By and large their impact on an individual’s health is minimal until the person is plunged into a harmful environment.” The significance of the four aberrant genes just discussed, therefore, probably depends upon location—that is on geography and on society.

Genetic diseases, constrained by the slow pace of human reproduction, do not undergo rapid changes in incidence. One does not experience epidemics of genetic diseases. However, historical reviews<sup>4-5</sup> leave no doubt that for over two hundred years the incidence of schizophrenia has been rising rapidly

throughout the Industrialized World. That is, we have been experiencing a pandemic of schizophrenia, the invisible plague. This implies that the environmental and/or social trigger(s) for schizophrenia must have become increasingly common as societies industrialized. Or, put another way, schizophrenia is one of the costs that society, as a whole, has been willing to inflict on certain genetically susceptible individuals in order to gain the benefits of industrialization. If the adrenochrome hypothesis is correct, it follows that the environmental trigger(s) for schizophrenia must be substances, processes, or activities that encourage the formation of adrenaline and its oxidation into adrenochrome. Alternatively, such a trigger(s) might inhibit adrenochrome's breakdown, again causing brain levels to rise. This chapter sets out to try to answer two basic questions about schizophrenia. What are the triggers that turn on aberrant genes? And why do they particularly affect young people?

## STRESS

Stress is the easiest way to promote the metabolism of adrenaline in the human body. Although medical interest in stress can be traced back to Hippocrates,<sup>6</sup> it was not until the 1920s that physiologist Walter Cannon<sup>7</sup> confirmed that response to stress is part of a unified mind-body system. Cannon was able to show that various stressors, including extreme cold, lack of oxygen, and emotion-arousing incidents trigger an outpouring of epinephrine (adrenaline) and norepinephrine (noradrenaline). These enter the bloodstream from sympathetic nerve endings in the inner adrenal glands.<sup>8</sup> In those stressed, the sympathetic nervous system increases respiration and heart rate, diverts blood to skeletal muscles, and releases fat from storage. All these changes prepare the body for what Cannon called "fight or flight" and are obviously part of a response system that has evolved in an effort to deal with perceived threats.

Unfortunately, in situations of chronic stress, the “fight or flight” response becomes counterproductive, leading to a cumulative build up of adrenaline, noradrenaline, and cortisol. If these substances are not properly metabolized, long-term stress appears to promote disorders ranging from headaches and high blood pressure to rheumatoid arthritis and allergies.<sup>9</sup> What is significant here is that the “fight or flight” response to stress is associated with an elevation of adrenaline, oxidation of which can lead to an excess of adrenochrome. Perhaps it is not surprising, then, that chronic stress is often linked to anxiety, poor concentration, depression, anger, frustration, fear, and sadness.<sup>10</sup> Of course, if the individual being stressed carries one of the genetic aberrations linked to schizophrenia, adrenochrome levels are likely to be higher than normal and may be linked to the paranoia and hallucinations that this indole causes when taken accidentally or experimentally.<sup>11</sup> In summary, stress may be a trigger for schizophrenia because it increases the production of the precursors of adrenochrome.

Before the rise of the dopamine hypothesis, in the first 50 years of the 20th century, psychosocial explanations of schizophrenia predominated. Such psychosocial models included beliefs that schizophrenia was triggered by traumatic childhood experiences, abnormal family communication, inappropriate child-rearing practices, and cultural and social breakdown.<sup>12</sup> To illustrate, it was discovered that schizophrenia was relatively rare amongst the Hutterites,<sup>13</sup> a religious group that originated in 1530. Naturally, those supporting psychosocial explanations of schizophrenia accounted for this anomaly by pointing to the low stress, and the relatively slow pace of life experienced in Hutterite communities. Such communal villages are invariably rural, being devoted to agriculture, crafts and value-added small scale manufacturing. Everybody is employed and is part of a close society. They are largely free, therefore, of many of the urban stressors that may perhaps

trigger schizophrenia. If adrenochrome is the initial biochemical cause of most schizophrenia, then such psychosocial explanations of the disorder begin to make sense. After all, stress increases the release of adrenaline which in turn can be oxidized to adrenochrome.

## ALLERGIES

Physicians at the Moscow Psychiatric Institute used long fasts to treat schizophrenia, greatly improving the symptoms of 64 percent of all chronic patients who completed their program.<sup>14</sup> This strongly suggests that there may be dietary triggers for the disorder. Further support for this possibility comes from the recognition that such fasting normalizes catecholamine levels in the urine of schizophrenics.<sup>15</sup>

Countries where the national diet traditionally contains large quantities of cow's milk and wheat have poor recovery rates for schizophrenia.<sup>16</sup> This is not unexpected as some schizophrenics greatly improve on gluten free diets,<sup>17</sup> perhaps because celiac disease is common in their families.<sup>18</sup> Indeed, Pfeiffer claimed that 10 percent of schizophrenics suffer from a gluten allergy.<sup>19</sup> Hoffer also discovered that, in some fasting schizophrenics, the reintroduction of cow's milk caused hallucinations.<sup>20</sup> Indeed, 120 of Hoffer's "problem patients," those who had not responded well to orthomolecular treatment, experienced significant permanent improvements in their mental health after identifying and eliminating from their diets specific foods to which they were allergic.<sup>21</sup>

These clues to the etiology of schizophrenia suggest that diet often plays a key role in triggering the disorder. This may be one of the reasons why so many recovered schizophrenics believe that they were formerly hypoglycemic and that they had

greatly improved only after a major dietary change. How can so many different foods trigger one disease? The best way to understand a disorder is often to examine extreme cases. A few people are exceedingly allergic to a particular food, such as peanuts or salmon or to a product such as latex and can die rapidly if exposed to even small quantities of it.<sup>22-23</sup> Allergic reactions can include skin rashes, itching, hives, burning eyes, swollen lips and tongue, difficulty breathing, wheezing, dizziness, abdominal pain, nausea, and diarrhea. In rarer cases, a strongly allergic individual suffers shock; blood pressure drops markedly, the throat swells, and airways in the lungs constrict. Without immediate treatment with epinephrine, death from anaphalactic shock occurs.<sup>22-23</sup>

Interestingly, the treatment of choice for anaphylaxis, whether caused by latex,<sup>25</sup> peanuts, or insect stings,<sup>26</sup> is always epinephrine, a dilute solution of adrenaline. This is because, during an allergic reaction, the chronic inflammatory response is usually characterized by many polymorphonuclear leukocytes,<sup>27</sup> the presence of which have been demonstrated by Matthews and coworkers<sup>28</sup> to be associated with the oxidation of adrenaline to adrenochrome. In such an allergic reaction, oxidation of adrenaline to adrenochrome is detectable within 5 minutes and continues for at least 4 hours.

Of course, many people are allergic to substances that occur in water supplies or as air pollutants or as an integral part of products of one type or another.<sup>29</sup> This may be one of the reasons why schizophrenia's prevalence has markedly increased during the Industrial Revolution. Industrialization has brought with it an enormous range of pollutants that adversely affected air, water, and soil quality. By 1977, the American Chemical Society had registered some four million chemical compounds, 32,000 of which were in commercial use.<sup>30</sup> It is unknown how many of these are potentially dangerous, although there are

currently some 2,450 substances that are thought to cause cancer in the workplace. While attempts are generally made to establish the possible carcinogenicity of such industrial chemicals,<sup>31</sup> their potential effects on mental health rarely appear to be considered.

## HYPOGLYCEMIA

Hypoglycemia was initially described by Dr. Seale Harris<sup>32</sup> in 1924 when he discovered that sugar consumption stimulated the body to release insulin which, in turn, drove blood sugar levels down. Harris discovered that a high-protein, low-sugar diet, eaten at frequent small meals, maintained a normal and stable blood sugar level, so controlling hypoglycemia. Since the USA sugar consumption<sup>33</sup> per capita has increased by approximately a factor of 20 since 1822, it is not surprising that hypoglycemia has become rampant in its population.<sup>34</sup>

It may be recalled that many recovered schizophrenics felt that they had previously suffered from hypoglycemia. Schauss<sup>35</sup> also estimated that between 80 and 85 percent of criminals in USA prisons suffer from hypoglycemia, often eating an excess of sugary foods, and repeatedly drinking sugar-sweetened coffee and/or Kool-Aid. It is well known that when blood sugar levels drop, adrenaline is released from the adrenal glands because it is involved in the metabolism of glucose.<sup>36-37</sup> It follows, therefore, that anyone suffering from the large blood sugar swings characteristic of hypoglycemia (associated with a diet that is too rich in sugar) is going to overproduce adrenaline. Hypoglycemic individuals with one or more of the genetic aberrations seen in schizophrenia are, therefore, likely to suffer psychosis caused by adrenochrome created by the oxidation of this excess adrenaline.

## SUMMARY

It is widely believed that schizophrenics have fewer allergies than normal. The evidence just cited, however, suggests this is another error. It is more than likely that one or more of the biochemical anomalies seen in schizophrenia renders the normally used scratch or prick skin tests unreliable. According to Kail and coauthors,<sup>38</sup> "These tests are limited in that they only measure Type 1 or IgE-mediated, allergic responses (asthma, allergic rhinitis, eczema, and hives), which are primarily triggered by inhaled allergens such as pollen, mould, dust, and animal dander." These procedures have only about a 15 percent accuracy rate in spotting food-induced allergic reactions.<sup>39</sup> As a consequence, delayed food allergies, together with most chemical sensitivities, go undetected. Interestingly, the same type of problem is occurring in testing for tuberculosis. To quote Reichman and Tanne.<sup>40</sup>

*In ordinary circumstances, a positive tuberculin skin test indicates past or present latent tuberculosis infection, so most patients with active TB are assumed to have a positive skin test. But 27 of the 29 TB patients in our first report had negative skin tests. The tuberculin skin test measures a reaction to tuberculin by the patient's immune system, but these patients' immune systems were obviously so depleted by HIV that they couldn't muster a response to the tuberculin test.*

Certainly, schizophrenics can rarely respond in the normal way to a niacin skin challenge and often appear to have an increased tolerance for histamine.<sup>41</sup>

The evidence presented in this chapter, therefore, suggests that when individuals who carry specific genetic aberrations (such as the low enzyme activity variant of the catechol-O-methyltransferase gene or the GSTM1\*0 allele) are subjected to stress, or substances to which they are allergic, or an excess of sugar,

they over-produce adrenaline and subsequently adrenochrome. As a consequence, they experience psychotic episodes. Stress, allergic reactions, and the over-consumption of sugar are the environmental triggers that, together with one or more of these aberrant genes, cause schizophrenia. Such triggers lead to schizophrenia most often in the young for two basic reasons. Adolescents and young adults are affected by rising hormone levels, including adrenaline, that generally peak shortly before age 30 and then begin a gradual, but straightline, decline.<sup>42</sup> At some point, probably during a period of stress, or after a sugar binge that adolescents are famous for, adrenaline production rises to a level at which associated adrenochrome becomes elevated enough to cause the first schizophrenic episode.

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*It is frightening (or exciting) to contemplate how many new ideas are lying dormant in already collected information that is now put together in one way and could be rearranged in a better way. At first Einstein's theories were only minimally more adequate than the ones they replaced. The difference in explanation amounted to a better understanding of the wavelengths of light from the star Sirius and a very slight alteration in the orbit of the planet Mercury. In terms of detail this was like replacing a cup in a restaurant, but from that new way of looking at things came atomic energy.*

Edward de Bono<sup>1</sup>

The walls of geography departments are covered in maps because location is the key to integrating spatial data. At smaller scales, cities become points interconnected by networks of rivers, roads, and railways. This is my world. I think in terms of why diseases occur where they do. In biochemistry departments, the walls are papered with charts that look, at first glance, very like maps. Here the points, however, represent trace elements, hormones, fatty acids, and the other essential biochemical components of life. The networks that connect them are more like those of ancestral family trees, identifying what gives birth to what and how. They are lines of process that show how disruption can spread out in all directions like an advancing army. Such charts confirm just how interconnected the processes that occur in the human body really are.

If the adrenochrome excess hypothesis is correct, this adrenaline metabolite is bound to cause other biochemical imbalances. This chapter attempts to identify the most immediate of these cascades.

## ADRENOCHROME AND TRIIODOTHYRONINE

Even before birth, those unfortunately destined to become schizophrenics probably suffer from abnormal thyroids. They demonstrate minor fetal physical anomalies, developed in the first trimester, that are similar to those found in infants born to women abusing alcohol during pregnancy.<sup>2</sup> Evidence is increasing that fetal alcohol syndrome is caused by alcohol's negative impacts on the thyroid gland.<sup>3</sup> The elevation of brain dopamine receptors also discovered in schizophrenics is similar to that observed in rats that have been fed diets that are deficient in iodine.<sup>4</sup> The thyroid gland is very susceptible to radioactive iodine damage and the prevalence of schizophrenia is higher than normal in both fetuses irradiated by atomic bomb fallout<sup>5</sup> and workers who were involved in the dangerous clean-up that followed the Chernobyl nuclear power plant disaster.<sup>6</sup>

There is also direct evidence of malfunctioning thyroid glands in psychotic inpatients early after hospitalization when their thyroid hormone imbalances are strongly positively correlated with the severity of their symptoms.<sup>7</sup> A wide range of thyroid irregularities also have been identified in "permanently hospitalized chronic schizophrenics."<sup>8</sup> In addition, Skoliarova<sup>9</sup> has described a series of autopsies carried out on schizophrenics almost immediately after death. In all cases, they had suffered from a clear, visible deterioration of the thyroid gland, rarely seen in any other type of patient. According to Hoffer and Osmond,<sup>10</sup> several researchers have shown that thyroid

hormone (either in the form of dried gland or as the pure hormone triiodothyronine) improves the cure rates for schizophrenia far above the natural untreated rates, but also much above that achieved by conventional treatments, including tranquilizer use. As previously described, for example, Danziger<sup>11</sup> prescribed desiccated thyroid for 120 schizophrenics, with doses ranging from 120 to 1,200 milligrams. Every one of the 80 patients who had been ill for 6 months or less and who completed this treatment, recovered.

The geographical evidence<sup>12</sup> strongly suggests that any such benefit in schizophrenia from thyroid supplements must be coming from extra triiodothyronine, rather than from thyroxine. This is because, in the USA, there is no significant correlation between the prevalence of iodine deficiency disorder, goitre, and schizophrenia.<sup>13</sup> Schizophrenia is, however, considerably more common in low selenium states.<sup>14</sup> Indeed, variations in the prevalence of schizophrenics in state and county mental hospitals in the USA suggests a selenium deficiency relative risk of 1.77:1.<sup>15</sup>

Selenium plays a key role in the production of triiodothyronine, but not of thyroxine. Researchers at the Hahn-Meitner Institute in Berlin,<sup>16</sup> for example, found that selenium is necessary to produce deiodinase, the enzyme required to convert thyroxine into triiodothyronine. If there is a selenium deficiency, deiodinase is depleted and adequate quantities of triiodothyronine cannot be produced. Naturally, this is most likely to occur when diet is low in selenium, often reflecting a local soil inadequacy.

Taken as a whole, this evidence suggests that there is a significant triiodothyronine deficiency in schizophrenia which eventually causes serious thyroid damage. This probably explains why initially the disorder is episodic but eventually, as

the thyroid is rendered unable to function effectively, becomes chronic, since it is well known that thyroid imbalances themselves result in psychosis.<sup>17</sup>

What, then, is the evidence that excess adrenaline and associated adrenochrome may be linked to the inadequate triiodothyronine levels seen in schizophrenics? There can be little doubt that both adrenaline and adrenochrome have significant impacts on the thyroid gland and its hormones. Maayan and Ingbar,<sup>18</sup> for example, showed that both of these substances greatly enhanced iodine metabolism in calf thyroid cells. One important result of this seems to be a decline in available triiodothyronine. It has been shown that adrenaline infused into healthy dogs quickly causes a decline in the conversion of thyroxine to triiodothyronine.<sup>19-20</sup> This “low T3 syndrome” has also been produced in rats infused with adrenaline.<sup>21</sup> Whether it is caused directly by excess adrenaline, or by adrenochrome associated with adrenaline oxidation, is unclear. The later possibility was explored by Maayan and Ingbar<sup>22</sup> who speculated that adrenaline’s apparent impacts on iodine metabolism activity and glucose oxidation might actually be due to its metabolite adrenochrome.

The best explanation of the available evidence is that both adrenaline and adrenochrome are antagonistic to triiodothyronine. Consequently, when certain genetically susceptible individuals are subjected to allergens, stress, or too much sugar, they produce an excess of adrenaline, some of which is quickly oxidized to adrenochrome. As a result, the normal operation of the thyroid gland is disrupted and triiodothyronine levels depressed. The resulting psychotic symptoms are known as schizophrenia and in their early stages can be reversed by high doses of triiodothyronine. Without such treatment, damage to the thyroid becomes permanent and the disorder chronic.

## ADRENOCROME AND SEROTONIN

In *What Really Causes AIDS*,<sup>25</sup> I documented that whole blood serotonin levels are abnormally low in AIDS patients.<sup>24</sup> This deficiency of serotonin appears to occur because the HIV-1 virus encodes for the selenoenzyme glutathione peroxidase. Consequently, as it is replicated HIV-1 removes tryptophan (one of the four nutrients required to make glutathione peroxidase) from the human body. Interestingly, as viral replication lowers blood tryptophan and its metabolite serotonin levels in patients with AIDS, their neuropsychiatric symptoms worsen.<sup>25</sup> This suggests that serotonin deficiency may play a significant role in psychoses such as schizophrenia. Certainly, there is growing interest in developing drugs to alter the brain's response to this neurotransmitter.

There is relatively little literature, however, on the interactions of adrenochrome and serotonin. Two research articles by VanderWende and Johnson<sup>27-28</sup> appear critical. In these publications, the authors described epinephrine's (adrenaline) and adrenochrome's impacts on rat brain enzyme preparations, paying special attention to serotonin's impact on epinephrine oxidation. Their results were very surprising. To quote these authors directly: "Adrenochrome formation from epinephrine is either accelerated or inhibited by serotonin, the effect being dependent on the relative concentrations of the indoleamine compared to the catecholamine." Put more simply, when the rat brain tissue concentration of serotonin was lower than that of adrenaline, adrenochrome formation was accelerated, but when the serotonin concentration was greater than that of adrenaline, the formation of adrenochrome was inhibited.<sup>29</sup> If, as the evidence presented so far in this book suggests, adrenochrome excess is the key to schizophrenia, then serotonin must be of major significance in both preventing and promoting this disorder. This Jekyll and Hyde relationship also

explains why acute schizophrenic episodes may occur so suddenly, since a minor increase in adrenaline or fall in serotonin may push their relationship over a system threshold, rapidly causing an increase in adrenaline oxidation and associated adrenochrome.

There is another aspect of serotonin that also may be of significance in the etiology of schizophrenia. Khazali<sup>30</sup> injected cows with serotonin at levels of 1, 2, and 4 milligrams per kilogram over a 15 day period, while a control group was given saline. Blood samples were collected before and after this experiment and assayed for plasma thyroxine and triiodothyronine. It was discovered that injections of saline or 1 and 2 milligrams of serotonin per kilogram had no impact on the plasma concentrations of thyroid hormones. However, 15 days of serotonin injections at 4 milligrams per kilogram did significantly increase serum levels of both thyroxine and triiodothyronine. It would appear, therefore, that there may also be a dose-response relationship between serotonin and triiodothyronine. Interestingly, not only is serotonin depressed in AIDS patients, but so, too, is triiodothyronine.<sup>31</sup> Further evidence to support a connection between serotonin and triiodothyronine has been provided by Sandrini and coworkers,<sup>32</sup> who administered triiodothyronine to rats and then monitored their brain serotonin levels. Both acute (once only) and chronic (once a day for either 3 or 7 days) treatments increased serotonin levels in the rat cerebral cortex, but not in the hippocampus. It has been found also that adding triiodothyronine to the medications of patients with post-traumatic stress disorder, who are taking a selective serotonin reuptake inhibitor (such as paroxetine or fluoxetine), seems to be beneficial.<sup>33</sup> There appears to be little doubt, therefore, that not only does adrenochrome significantly impact on triiodothyronine and serotonin, but that these two latter substances are also strongly interactive.

## ADRENOCROME AND THE ANTIOXIDANT DEFENCE SYSTEM

Schizophrenics have impaired antioxidant defence systems which are associated with both excessive lipid peroxidation and abnormal free radical pathology.<sup>34-39</sup> These problems are obvious even in first episode schizophrenics, those who have never received medication<sup>40</sup> for this illness, and so they must be characteristic of the disorder and not a consequence of the drugs used to treat it. Such failures in the antioxidant defence system seem to continue and ultimately cause serious brain damage in chronic schizophrenics.<sup>41</sup> Buckman and co-workers,<sup>42</sup> for example, have demonstrated that long-term inadequencies in antioxidant defence systems (illustrated by depleted glutathione peroxidase stores), are associated, in chronic schizophrenics, with large fluid-filled brain ventricles. That is, the more depleted chronic schizophrenics are of glutathione peroxidase (a key enzyme protecting against free radicals), the more obvious their brain damage. While there have been several studies showing abnormally low glutathione peroxidase activity in schizophrenics, there are clearly problems with other antioxidant enzymes, including catalase and superoxide dismutase.<sup>43-45</sup>

The key question here is, how likely is it that this disruption of the antioxidant defence system, observed in schizophrenia, is caused by an excess of adrenochrome. Smythies<sup>46</sup> has described six mechanisms of defense against cytotoxic quinones such as adrenochrome, derived from catecholamines. The first of these mechanisms is reduction by antioxidants, such as ascorbate and glutathione. Interestingly, Fu and colleagues<sup>47</sup> have dosed rats with 80 milligrams per kilogram of 3-nitropropionic acid. Using an electron spin resonance technique they were able to observe free radical signals. It was discovered that 3-nitropropionic acid enhanced adrenochrome formation from adrenaline in both the rat liver and brain. As a

consequence, glutathione peroxidase and superoxide dismutase activity significantly increased in the liver while malonidialdehyde levels rose. Superoxide dismutase activity also increased in the brain, suggesting that 3-nitropropionic acid-induced adrenochrome activity was causing lipid peroxidation damage. This study provides direct observational evidence that adrenochrome creates free radicals that lead to increased oxidative stress and is probably one of the main causes of the depletion of glutathione peroxidase, superoxide dismutate and catalase seen in schizophrenics.

The damage adrenochrome causes to the antioxidant defence system also has repercussions in the operation of the thyroid gland and the production of triiodothyronine. Mutaku and co-workers,<sup>48</sup> for example, induced goitre in rats that were either vitamin E deficient or had received an adequate supply of this vitamin. Those lacking in this essential antioxidant developed goitres that included significantly increased necrosis, indicating that much of the cell death in goitre is related to the oxidative status of the cells. Beyond this, animal studies<sup>49-51</sup> have shown that triiodothyronine promotes superoxide dismutase, catalase, and glutathione activities, suggesting that the antioxidant defence system is considerably influenced by the thyroid state of the body.

Several studies also have demonstrated that serotonin is an antioxidant<sup>52-53</sup> and therefore is involved in reducing free radical damage. Since oxidative stress impairs the thyroid<sup>54</sup> and so reduces triiodothyronine levels, lipid peroxidation must also have a direct impact on brain levels of serotonin. Reactive oxygen species also play a role in major depression, and treatment with selective serotonin uptake inhibitors has a suppressive effect on both antioxidative enzyme activities and lipid peroxidation.<sup>55</sup>

## SUMMARY

Adrenochrome is a highly reactive neurotoxin that, in schizophrenia, undermines at least three major biochemical systems. It is an antagonist of the hormone triiodothyronine and can damage the thyroid. In chronic schizophrenics, this gland impairment appears permanent. Adrenochrome also has a Jekyll and Hyde relationship with serotonin and so also impacts on tryptophan and its other chief metabolite niacin. At low levels, serotonin appears to stimulate adrenochrome formation, while at higher levels it retards the process. Adrenochrome also generates numerous free radicals causing oxidative stress, eventually exhausting the schizophrenic antioxidant defence systems, so creating deficiencies of glutathione peroxidase, superoxide dismutase, and catalase. Complicating the impacts of high adrenochrome conversion from adrenaline are the many interactions that normally occur between triiodothyronine, serotonin, and the three major components of the antioxidant defence system.

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*To this purpose the philosophers say that Nature does nothing in vain, and more is in vain when less will serve; for Nature is pleased with simplicity, and affects not the pomp of superfluous causes.*

Isaac Newton, "Rules of Reasoning in Philosophy,"  
*Principia Mathematica*, 1687.

*Mainstream institutions favor “hypothesis-driven” rather than “hypothesis-generating” research. In the former, a scientist starts with a supposition and conducts the experiment to prove or disprove the idea; whatever the results, at least in the end there’s a paper to write up, something to show for the work. But in hypothesis-generating research—the engine behind today’s search for new pathogens—the scientist inches forward by hunch and intuition, gathering clues, speculating on what they mean. “Nobody’s funding hypothesis-generating research,” says Morens. “Within science, that’s considered the lowest level of research—out of the primeval ooze.”*

Madeline Drexler (2002).

*Secret Agents: The Menace  
of Emerging Infections*<sup>1</sup>

So here we are, like our ancestors before us, trying to drag ourselves out of the primeval ooze. What makes the process more frustrating is that the adrenochrome hypothesis was first put forward some 50 years ago.<sup>2</sup> Since then its proponents have been repeatedly vilified for being different and probably right, as is the tradition in medicine.<sup>3</sup> When a keen, green undergraduate, I had the luck to study in one of the world’s truly great geology departments. Several of my former professors, though long retired, are still known and revered by the profession. Interestingly though, in the 2 years I spent studying the discipline, Continental Drift was hardly ever mentioned.

When it was, it was only so that it could be discounted as an absurd idea that had long outlived its usefulness, the stuff of cranks and fringe members, too ignorant to understand its inherent weaknesses. Of course things have changed. It is now no longer absurd to postulate global crustal movements, rather the reverse. The cranks are now those who deny Plate Tectonics and Continental Drift. Clearly, major hypotheses come and go. Just because the adrenochrome hypothesis is half a century old and largely ignored, except by orthomolecular physicians, does not mean that it is incorrect.

The most effective way to test the validity of the adrenochrome hypothesis is to utilize it in attempts to explain the evidence that has been collected about schizophrenia by disciplines as diverse as genetics and history. That is, to see whether the schizophrenia jigsaw puzzle can be completed using the adrenochrome hypothesis as its dominant theme. To assist in this process, Table 1 lists the clues identified in the earlier chapters. For ease of identification, each clue is numbered according to the chapter in which it was first discussed and it is lettered to identify its position within that chapter. To illustrate, clue 5A (the elevation of schizophrenia in irradiated populations) is the first clue in Chapter 5—*Biochemical Abnormalities*.

What follows is my effort to explain each of these clues, using the adrenochrome hypothesis as a starting point. I cannot adequately explain some of them. This may be because the adrenochrome hypothesis is incorrect or the data the clue is based on was in error, or I am too ignorant to be aware of the real link between the tested hypothesis and the clue. The goal, therefore, must realistically be to explain the majority of the clues in Table 1 and to do so in a manner that is more convincing than explanations that have been put forward using competing hypotheses.

## OCCAM'S RAZOR

The principle “Pluralitas non est ponenda sine neccesitate” or “plurality should not be posited without necessity” is often accredited to the medieval Franciscan monk and English philosopher William of Occam (ca. 1285-1349).<sup>4</sup> Known as Occam’s razor, or the principle of parsimony, it is now interpreted to mean “don’t multiply hypotheses unnecessarily” or “the simpler the explanation, the better.” In its crudest form it has been distilled into “keep it simple, stupid.” For any given set of facts, such as those discussed in the preceding 10 chapters to explain why certain people develop schizophrenia, there are an endless number of theories that could be used to explain them.<sup>5</sup> To illustrate:

*If you have a graph with four points in a line then the simplest theory that explains them is a linear relationship, but you can draw an infinite number of different curves that all pass through the four points. There is no evidence that the straight line is the right one, but it is the simplest possible solution. So you might as well use it until someone comes along with a point off the straight line. Also, if you have a few thousand points on the line and someone suggests that there is a point that is off the line, it’s a pretty fair bet that they are wrong.*<sup>6</sup>

What follows is this author’s attempt to draw a straight line connecting the clues identified in the previous chapters. That is, an attempt to put those pieces of the schizophrenia jigsaw puzzle together in the simplest, most logical manner and yet still create a convincing picture. If this can be accomplished using the adrenochrome hypothesis, the case for change in the approach to the prevention and treatment of schizophrenia will be undeniable.

## TABLE 1 THE PIECES OF THE JIGSAW PUZZLE

### Chapter 1 Schizophrenia: From Bedlam to Babel

- A. Afflicts young adults
- B. Episodic
- C. Often becomes chronic without remission
- D. Disorder of thought
- E. Disorder of perception
- F. Disorder of emotion
- G. Disorder of sensory stimuli
- H. Rapid mood swings
- I. Fatigue
- J. Four major subtypes
- K. Only one in five recover to lead nearly normal life after initial schizophrenic episode
- L. Suicide common
- M. Recovery rate no better than century ago
- N. Whole body disorder
- O. Probably syndrome with environmental and genetic triggers

### Chapter 2 The Schizophrenia Pandemic

- A. Schizophrenia (insanity) known for thousands of years
- B. Increased rapidly since end of seventeenth century
- C. Prevalence rises as countries or regions westernize
- D. Baseline rate one case per 2000 people before Industrial Revolution
- E. England, Ireland, Canada, USA prevalence of insanity increased at least sevenfold between mid-eighteenth and mid-twentieth centuries (sixteen times in Ireland)
- F. Schizophrenia most common in urban areas

### Chapter 3 Genesis: In the Beginning

- A. Minor fetal abnormalities common
- B. Birth difficult
- C. One twin dies, other more likely to become schizophrenic
- D. Low birth weight
- E. Prolonged labour
- F. Larger brain cavities (ventricles)
- G. Malfunctioning thalamus
- H. Abnormalities of subplate neurons
- I. Elevation of dopamine D4-like receptors
- J. Elevation of dopamine D2-like receptors
- K. Enlarged brain ventricles linked to depressed glutathione peroxidase
- L. Thyroid gland deterioration in all schizophrenics

### Chapter 4 The Genetic Basis of Schizophrenia

- A. Common mental illness in Developed World (1 in 100)
- B. More common in relatives of schizophrenics
- C. More common in specific families
- D. Roughly 50 percent of identical twins will develop the disorder if the other already has it
- E. Must have counterbalancing advantage or trait would have died out because of low birth rate in schizophrenics — balance morphism
- F. Common in DiGeorge syndrome (22q deletion syndrome)
- G. Genetic low activity abnormality in enzyme catechol-O-methyltransferase (metabolizes epinephrine to metanephrine) in some schizophrenics
- H. Low activity COMT gene associated with aggression in schizophrenics (homicide/violent suicide)
- I. Genetic high activity glutathione S-transferase (GSTM1)

abnormality (promotes adrenochrome production) in some schizophrenics

- J. Low activity methylenetetrahydrofolate reductase (MTHFR) gene (metabolizes homocysteine) in some schizophrenics
- K. Nogo variant gene in some schizophrenics
- L. Genetic evidence suggests need for environmental trigger

## Chapter 5 Biochemical Abnormalities

- A. Schizophrenia more common in irradiated populations
- B. Abnormal thyroid function including elevated thyroxine in recently hospitalized acute schizophrenics
- C. Acute schizophrenic symptoms proportional to thyroid hormone imbalance
- D. Deficient in niacin (vitamin B3)
- E. Do not flush when given high dose niacin
- F. "Kryptopyrrole" levels often elevated
- G. Depressed antioxidant defence system
- H. Schizophrenics improve with n-3 fatty acid supplements
- I. Membrane phospholipid abnormalities linked to leak of arachidonic acid and other fatty acids
- J. Abnormal brain tryptophan levels
- K. Low tryptophan diets increase negative symptoms and cognition
- L. Histamine imbalances
- M. Copper imbalances
- N. Glutamate imbalances linked to symptoms
- O. No evidence of metabolite of dopamine (homovanillic acid) excess
- P. No convincing experimental evidence of dopamine excess
- Q. Homocysteine imbalances

## Chapter 6 Pulling the Trigger: Location, Location, Location

- A. Schizophrenia commonest in Ireland, Northern Sweden, and Croatia
- B. Prevalence rates strongly reflect better recovery rates in countries where diet includes little wheat or milk
- C. Common in selenium deficient states of the USA
- D. Common in the more industrialized USA
- E. Less common in high soil calcium states
- F. Similar prevalence rates to mortality from cancer of the esophagus
- G. Seasonality of schizophrenic births
- H. Less common in areas of high sunlight
- I. Schizophrenia most common in urban areas in zone of transition (around Central Business District)
- J. More common in poor in England, Ireland, US, and Japan
- K. More common in rich in India and Italy

## Chapter 7 No Barking Dogs: Medical Anomalies

- A. Schizophrenics are heavy smokers yet lung cancer rare
- B. Rheumatoid arthritis uncommon in schizophrenics
- C. High pain threshold
- D. Elevated temperature (fevers) reduces symptoms temporarily
- E. Associated with herpes simplex virus type 1
- F. Relatives of schizophrenics commonly develop celiac disease
- G. Some schizophrenics improve on gluten-free diets
- H. Positive association between Ixodid ticks and schizophrenia prevalence in US, Croatia, Norway, Finland, Germany, Iceland, and Switzerland

## Chapter 8 Unconventional Treatments

- A. Schizophrenics improve markedly with fasting
- B. Fasting lowers histamine levels
- C. Fasting normalizes catecholamines
- D. Serotonin normalized by fasting
- E. Cow's milk a hallucigen in some schizophrenics
- F. Histamine injections improve some catatonic schizophrenics
- G. High dose of desiccated thyroid most successful treatment
- H. Triiodothyronine at high dosages helps chronic schizophrenics
- I. Excess of copper and depressed histamine in 50 percent of schizophrenics, respond to niacinamide, niacin, folic acid, zinc, and manganese
- J. Elevated histamine and low copper in 20 percent of schizophrenics, respond to calcium, methionine, zinc, and manganese
- K. Pyroluria caused by zinc and vitamin B6 deficiency
- L. Wheat gluten allergy in 10 percent of schizophrenics
- M. Hypoglycemia in 20 percent of schizophrenics
- N. Orthomolecular treatment designed to block conversion of noradrenalin to adrenaline and then to adrenochrome works on 90 percent of acute and 50 percent of chronic schizophrenics
- O. Above treatment includes high doses of niacin, vitamin C, and omega 3 essential fatty acids (high in eicosapentaenoic acid)

## Chapter 9 Conventional Treatments

- A. Insulin treatment producing coma an effective treatment
- B. Insulin treatment alters tryptophan levels, enhancing the tryptophan to tyrosine ratio in plasma, probably increasing brain serotonin
- C. Electroconvulsive shock treatment lowers plasma levels of MHPG, a major metabolite of noradrenaline

- D. Niacin given in high doses prevents electroconvulsive shock treatment's memory loss side effects
- E. Neuroleptics block dopamine D2 and D4 receptors
- F. Amphetamines release dopamine and exacerbate schizophrenia's positive symptoms
- G. Atypical neuroleptics block dopamine receptors and 5-HT2 subtype of serotonin receptors
- H. Parkinson-like symptoms side effect of some neuroleptics
- I. Drugs improve symptoms by only 15-25 percent
- J. Beta-adrenergic receptor antagonists (beta-blockers) do not work

### Chapter 10 Regression Analysis: The Road Back

- A. Relatively few recovered schizophrenics give credit to drugs
- B. Work, respect and loving environment with little stress helpful in recovery
- C. Many recovered schizophrenics formerly hypoglycemic, altered diets
- D. High dose niacin, vitamin C often used by recovered schizophrenics
- E. High dose desiccated thyroid used by some recovered schizophrenics
- F. Nutritional supplements reduce violence in prisons

### THE ADRENOCROME HYPOTHESIS: READY FOR TESTING

Adrenochrome is a hallucinogen, a neurotoxin, and a free radical generator and there are certainly two, possibly three, and maybe even more genetic aberrations that increase the proportion of adrenochrome and its derivatives amongst metabolites of adrenaline.<sup>7-10</sup> The inheritance of such a genetic variant does not necessarily lead to the development of schizophrenia. However,

when high stress, excess sugar consumption, allergic reactions, or a lack of exercise stimulate either the overproduction of adrenaline or its rapid oxidation, then brain adrenochrome and its derivatives appear to rise to levels at which psychosis occurs. The resulting symptoms are known as schizophrenia.

## From Bedlam to Babel

The initial chapter of this book discusses the clinical symptoms of schizophrenia, providing 15 basic clues (Table 1). Schizophrenia begins as an episodic disorder that afflicts young adults but often becomes chronic. This mental illness is associated with fatigue, mood swings, hallucinations, and sometimes with paranoia. Using variations in symptoms, the disorder can be divided into four major subtypes. Available drugs rarely lead to a cure and have often caused Parkinson's-like symptoms. Suicide is common amongst schizophrenics, and so is violence against others.

Let us consider each of these clinical characteristics in order. It is probable that the first schizophrenic episode occurs in genetically susceptible young adults when their hormone production has begun to increase and the affected individual has been exposed to one or more adrenaline triggers (high sugar intake, stress or an allergen). In the early stages of the disorder, a new location may lead to dietary, allergy, or other changes that will permit adrenochrome production to fall and psychosis to retreat. However, if this pattern of exposure to adrenaline triggers is repeated too often, excess adrenochrome will begin to seriously damage the thyroid gland, disrupt serotonin levels, and encourage excessive free radical damage to the brain. At this point, a permanent deficiency of triiodothyronine appears to occur which, in and of itself, may cause psychosis.<sup>11</sup> Schizophrenia, as a result, is now chronic.

As has been discussed, if intelligent, healthy individuals are given adrenochrome, they quickly begin to hallucinate and subsequently become paranoid. Cats injected with one milligram of adrenochrome became drowsy for 24 hours. “The electroencephalographic changes accompanying these lethargic, trance-like states were occipital 4cps, slow waves with low-voltage spike components, spreading to the frontal regions and then diffusely over the brain.”<sup>12</sup> Similar abnormal waves have been recorded in the brains of humans given adrenochrome.<sup>13</sup> At lower doses, cats displayed a moderate insensitivity to pain.

How could an excess of adrenochrome explain four distinct types of schizophrenia—simple, hebephrenic, catatonic, and paranoia? There seem to be two possible answers to this question. Firstly, the associated genetic aberrations themselves do not lead only to an excess of adrenochrome. Schizophrenics with the low enzyme activity variant of the catechol-O-methyltransferase (COMT), for example, will also have far less metanephrine than normal.<sup>14</sup> Schizophrenics with other variants will not. Similarly, schizophrenics carrying the C677T allele of the gene coding for methylenetetrahydrofolate will be short of methionine while simultaneously subjected to elevated homocysteine.<sup>15-16</sup> It is possible, therefore, that some of the symptoms used to differentiate and subdivide schizophrenics are caused by the other biochemical abnormalities accompanying excess adrenochrome. This idea is supported by the coincidence that, to date, four genetic aberrations have been identified in subgroups of schizophrenics.

There is yet another intriguing possibility. Schwarz and co-workers<sup>17</sup> describe giving adrenochrome to two schizophrenic patients. Fifty milligrams of adrenochrome quickly altered the nature of their brain waves as sharp increases in the number and voltage of focal sharp waves became obvious on their electrograms. Adrenochrome also had a significant impact on their

behaviour. One schizophrenic<sup>18</sup> demonstrated a loosening of associations and an increase in disturbances of body image. He raised his hand, gazed at it, and said that his arm was wiggling and waving. This he found amazing. It seems clear that he was experiencing a type of hallucination that was new to him. The second schizophrenic<sup>19</sup> patient:

*experienced catalepsy on two occasions, which persisted for more than 30 minutes. At these times, his upper extremities were held in unnatural positions that volunteers who served as controls could not maintain for long. This was not his usual reaction, and a similar state did not develop with either mescaline or LSD-25.*

If this schizophrenic had normally displayed such catalepsy he would have been classified as a catatonic, but this state was only induced by additional adrenochrome.

The experiences of these two schizophrenics when administered adrenochrome hints that some of the characteristic clinical symptoms, used to subdivide schizophrenics into four or more classes, may be simply a reflection of differences in the amount of excess adrenochrome normally produced. I realized that this is an idea that will not be readily accepted. However, there is another important clue supporting it. Between 1946 and 1956, Danziger<sup>20</sup> prescribed high dose desiccated thyroid for many schizophrenics who had been ill for 6 months or less. Everyone who successfully completed his or her program recovered. These 80 former schizophrenics only suffered relapses if they then discontinued their thyroid medication while at home. To me this suggests that, however one classifies schizophrenics, they have a great deal in common, including a malfunctioning thyroid gland.

Available drugs rarely lead to cures. Some of the conventional antipsychotics cause Parkinsonism as a side-effect. This is

due to the fact that these drugs were specifically developed to treat an excess of brain dopamine. There is, in fact, no excess of this neurotransmitter in schizophrenia. Drug interference with dopamine in schizophrenics, therefore, often causes a medically-induced version of Parkinson's disease, a well established dopamine deficiency disorder.<sup>21</sup>

Adrenochrome results in paranoia in healthy, intelligent researchers. It might be anticipated, therefore, that the low enzyme variant of the catechol-O-methyltransferase (COMT) gene, which promotes adrenochrome formation, is associated with aggression, homicides, and violent suicides.<sup>22-24</sup> As a consequence, individuals with this variant make up a significant number of the inmates of facilities catering to the criminally insane, in countries as diverse as the USA, Finland, Wales, and Israel. Interestingly, the suicide rate amongst schizophrenics drops markedly if they receive orthomolecular treatments designed to lower their brain adrenochrome levels.<sup>25</sup>

## The Invisible Pandemic

In this volume's second chapter, the history of schizophrenia is briefly reviewed, providing six more significant clues about the etiology of this mental illness. Schizophrenia has been known for thousands of years. Prior to the Industrial Revolution, traditional baseline prevalence seems to have been roughly one case per 2,000 people.<sup>26</sup> This figure began to change at the end of the 16th century as prevalence started to rise with industrialization. As a result, in England, Ireland, Canada, and the US insanity rates (largely schizophrenia) increased at least 7-fold between the mid-18th and mid-20th centuries. In Ireland, the prevalence of insanity may have risen as much as 16-fold. In all of these countries, schizophrenia is most common in urban areas.<sup>27</sup>

Can the adrenochrome hypothesis account for such historical increases in this mental illness and for the rural-urban differences in the prevalence of schizophrenia? As Torrey and Miller<sup>28</sup> point out, “the epidemic of insanity that has occurred over the past two centuries is a strong argument against these diseases [schizophrenia and manic-depression] being primarily genetic in origin.” However, whether or not the prevalence of a disease that has a strong genetic component becomes epidemic depends to a great extent on whether or not there are changes in the environment that “switch on” this aberrant gene(s).

Industrialization has changed the human environment in numerous ways, several of which significantly promote the production of adrenaline and/or its oxidation to adrenochrome and its derivatives. Over the past two hundred years, for example, the quantity and quality of the food supply has altered dramatically. A wide diversity of both imported and processed foods are now available, increasing the probability that any individual may be exposed to something in diet to which he or she is allergic. Similarly, the amount of sugar being consumed, and, therefore, the chance of developing hypoglycemia, has greatly increased,<sup>29</sup> so stimulating adrenaline production in the average citizen who is now quite likely to be diabetic and obese. Beyond this, soils, air, and water are polluted by over 32,000 chemicals<sup>30</sup> that are in widespread commercial use. These substances again increase the probability of allergic reactions and, consequently, the oxidation of adrenaline to adrenochrome. In the past two hundred years, industrialized societies have become increasingly noisy. Both animal studies<sup>31</sup> and research with human subjects<sup>32</sup> adversely affected by traffic noise have shown that noise significantly affects catecholamine levels, stimulating the adrenal glands to release both noradrenaline and adrenaline. Simply put, during the past two hundred years, cities have become increasingly noisy and polluted by novel

chemicals. The pace of life is faster and stress levels higher. All too frequently, inhabitants now tend to eat fast foods that are high in sugar, or imported or processed products to which some of them are allergic. All of these trends are impacting on the human adrenal glands, overstimulating them to produce excess adrenaline and/or promoting the oxidation of adrenaline to adrenochrome. As Torrey and Miller<sup>33</sup> have pointed out, the percentage of the population that carries genetic variants which increase susceptibility to schizophrenia may not have altered much in the past 200 years, but the trigger(s) that promote their negative implications for mental health certainly have. It is now much harder for genetically susceptible individuals to avoid the harmful environmental stimuli that 'switch on' such aberrant genes. This is particularly true for those who live in those areas where all such trends have been magnified.

### Genesis: In the Beginning

The third chapter of this volume traces the clinical symptoms of schizophrenia from the womb to the autopsy room. It documents that those destined to become schizophrenics are often born with minor physical abnormalities, very like those seen in fetal alcohol syndrome. These develop in the fetus during the first trimester. Births are typically difficult and prolonged, and birth weights usually low. Physical anatomical changes increase later in life, especially if schizophrenia becomes chronic. These include overdeveloped, fluid-filled brain ventricles and a badly damaged thyroid gland.

Such physical abnormalities can also be explained by the adrenochrome hypothesis. As previously described, adrenochrome is antagonistic with triiodothyronine, serotonin (at high levels), and the major enzymes of the antioxidant defence system

(glutathione peroxidase, superoxide dismutase, and catalase). As a consequence, schizophrenics tend to suffer from severe deficiencies of these substances. In myxedematous cretinism, Kashin-Beck disease (grade III), and fetal alcohol syndrome,<sup>34</sup> there are serious fetal abnormalities that appear linked to triiodothyronine deficiencies. It seems likely, therefore, that inadequate fetal triiodothyronine, related to excess adrenochrome, may cause the minor birth defects that occur frequently in schizophrenics. Similarly, in regions where goitre is common, so too are stillbirths. This suggests that inadequacies in thyroid hormones may also account for the difficult births and low birthweights seen in infants who later became schizophrenic. They may also be responsible for the elevation of dopamine D2 and D4-like receptors seen in the brains of schizophrenics. Such receptors seem to be more common in rats fed iodine deficient diets.<sup>35</sup> Buckman and coworkers<sup>36</sup> have shown that the atrophy and large fluid-filled ventricles, seen in chronic schizophrenics, are strongly linked to low blood glutathione peroxidase levels. This suggests that they are caused, at least in part, by free radical damage, which is itself a consequence of adrenochrome's negative impact on the antioxidant defence system. There is also evidence to suggest that the damage seen in the chronic schizophrenic thyroid is also caused by abnormal oxidative stress.

## The Genetic Basis

The current evidence suggests that there are probably four genetic variants that are abnormally common in the schizophrenic population.<sup>37-39</sup> The first of these discussed in the fourth chapter is a low activity form of the gene which codes for catechol-O-methyltransferase. This enzyme converts epinephrine (adrenaline) to the inactive metabolite metanephrine. Since this process is inefficient in many schizophrenics, it is likely

that more adrenaline than normal is oxidized to adrenochrome and its derivatives.

There is also a particular variant of the glutathione-S-transferase (GSTM1) gene that commonly occurs in schizophrenics. This allele encourages strong catalytic activity for adrenochrome, ensuring that high levels of this adrenaline metabolite occur in the brains of those who carry this variant.

There appears to be a third genetic aberration that is abnormally common in schizophrenia. Many schizophrenics seem to carry a variant of the methylenetetrahydrofolate reductase (MTHFR) gene that reduces their ability to metabolize homocysteine effectively. This variant obviously causes severe biochemical abnormalities, including elevated homocysteine and depressed methionine. The effects of these imbalances and associated biochemical cascades that they must cause on brain adrenochrome levels is, as yet, unclear. However, animal experiments suggest that methionine decreases brain adrenochrome. If this is correct, this variant of the methylenetetrahydrofolate reductase gene must increase this hallucinogenic indole.

Recent work also has suggested that some schizophrenics have a variant Nogo gene which overproduces proteins that may reduce the number of nerve endings in regions of the brain linked to schizophrenia. If this is the case, this variant gene may make some individuals more susceptible to damage from adrenochrome and its derivatives.

Such genetic aberrations are obviously inherited. Their frequent presence in the human population helps to explain both why schizophrenia is common and the high frequency with which this mental illness occurs in families of schizophrenics. The advantages such a genetic variation carries with it are discussed in detail in the following chapter.

## Biochemical Abnormalities

This book's fifth chapter discussed 10 classes of biochemical abnormalities identified in schizophrenia. Among them are triiodothyronine deficiency, inadequate glutathione peroxidase, catalase and superoxide dismutase, and low serotonin. It has been demonstrated previously that adrenochrome is a strong antagonist of all these named substances and that their depletion in schizophrenics is to the expected.

Beyond these biochemical abnormalities, schizophrenics also display niacin and tryptophan deficiencies. Tryptophan is the least abundant essential amino acid in foods, a characteristic that, in the past, has led to other serious health problems. One of these was pellagra, which is thought to be due to a codeficiency of both tryptophan and niacin. As a consequence of these two deficiencies (caused by eating a diet too rich in corn), individuals could not produce adequate nicotinamide adenine dinucleotide and so developed pellagra. This disease has symptoms known as the four Ds, namely dermatitis, diarrhea, dementia, and ultimately death.<sup>40</sup> Adrenochrome excess appears to cause a serotonin deficiency. This, in turn, increases the demand for tryptophan, from which serotonin is metabolized. As schizophrenics become short of tryptophan, niacin levels also fall since this is, in part, created in the body from tryptophan. Adrenochrome's antagonism with serotonin, therefore, is the root cause not only of serotonin's shortage in schizophrenia, but also of the deficiencies of tryptophan and niacin that accompany it.

There is strong evidence of abnormalities in fatty acid metabolism in schizophrenia. Highly unsaturated fatty acids are readily oxidized and it seems likely that adrenochrome's antagonism with the antioxidant defence system (glutathione peroxidase, superoxide dismutate, and catalase) causes deficiencies of brain

fatty acids. Buckman and coworkers<sup>41</sup> have shown that depleted blood glutathione peroxidase is positively linked to brain atrophy and the size of associated ventricles. Conversely, Peet and coworkers have demonstrated that essential fatty acid supplements can help to repair such brain damage in schizophrenics.<sup>42</sup> Interestingly, Rudin and colleagues<sup>43</sup> showed that linseed oil, which contains high levels of alpha linolenic acid (necessary for prostaglandin production) is helpful in the treatment of schizophrenia, provided it is given after adequate selenium supplementation. To quote them directly:

*“If a primate is deficient in the antioxidant element selenium, providing supplemental essential fatty acids will only make the selenium deficiency worse. Whatever selenium stores are in the body will be used up that much sooner in an attempt to protect the EFA [essential fatty acids] from oxidative damage.”*

These experiments and observations strongly suggest that the abnormalities in fatty acid metabolism seen in schizophrenia are associated with deficiencies in the selenoenzyme glutathione peroxidase and in the other major components of the antioxidant defence system, caused initially by adrenochrome antagonism.

Histamine imbalances also are common in schizophrenia. According to Pfeiffer,<sup>44</sup> roughly half of schizophrenics have depressed blood histamine, while a further 20 percent have an excess of it. Those with low histamine he termed histapenics, while those with elevated histamine were called histadelics.

How can there be such major differences in histamine amongst these two groups of schizophrenics? Histamine is formed from the amino acid histidine and largely stored in most cells. Pfeiffer<sup>45</sup> showed that schizophrenics with abnormally elevated histamine were typically highly allergic to something in the

environment. As a consequence, they also had high levels of IgE, a blood protein indicative of inhalant allergic reactions. Such schizophrenics appear to be rapidly oxidizing adrenaline to adrenochrome because of this allergy, and so are creating large quantities of histamine. In addition, schizophrenics with the methylenetetrahydrofolate reductase (MTHFR) genetic aberration cannot effectively convert homocysteine back to methionine. Consequently, they are deficient in the methionine needed to drive the methylation process that inactivates histamine and so relieve allergic responses. Schizophrenics who have the methylenetetrahydrofolate reductase genetic aberration, or who for other reasons are highly allergic, therefore suffer from very high histamine levels. This is why Pfeiffer<sup>46</sup> was able to help many of them by giving them supplements of methionine and so encouraging methylation and the metabolism of histamine.

Conversely, Pfeiffer<sup>47</sup> found that schizophrenics with depressed histamine could be aided by high doses of tryptophan, niacin, niacinamide and folic acid. This was because adrenaline is a histamine antagonist. In anaphylactic shock, brought on by an allergic reaction, the patient is injected with epinephrine (adrenaline) in part to counteract the dangerously high histamine levels that are occurring.<sup>48</sup> This suggests that the high levels of adrenaline created by the triggers of schizophrenia (such as stress and sugar) are greatly reducing histamine levels in some patients, with adverse effects, which is probably why methyl acceptors such as niacin and niacinamide are of value in such cases.<sup>49</sup> They reduce adrenaline formation by reducing noradrenalin levels and so allow histamine levels to rise back towards normal.

The high levels of homocysteine, observed in many schizophrenics, is easy to explain. Regland and coworkers<sup>50</sup> have shown that schizophrenics who carry allelic variants of the

methylenetetrahydrofolate reductase (MTHFR) gene, specifically MTHFR C677T and C677TT, have a reduced ability to metabolize homocysteine. As a result, they typically display depressed methionine and elevated homocysteine levels.

Obviously, elevated homocysteine is a threat to health since it is a potent neurotoxin that has been implicated in several disorders, including cardiovascular<sup>51</sup> and Alzheimer's diseases.<sup>52</sup> Interestingly, the high levels of homocysteine identified in a subgroup of schizophrenics appears to explain, at least in part, why glutamate may play a role in this disorder. As Ho and coworkers<sup>53</sup> have pointed out, homocysteine is at least as excitotoxic as glutamate. Beyond this, it also enhances glutamate excitotoxicity. That is, homocysteine can damage cerebellar neurons in its own right, but also stimulates glutamate to cause additional havoc. It seems that even at relatively low concentrations, homocysteine has a lethal impact on a type of glutamate receptor called NMDA (N-methyl-D-aspartate) receptors,<sup>54</sup> damage to which appears to play a role in schizophrenia. Smythies<sup>55</sup> has also argued that dopaminochrome (and therefore possibly adrenochrome) may also play a role in damaging NMDA receptors. Certainly, Berman and Hastings<sup>56</sup> have shown that reactive oxygen species and dopamine oxidation products can modify glutamate transport function, causing elevated levels implicated in neuro-degeneration.

Many schizophrenics display high levels of "kryptopyrrole" in their urine.<sup>57</sup> Grossly elevated "kryptopyrrole" occurred in the urine of Arthur Shawcross,<sup>58</sup> a serial killer responsible for at least 13 murders. Shawcross carried the XYY chromosome anomaly, suggesting a strong genetic aspect in excess "kryptopyrrole". This is supported by the presence of this substance in patients with pyroluria,<sup>59</sup> where it is thought to be a genetically determined chemical imbalance that involves abnormalities in hemoglobin synthesis. "Kryptopyrrole" has no known

function in the human body, but it binds to pyridoxine (vitamin B6) and to zinc, making them unavailable as co-factors in enzymes or for metabolism. High levels of “kryptopyrrole” in pyroluria also cause a deficiency of arachidonic acid, an omega-6 fatty acid.<sup>60</sup>

Hoffer<sup>61</sup> has shown that alcoholics can be made to produce “kryptopyrrole” in their urine by giving them LSD. It would appear, therefore, that some or all of the indoles, including LSD and adrenochrome, can promote the production of “kryptopyrrole”, a process which in turn robs the body of vitamin B6, zinc, and arachidonic acid. Certain individuals appear to be genetically susceptible to this process since pyroluria seems to have a genetic dimension. Beyond this, Hoffer<sup>62</sup> has reported higher than normal levels of “kryptopyrrole” in the urine of siblings of schizophrenics who are not, themselves, mentally ill. The extraordinarily elevated “kryptopyrrole” seen in the serial killer Arthur Shawcross also seems to have been linked to his XYY chromosome anomaly.<sup>63</sup> The best evidence that the elevated “kryptopyrrole” seen in schizophrenics is caused by excess adrenochrome has been provided by Hoffer,<sup>64</sup> who has demonstrated that when patients with high levels of “kryptopyrrole” in their urine are given megadoses of niacin to reduce the body’s adrenochrome production, “kryptopyrrole” excretion drops rapidly and the symptoms of schizophrenia decline. Conversely, even in patients who are not schizophrenic, but are excreting large amounts of “kryptopyrrole”, niacin will be of great benefit, as, for example, in children who are wrongly thought to be retarded.<sup>65</sup>

### **Pulling the Trigger: Location, Location, Location**

Internationally, schizophrenia is most prevalent in northern Sweden, Ireland, and Croatia.<sup>66</sup> It cannot logically be argued

that those areas are subjected to the most stress, sugar consumption, or exposure to substances likely to cause allergic reactions. That is, the triggers for schizophrenia do not seem to be unusually common in regions where this mental illness peaks. If the adrenochrome hypothesis is correct, therefore, those must be areas where one or more of the genetic aberrations that promote excess production of this indole are particularly widespread.

This appears to be the case. Prasmusinto and coworkers,<sup>67</sup> for example, have compared the frequency with which the C677T polymorphism of the methylenetetrahydrofolate reductase (MTHFR) gene occurred in both German-Croatians and Indonesians. As discussed previously, this allele decreases the ability to metabolize homocysteine effectively and is probably associated with elevated adrenochrome and its derivatives in some schizophrenics. The research by Prasmusinto and colleagues<sup>68</sup> established that this genetic aberration was much more common in Croatians than in Indonesians ( $p=0.0033$ ). Similarly, Brattstrom and fellow researchers<sup>69</sup> have established that in Sweden, 29.1 percent of newborns carry the C677T/MTHFR mutation. The level in the Swedish elderly is 27.0 percent. Clearly, this polymorphism is extremely common in Sweden, being present in almost one third of the population. This allele has also been reported at high levels in the Irish population.<sup>70</sup>

At the national level, it is also obvious that schizophrenia is more common in industrialized nations, especially in the zones of transition that surround the Central Business Districts.<sup>71</sup> These, of course, are areas of high noise and pollution, triggers known to stimulate adrenaline production. Beyond this, Christensen and colleagues<sup>72</sup> have demonstrated that schizophrenics are much more likely to recover in countries where national diets are high in unsaturated fatty acids. Such fats

are normally derived from vegetables, fish, and seafoods and are essential for prostaglandin manufacture. Diets high in ethyl-eicosapentaenoate have been shown to repair some of the brain atrophy and abnormal ventricles seen in chronic schizophrenics.<sup>73</sup> In addition, many schizophrenics and their relatives are severely allergic to wheat and/or milk.<sup>74-75</sup> As a result, countries where such foods make up a substantial part of the normal diet are likely to have a significant number of schizophrenics who are suffering from excess adrenochrome and its derivatives, triggered by allergies to either wheat and/or milk. The class variations in the prevalence of schizophrenics seen in Europe, Ireland, the US, Japan, India, and Italy<sup>76</sup> also probably reflect dietary factors. In such countries there are significant class differences in both the consumption of sugar and of essential fatty acids which are likely to influence adrenaline production, essential fatty acid availability, and exposure to potential allergens.

In the US,<sup>77</sup> and to a lesser extent in Italy,<sup>78</sup> it has been demonstrated that schizophrenia is more common in low soil selenium and calcium regions. This is relatively easy to explain since the production of the two adrenochrome antagonists, glutathione peroxidase and triiodothyronine, requires selenium. Glutathione peroxidase is a selenoenzyme that is known to rise and fall in the human body with selenium availability. Triiodothyronine cannot be produced from thyroxine without the selenoenzyme deiodinase. As might be expected, then, people living in selenium deficient regions tend to have depressed glutathione peroxidase<sup>79</sup> and triiodothyronine<sup>80</sup> levels. Under such circumstances, adrenochrome is likely to be more damaging. Calcium salts reduce the adrenaline-secreting effects of potassium,<sup>81</sup> so it is probable that individuals living in high calcium environments are less prone to produce excess adrenaline and, therefore, adrenochrome. The fact that schizophrenia is not as common in areas of high sunlight may reflect

the ease with which vitamin D is produced. Deficiencies of this vitamin are related to obesity.<sup>82</sup> This may be due to a lack of active vitamin D which increases calcium absorption in the digestive tract and so helps reduce the adrenaline-secreting effects of potassium.<sup>83</sup>

Since cancer of the esophagus is also most common in low selenium, depressed calcium regions, it is not surprising that it has a prevalence pattern similar to that of schizophrenia.

The skin's ability to manufacture vitamin D, selenium levels in foods, and the calcium content of drinking water all depend on the time of year. It is possible, therefore, that one or more of these factors is responsible for the well known seasonal variations in the birthdates of schizophrenics.<sup>86</sup>

### No Barking Dogs: Medical Anomalies

Schizophrenics are typically heavy smokers but very rarely develop lung cancer.<sup>86</sup> If the adrenochrome theory is correct, many schizophrenics may be deficient in brain adrenaline because too much of it is oxidized to adrenochrome. Animal tests<sup>87-88</sup> have shown that nicotine increases adrenaline turnover in the hypothalamus, especially the median eminence. This nicotine-adrenaline relationship seems to have a therapeutic role in many neuropsychiatric disorders including depression, Tourette's syndrome, and schizophrenia.<sup>89</sup> It seems likely, therefore, that, in the short-term, elevated nicotine from tobacco helps alleviate the adverse impacts of low brain adrenaline experienced because of its excessive oxidation to adrenochrome. This is why so many schizophrenics smoke as a form of self-medication.

Yamafuji and coworkers<sup>90</sup> have argued that noradrenaline or adrenaline have antitumor properties. It seems more likely

from the available evidence that it is not adrenaline, but its oxidation product adrenochrome, or derivative(s) from it, that are protective against some cancers. After all, the triggers of adrenaline production (sugar consumption, stress, and allergies), have all been increasing at the very time that cancer rates have been rapidly rising.<sup>91</sup> This suggests that adrenaline itself cannot be protective against cancer.

There is, however, growing evidence that adrenochrome is protecting schizophrenics against lung cancer. Parnate, an antidepressant, is an amine blocker that encourages adrenochrome production in patients receiving it.<sup>92</sup> As a result, some become psychotic. One of these was a 14 year old male with a brain tumour that required monthly fluid-drainage. For the 5 years after a parnate-induced psychotic episode the patient remained in good health, suggesting that the adrenochrome high produced by this drug either cured or greatly reduced the size of the brain tumour. Beyond this, a new product called IntraDose, which contains cisplatin and epinephrine (adrenaline), is being tested as a treatment for liver cancer, cancer of the head and neck and breast, and malignant melanoma. In all of these types of cancer the treatment is showing great promise. In liver cancer,<sup>93</sup> for example, 38 patients were treated with IntraDose and 55 (21) percent of these responded to the drug. In nine of these cases the tumour disappeared, while in the other 12 there was a reduction in viable tumour mass of more than 50 percent. Excellent responses were also achieved in malignant melanoma patients<sup>94</sup> and those with head and neck cancers<sup>95</sup> and breast cancer.<sup>96</sup> Cisplatin is a very powerful oxidant which will almost certainly convert any adrenaline to adrenochrome when the two are injected together into a tumour mass. There is, therefore, growing experimental proof that adrenochrome is an effective treatment for many cancers. This probably explains the resistance of schizophrenics to lung cancer, despite heavy smoking.

Schizophrenic patients have an insensitivity to pain that can be life threatening.<sup>97</sup> Among a group of schizophrenics experiencing a myocardial infarction (heart attack), for example, only 18 percent reported pain, compared to 90 percent of those experiencing attacks who were not schizophrenic. Such a reduced pain sensitivity has been recorded for third-degree burns, cancer, peptic ulcers, fractures, and arthritis in many schizophrenics. Indeed, one 46-year old woman with long-term schizoid psychosis who collapsed and died on the street was found to have swallowed 422, mostly metal, objects.<sup>98</sup>

Schwarz and coworkers<sup>99</sup> gave between 0.125 and 1 mg of pure adrenochrome intraventricularly to several cats. "After about 20 minutes the cats became moderately insensitive to painful stimulation. There was no prompt withdrawal or voicing of pain when the paw was squeezed or the ear was pinched." Clearly, adrenochrome can reduce pain sensitivity. Horrobin<sup>100</sup> argued that an inability to flush, the failure to feel pain, the beneficial effects of fever, and the resistance to arthritis seen in schizophrenics were all linked to arachidonic acid abnormalities.

Arachidonic acid is usually locked up in membrane phospholipids, but for the body to react to many different stimuli it must be released as free arachidonic acid which can then regulate cell function in appropriate ways.<sup>101</sup> Some arachidonic acid is also then converted to prostaglandins that open up blood vessels to allow faster blood flow. Horrobin<sup>102</sup> argued that in schizophrenics, a shortage of free arachidonic acid could explain a lack of prostaglandins and, hence, of flushing.

Arachidonic acid also is required to form prostaglandins that respond to insult by mounting an inflammatory response. Of course, many schizophrenics are histamine deficient which will also reduce their response to injury or infection. Arthritis is often treated with non-steroidal, anti-inflammatory drugs, such

as ibuprofen and aspirin, that work by blocking the conversion of arachidonic acid to prostaglandins. Steroids, such as hydrocortisone cream, in contrast, block the release of arachidonic acid from the phospholipids. In either case, these drugs cause a shortage of prostaglandins by interfering with the supply of arachidonic acid.<sup>103</sup>

The surprising but temporary improvement in schizophrenia that is associated with fever can also be explained by an arachidonic acid abnormality in this mental illness. During a fever, arachidonic acid is very rapidly released from the cell membranes since it helps to defend against infection.<sup>104</sup> If schizophrenics are usually deficient in arachidonic acid, fever may move body levels towards the norm improving brain function and reducing psychotic symptoms. Schizophrenics are deficient in arachidonic acid<sup>105</sup> for at least two reasons. Firstly, it is an essential unsaturated fatty acid that will be subjected to free radical damage due to the impairment of the body's antioxidant defence system caused by adrenochrome.<sup>106</sup> Secondly, as described, some 75 percent of acute schizophrenics display elevated "kryptopyrrole" in their urine. This binds to pyridoxine (vitamin B6) and zinc which are then excreted with it. In addition, "kryptopyrrole" also seems associated with a loss of arachidonic acid which, as a result, is also deficient in patients with pyroluria.<sup>107</sup>

The links between schizophrenia, celiac disease, and wheat consumption seem relatively easy to explain.<sup>108</sup> This grain contains the protein gluten, an intolerance to which appears to be the allergic cause of celiac disease. The chief symptoms of this illness are recurrent diarrhea accompanied by severe cramps, alternating with constipation.<sup>109</sup> Celiac disease is often known as malabsorption syndrome because it is associated with an inability to absorb fats, some sugars, and starches. It also frequently leads to vitamin A, E, and selenium deficiencies.

Any schizophrenic inheriting the genetic aberration responsible for celiac disease, or who is heterozygotic for it, is probably allergic to gluten and so will over-produce adrenochrome.<sup>110</sup> Beyond this, they are likely to be deficient in the antioxidants needed to mitigate adrenochrome's generation of free radicals and in the essential fatty acids that are so important in brain function.<sup>116</sup> It is possible, therefore, that schizophrenics who are allergic to gluten have difficulty in absorbing not only the essential fatty acids, but also the antioxidants that are needed to protect them. Beyond this, if selenium deficient, they are likely to produce inadequate triiodothyronine, the adrenochrome antagonist.<sup>112</sup>

There is a growing body of evidence that maternal infections during pregnancy may be linked to schizophrenia and other psychoses in adulthood. Buka and coworkers,<sup>113</sup> for example, have demonstrated that the offspring of mothers with elevated levels of total IgG and IgM immunoglobulins and antibodies to herpes simplex virus type 2 are at an increased risk of subsequently developing schizophrenia as well as other psychotic illnesses. Herpes simplex virus DNA also appears to be abnormally common in very aggressive, mentally retarded patients, or those with paranoid schizophrenia.<sup>114</sup> In addition, there is an interesting correlation between elevated schizophrenia and regions where Ixodid ticks,<sup>115</sup> and therefore infection by *Borrelia burgdorferi*, are commonplace. What is clear, however, is that the subsequent appearance of schizophrenia that may follow such maternal infection does not occur as the result of active viral infection or reactivation.<sup>116</sup> Any impact must result from brain damage in the fetus that increases future susceptibility to schizophrenia. Support for this possibility comes from the observation that, in rats, maternal herpes simplex virus type 1 inhibits acoustic startle in offspring.<sup>117</sup> This function is also known to be diminished in schizophrenia.<sup>118</sup>

Buka and colleagues<sup>119</sup> have shown that mothers of infants who are likely to become schizophrenics tend to suffer from at least two health problems. Firstly, their elevated levels of IgG and IgM immunoglobulins strongly support that they are highly allergic to something in their environment. As a result, they can be expected to be over oxidizing adrenaline to adrenochrome. Secondly, they are persistently infected by the herpes simplex virus type 2. Similarly, schizophrenia is elevated in regions where Ixodid ticks, carrying *Borrelia burgdorferi*, are common.

Why these relationships occur is as yet unclear, but what is apparent is that viral infection can greatly reduce the body's ability to detoxify adrenochrome, so exposing the developing fetus to elevated levels of this dangerous indole. This association can be best documented with respect to the hepatitis B virus. Persistent infection with the hepatitis B virus, together with exposure to chemical carcinogens, is known to cause elevated liver cancer in endemic areas.<sup>120</sup> Hepatitis B virus infection significantly decreases glutathione S-transferase and selenium-independent glutathione peroxidase activity in infected cells.<sup>112</sup> The body normally detoxifies adrenochrome by conjugating it with glutathione in the presence of glutathione S-transferase.<sup>122</sup>

It follows, therefore, that pregnant women who are suffering allergic reactions will over produce adrenochrome. However, if they are also infected with the hepatitis B virus they will be deficient in both glutathione and glutathione S-transferase, the two compounds required to detoxify it. As a consequence, it is very likely that their developing fetus will be exposed to elevated levels of this indole, a process that seems to be most damaging to growth and development in the first trimester. This is perhaps not too surprising since it is known that newborns (especially if they are preterm infants) are at a high risk of oxidative stress and very susceptible to free radical damage.<sup>123</sup>

This seems to be because the brains of the very young, and presumably of fetuses, are rich in polyunsaturated fatty acids, yet have a relative deficiency of glutathione peroxidase and superoxide dismutase. In summary, pregnant women who are both highly allergic and infected by pathogens that cause glutathione and/or glutathione S-transferase deficiencies appear likely to give birth to infants that have been overexposed, in the womb, to an excess of adrenochrome and its derivatives. This may explain the apparent relationships between maternal exposure to herpes simplex virus type 2<sup>124</sup> or to *Borrelia burgdorferi*<sup>125</sup> and the higher risk of schizophrenia in subsequent offspring. Certainly, there is growing evidence that glutathione S-transferase may play a role in the recurrence of herpes simplex viruses.<sup>126</sup>

## Unconventional Treatments

Controlled fasting, in combination with detoxification and vigorous exercise, was pioneered as a treatment for schizophrenia by Dr. Uri Nickolayev at the Moscow Psychiatric Institute.<sup>127</sup> Fasting will prevent allergic reactions in patients who normally eat foods with which they are biologically incompatible. As a result, the production of adrenochrome and its derivatives will fall during fasting, perhaps explaining the normalizing of catecholamines in the urine of such patients. In addition, fasting will reduce the negative adrenaline triggering effect of sugar, while vigorous exercise will also lower adrenaline levels. Such dietary changes will also cause alterations in serotonin and histamine levels, both of which are usually abnormal in schizophrenia. Many schizophrenics, therefore, improve while fasting and remain well on simple diets.

Histamine therapy seems to be of lasting benefit to roughly one third of schizophrenics.<sup>128</sup> This is perhaps to be anticipated

since Pfeiffer<sup>129</sup> has documented that some 50 percent of all schizophrenics suffer from histopenia, which has depressed blood histamine as one of its major symptoms. This seems to be because adrenaline is a histamine antagonist and triggers (such as stress and sugar) that stimulate the production of adrenaline, therefore, tend to cause a depression in histamine. In such cases, additional histamine helps to reduce schizophrenia's symptoms, since it reduces the body's stores of adrenaline and, therefore, of adrenochrome.

High daily doses of desiccated thyroid are an extremely effective treatment for acute schizophrenia. As Danziger<sup>130</sup> established, every one of 80 acute schizophrenics receiving between 120 to 1200 milligrams of desiccated thyroid who completed his program recovered if they had been ill for only 6 months or less. This appears to be because triiodothyronine is a major adrenochrome antagonist and can help to block this indole's psychotic impacts. Even chronic schizophrenics benefit greatly from desiccated thyroid because repeated exposure to adrenochrome (and related depressed antioxidant defence system enzymes) causes permanent thyroid damage. Desiccated thyroid, therefore, provides the triiodothyronine that chronic schizophrenics have great difficulty in producing themselves. Simpson and Amunso<sup>131</sup> claimed that triiodothyronine was ineffective in the treatment of chronic schizophrenia. However, they used dosages that were a small fraction of those prescribed by Danziger.<sup>132</sup> Beyond this, it should be recalled that schizophrenics have an unusual insensitivity to thyroid hormones.<sup>133</sup> Large doses do not increase their oxygen consumption nor do they cause the hyperthyroidism one would normally expect to develop. Hoskins,<sup>134</sup> for example, reported that schizophrenics were unusually resistant to large doses of thyroid, finding 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. Carl Pfeiffer<sup>135</sup> was effective in treating

many schizophrenics because he recognized that they could be classified biochemically. Distinct differences occur because of the variety of allergies involved and the four or more genetic aberrations found in different forms of this mental illness. As a consequence, while the reduction of adrenochrome may be of value to all schizophrenics (as shown by Danziger), there still remain symptoms with a genetic origin. For example, as Regland and coworkers<sup>136</sup> have shown, schizophrenics carrying the C677TT variant of the methylenetetrahydrofolate reductase gene have great difficulty in metabolizing homocysteine. As a result, they display depressed methionine and elevated homocysteine levels. It is to be expected, therefore, that such schizophrenics respond well to methionine supplements. In short, there is nothing in the Carl Pfeiffer protocols<sup>137</sup> that is inconsistent with the belief that all schizophrenics suffer from an overexposure to adrenochrome. This does not mean that this is necessarily their only biochemical problem.

It is not surprising that the successes achieved using the Hoffer protocol can be explained by the adrenochrome hypothesis. After all, Dr. Abram Hoffer<sup>138</sup> was one of the originators, some 50 years ago, of this hypothesis. This emphasis on the removal from the diet of high sugar foods and substances to which the schizophrenic patient is allergic reduces the production of adrenaline and so its associated metabolite adrenochrome. Beyond this, elevated doses of vitamins and minerals help to support the antioxidant defence system. However, the traditional keystone to the protocol is the prescription of high daily doses of niacin.<sup>139</sup> This vitamin is essential in the treatment of schizophrenia because the oxidation of adrenaline to adrenochrome occurs in two steps. Initially, adrenaline loses one electron to form oxidized adrenaline, a highly reactive molecule. In the presence of nicotinamide adenine dinucleotide, which is created in both oxidized (NAD) and reduced forms (NADH) from niacin, oxidized adrenaline recaptures one electron to reform

adrenaline. If NAD and NADH are in short supply, however, oxidized adrenaline loses another electron and is converted to adrenochrome. This second reaction is not reversible. Adrenochrome, therefore, cannot be converted back to adrenaline. This explains why many schizophrenics display depressed levels of adrenaline and elevated levels of adrenochrome.

High doses of niacin, therefore, reduce adrenochrome production in schizophrenics. Hoffer,<sup>140</sup> for example, examined the results of all of the schizophrenic patients treated by four different psychiatrists between October 1, 1955 and December 31, 1962 at the University Hospital in Saskatoon, Canada. These patients were re-evaluated after August 17, 1964. Two of the psychiatrists included rarely used niacin in their treatments, and then only after it became obvious that everything else had failed. It was never recommended for use after discharge. Their main treatments were tranquilizers, psychotherapy, and electroconvulsive treatment (ECT). In contrast, the other two psychiatrists routinely used niacin and urged their patients to stay on it after discharge. Schizophrenics were randomly assigned to one of these doctors on first admission to the hospital.

During study period there were 232 admissions who received no niacin. This group needed a total of 35,032 days or 96 years in hospital over a 6-year period. Three of them committed suicide. In contrast, the niacin group needed 7,424 days, or 20 years in hospital. There were no suicides in its members.<sup>141</sup>

There has been at least one negative trial using nicotinamide,<sup>142-143</sup> while orthomolecular physicians continue to swear by its value in treating schizophrenia.<sup>144-146</sup> This discrepancy may stem from the fact that this trial used doses that were too low and treatment periods that were not long enough. Hoffer,<sup>147</sup> for example, has used up to 32 grams of niacin per day in

extreme cases and continues to give it to chronic patients for at least 5 years. Most of his patients take 12 grams daily or less and the vast majority between 3 and 6 grams. It should also be remembered that they were usually on a sugar restricted diet, reducing their adrenaline and hence adrenochrome production.

## Conventional Treatment

There is good evidence from Switzerland and elsewhere that insulin coma therapy shortens the duration of a schizophrenic attack in many patients, especially if given early in the illness.<sup>148</sup> Unfortunately, this improvement proves temporary. Baumann and MGaillard<sup>149</sup> argued the reason insulin coma therapy was beneficial to schizophrenics was because it increased brain tryptophan uptake and so enhanced cerebral serotonin synthesis. This explanation is compatible with the adrenochrome hypothesis since this damaging indole is a serotonin antagonist. As a consequence, any treatment that increases serotonin production in schizophrenia is likely to temporarily mitigate the negative impacts of adrenochrome, while simultaneously replacing serotonin that has been lost. Naturally, unless the treatment is regularly repeated, its effects will be temporary.

Electroconvulsive therapy also appears to be beneficial in the treatment of schizophrenia, provided that it is given after a few weeks of high niacin supplementation to prevent the memory loss with which it is normally associated.<sup>150-151</sup> It is still not entirely clear why electroconvulsive therapy can be useful in schizophrenia, but it appears to slow the metabolism of noradrenaline.<sup>152</sup> If this is the case, it is possible that it reduces adrenaline and so adrenochrome levels.

Drugs, on average, still improve schizophrenic symptoms, but by only 15 to 25 percent, leaving 75 to 85 percent unresolved.<sup>153</sup>

Some drugs are also linked to side-effects such as Parkinsonism and tardive dyskinesia. The reasons for this association seem obvious. Most neuroleptics are designed to address a dopamine excess that does not exist in schizophrenia. As a consequence, they may create a deficiency of dopamine with side effects that mirror Parkinson's disease. These drugs also interfere with the metabolism of other catecholamines, producing various negative effects. Ultimately, however, they may have an impact on adrenochrome production, so mitigating some of its adverse effects. Other drugs designed to address serotonin and glutamate<sup>154-155</sup> imbalances are attempting to stop dominoes further down the adrenochrome cascade from falling. Their effects can be expected to be beneficial but minor because they do not address the fundamental causes of the illness.

### Regression Analysis: The Road Back

Very few recovered schizophrenics feel that conventional drug treatments were the key to their recovery. There is much more support amongst them for the orthomolecular treatments of Hoffer,<sup>156</sup> Pfeiffer,<sup>157</sup> Danziger,<sup>157</sup> and others that rely on high doses of adrenochrome antagonists (such as triiodothyronine) or methyl acceptors (like niacinamide and niacin) that reduce the conversion rate of noradrenaline to adrenaline and its metabolite adrenochrome. Beyond this, many also believe they were formerly hypoglycemic or addicted to foods to which they were allergic. These views are also consistent with the adrenochrome hypothesis because such diets ultimately either stimulate the overproduction of adrenaline or its rapid oxidation. This is also true of stress, which most recovered schizophrenics have learned to avoid as far as is possible.

## SUMMARY

In his book, *Science is God*, Horrobin<sup>159</sup> claims that:

*A good hypothesis has three major characteristics. It accounts for those facts in a precise, direct way. It makes predictions which are amenable to experimental testing and which suggest the direction in which further progress may be made.*

I feel confident that to this point “What Really Causes Schizophrenia” has demonstrated that the adrenochrome hypothesis can account for most of the available facts in a precise, direct way. Indeed, I would like to challenge supporters of the dopamine or glutamate hypotheses to explain the observations in Table 1 in a more convincing manner. What remains, then, is to demonstrate how progress in the prevention and treatment of schizophrenia can be made by better application of the adrenochrome hypothesis.

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*And slowly answer'd Arthur from the barge:  
"The old order changeth, yielding place to new,  
And God fulfils himself in many ways,  
Lest one good custom should corrupt the world."*

The Idylls of the King  
The Passing of Arthur  
Alfred, Lord Tennyson

*The escalating costs of the health care system will bankrupt both states and individuals. These costs largely arise because we are spending vast amounts on marginally useful treatments that ensure that patients return to the health care system again and again. The only way this will change is if we find dramatically effective treatments that remove patients from the health care system altogether. And the only way to make such discoveries will be to test greater numbers of scientifically much more diverse approaches to treatment. That, I believe, is the ethical imperative of all involved in medical research. And because the introduction of highly effective treatments is the only possible basis for a dramatic reduction in costs, it happens to be a financial imperative as well.*

D.F. Horrobin (2002)<sup>1</sup>

On October 27, 2000, King County in Washington State, by a vote of 11 to 1, passed a very unusual ordinance.<sup>2</sup> This directed psychiatrists working in the state mental health system to make their patients well and to report annually on how successful they had been in achieving this goal. The ordinance defined exactly what was to be considered a mental health recovery. Such a former patient had to be able to meet four criteria. They must have become well enough to engage in volunteer work, or be employed full or part-time, or be engaged in culturally appropriate activities, or be pursuing educational or vocational opportunities. Secondly, a recovered

mental patient had to be living independently or in supported housing. Thirdly, they must have been discharged from the county's publicly funded mental health system or, at most, be receiving only infrequent maintenance services. Lastly, when tested they must be able to score 81 or more on the Global Assessment of Function Scale. This scale measures such things as aggression, ability to communicate, and level of personal hygiene.

It is now some 3 years since this ordinance was passed and the required initial report on the efficacy of the system has been issued,<sup>3</sup> covering the period January 1 through December 31, 2001. King County, Washington is not a rural backwater. It is one of the most progressive counties in the US, the location of Seattle. So what did the residents of King County get for the more than \$90 million they spent on mental health in 2001? According to the first mandated report, 7,831 mental patients, mainly schizophrenics and patients with major depression, were treated during the year. Of these, 6,949 (88.7%) showed no change, 597 (8%) displayed some improvement, 285 (4%) regressed, and four (0.05%) recovered. Put another way, if you suffered from schizophrenia, major depression, or other mental illness in King County during 2001, your chance of a full recovery was less than one in one thousand. That is, the residents of the Seattle area are paying over \$22 million for each mental health recovery. In Medieval times, victims of the bubonic plague had a far better chance of recovery than this. Treated with hot onion, fig, and treacle poultices or partially plucked pigeons to draw off poisons from their swollen lymph nodes, they were much more likely to completely recover than schizophrenics receiving the best treatments that modern psychiatry has to offer.<sup>4</sup> If you believe that this is acceptable, throw this book away. If not, seriously consider the alternative treatments that stem from an acceptance of the adrenochrome hypotheses.

## IMPLICATIONS OF THESE STATISTICS

I am now going to plagiarize from myself, almost repeating a couple of pages that were written for *What Really Causes Aids*.<sup>5</sup> These sentiments are just as relevant here as they were to the discussion of why HIV-1 is powering the global pandemic. Health has become the end product of applied science in which answers to every human illness can be discovered ultimately by laboratory research. Thomas<sup>6</sup> best expressed belief in this biomedical paradigm when he claimed: “For every disease there is a single key mechanism that dominates all others. If one can find it and then think one’s way around it, one can control the disorder.” In truth, the situation is not so simple, whether the ultimate agent of mortality is an earthquake, automobile, genetic aberration, or virus.<sup>7</sup> To illustrate, if asked the question “Why did Marie Antoinette die?” one could reasonably reply, “She had her head cut off by a guillotine.” However, a more comprehensive list of causes of her early demise would have to include every event that led to the invention and development of this instrument of execution, all of the factors that provoked the French Revolution and the Reign of Terror associated with it, each step in the evolution of humanity that gave our species the brains and bodies capable of designing and constructing the guillotine, and so on *ad infinitum*. In truth, as pointed out by Bohm,<sup>8</sup> while we usually choose to ignore the vast cascade of variables that stand behind any event, it is still important to accept that no single cause and effect relationship can really be separated from the universe as a whole. Like the strands that make up a rope, events converge and combine to create an evermore binding set of circumstances, that, in total, produce some eventual consequence, whether a pandemic, avalanche, or chronic schizophrenia.

Growing acceptance of this interconnectedness of reality has had important repercussions in disaster planning.<sup>9</sup> As this

discipline matured, emphasis tended to move away from the development of optimum methods of trying to deal with the destruction, deaths, and injuries caused by hazards towards greater emphasis on preventing disaster. Ultimately, this trend will have to lead to the design of more resilient systems, capable of withstanding stress with grace.<sup>10</sup>

It is clear from the cure rate admitted to by the King County mental health system that psychiatry is failing badly. A new approach is obviously essential; one that recognizes the holistic nature of mental health and, therefore, of necessity our answers to its problems. If, for example, we ask the question “Why did John Doe die a chronic schizophrenic?” one could reasonably answer that “He inherited an unfortunate genetic aberration.” A more realistic list of the causes of this fate, however, would have to include his allergy to latex, cows milk, or gluten or some other allergen that encouraged the oxidation of his adrenaline. In addition, John Doe over-produced adrenaline because of his stressful lifestyle and poor diet that provided too much sugar and too few vitamins and minerals. However, the inadequacy of his diet was due, at least in part, to the Green Revolution and its overuse of fertilizers and to the impact of acid rain and heavy metal pollutants on soils. But didn't John Doe die a chronic schizophrenic because of a medical profession that failed to accept the obvious: that there is no dopamine excess in schizophrenia? This outdated, erroneous paradigm has misdirected efforts to block the ravages of schizophrenia by the use of drugs, which themselves have produced a wide range of dangerous side effects. Then again, John Doe became a chronic schizophrenic because of a political complacency that ignored pollution, environmental decay, and ever increasing noise, while simultaneously under funding the treatment of the mentally ill, forcing John Doe onto the streets, homeless and malnourished. The list of reasons that John Doe died a chronic schizophrenic is almost endless.

In truth, he died alone, talking to himself, lying in an alley because we live in a virtual reality world, and so did he, until reality came crashing through his delusions.

## THE "IDEAL" TREATMENT FOR SCHIZOPHRENIA

The "ideal" treatment for schizophrenia should involve eight steps, designed to reduce the production of adrenaline and slow down its metabolism to adrenochrome and other toxic indoles. Such a treatment should also attempt to reduce the further biochemical abnormalities that result from either an excess of adrenochrome and its metabolites, or from other impacts of the four genetic aberrations that appear associated with this mental illness.

### Treatment Facilities: Step One

Ideally, schizophrenics should be treated in quiet, rural areas where the air is relatively unpolluted. Such facilities should be located in selenium-enriched regions where the water is hard (high calcium and magnesium) and hours of strong sunshine high. They should be staffed by doctors and nurses who are willing to treat the patients with dignity and to provide them, when possible, with meaningful work opportunities.

Many schizophrenics are over-oxidizing adrenaline because of allergic reactions to the environment. They need extra-special surroundings because of such sensitivities. Ideally, a treatment clinic would be like the Lange Meridian Center<sup>11</sup> which was built using Bau-Biologie principles.<sup>12</sup> Bau-Biologie is a German term meaning "building biology," or "the relationship between buildings and life." This concept is promoted by the Institut für Baubiologie und Ökologie in Neubeuern, Germany.

Its major aim is to design and construct homes and workplaces that enhance health. The Meridian Center of Santa Monica, California applies such principles. Its carpets, for example, are hypoallergenic nylon and do not contain formaldehyde, moth proofing, stain repellents, pesticides, or any of the other toxic additives often used to treat carpets. All aspects of the clinic's interior including walls, paints, ceiling tiles, furniture, doors, fabrics, lighting, water, electrical installation, paper, gowns, cleaning products, and even decorative plants were selected because of their extremely low environmental toxicity. Some may even contribute to good human health. The basic principle behind such Bau-Biologie mental health clinics should be that they be expected to encourage positive regeneration, acting as healing places for the mind, spirit, and body. They should be low stress facilities where a schizophrenic is not subjected to environmental stimuli that are likely to encourage adrenaline production or its oxidation to adrenochrome and its metabolites.

### Genetic Screening: Step Two

All roads lead to Rome. All genetic aberrations occurring with abnormal frequency in schizophrenia appear either to lead to elevated adrenochrome and its derivatives or to an inability to withstand their impacts. It has been suggested here that there are at least four genetic aberrations that increase the risk of developing schizophrenia. To recap, these are: homozygosity for the Val-COMPT allele (the gene encoding catechol-O-methyltransferase); the GSTMI\*0 allele (a catalyst for adrenochrome); MTHFR C677TT (which reduces the metabolism of homocysteine) and a variant of the Nogo gene (with three extra chemical bases, known as CAA).

It is theoretically possible to determine the state of the chromosomes and indeed of the genes of a developing fetus.<sup>13</sup> A fine

needle is used to withdraw amniotic fluid and some of the embryo's cells. After culturing, these are available for diagnostic tests. Not only can chromosomes be examined by light microscopy, but also the base sequences can be chemically analysed to determine whether a chromosome carries an increased risk of disorders such as Huntington's chorea, muscular dystrophy, or haemophilia. It is quite possible that such testing could look for the four aberrations just listed and identify a predisposition to schizophrenia in the developing fetus. It is now possible to remove total cells and then genetically manipulate them by inserting selected DNA segments from other human body cells with the aid of a vector. After they have been multiplied in culture, they can be replaced into the fetus.<sup>14</sup> In theory, therefore, it may be possible, sometime in the future, to modify the genes of potential schizophrenics. As yet, this is science fiction and may remain so for a considerable time since gene therapy has, to date, promised far more than it has delivered.

Even though such genetic therapy may still lie in the distant future for schizophrenics, genetic screening does not. An essential early step in the treatment of an acute schizophrenic would appear to be genetic screening. This should be conducted to determine which, if any, of the four predisposing genetic aberrations are present. This information is critical to designing optimum future treatment. Even if such genetic facilities are unavailable, there appears to be a great deal to be gained from determining a patient's dominant biochemical abnormalities and their associated symptoms. Pfeiffer,<sup>15</sup> for example, has provided lists of physical characteristics that can be utilized to identify various subgroups of schizophrenics. To illustrate, he considered histapenics (low histamine, but with a high body burden of copper) typically to have canker sores, and excess fat in their lower extremities, experience difficulty with orgasms, ringing in the ears, and an ability to withstand pain.

In contrast, histadelic patients (excessive histamine) typically overproduce mucus and saliva, have a tendency to hyperactivity, can hear their own pulse on the pillow at night, tolerate a lot of alcohol, have large ears and long toes and fingers, and experience easy orgasms. Pfeiffer<sup>16</sup> gives far more detail on the characteristics of his various subgroups of schizophrenics in his excellent book *Nutrition and Mental Illness: An Orthomolecular Approach to Balancing Body Chemistry*. His insights should be used to classify schizophrenics, even if genetic data is available. It seems likely that eventually a classification of schizophrenics involving genetic, biochemical, and behavioural abnormalities will be developed.

### Allergy Testing: Step Three

Almost anything that is ingested, inhaled, or touched by a susceptible person can trigger allergies. Such allergens include drugs, foods, and their additives and colourings, insects, dust, plants moulds, household cleaners, metals, fabrics, latex, and industrial vapours.<sup>17</sup> In susceptible individuals such substances can result in one of four types of antibody-mediated reactions.<sup>18</sup> In Type I (IgE-Mediated) Immediate Hypersensitivity allergies, the antibody immunoglobulin E (IgE) is produced within minutes of exposure. When an allergic individual breathes in the pollen or other allergen causing their problem, their immune system signals B lymphocytes to produce IgE antibodies specifically designed to target the allergen's protein molecules. These IgE antibodies then become attached to the surfaces of mast cells in the respiratory and gastrointestinal tracts and to eosinophils, comparable cells in the bloodstream. During future exposures, the allergen will bind to the waiting IgE antibody receptors, triggering the release of histamine from mast cells and eosinophils. As a result, swelling, itching, redness, pain, watery eyes and nose, muscle contractions, and capillary permeability occurs as the body tries to rid itself of the

allergen. Such reactions also appear to be linked to the rapid oxidation of adrenaline to adrenochrome.<sup>19</sup>

Type I “classic” allergies are usually the result of reactions to airborne allergens including mould, pollen, dust mites, and animal dander. The same type of allergic reactions are also caused, in some people, by milk, eggs, corn, nuts, peanuts, strawberries, and chocolate. Pharmaceuticals such as penicillin (derived from mould) and aspirin, together with insect stings and latex, can also cause the worst form of Type I allergic reaction, anaphylaxis.<sup>20</sup> This requires immediate adrenaline injections to reverse the symptoms caused, in part, by the rapid oxidation of adrenaline to adrenochrome.

In Type II, Cytotoxic Allergies, antibodies inject toxic protein enzymes (cytotoxin) into antigen cells, killing them. If this process occurs in blood or tissue cells, it can result in immune hemolytic anaemia when too many red blood cells die. Intestinal cells often suffer the most damage from cytotoxic reactions because many of the allergens involved are foods.

In Type III, Arthus Allergies, the reaction may occur as much as 10 days after exposure. As in Type II, the antibody IgG binds to an invading protein, but in this case forms a circulating immune complex. In persons with weakened immunity, such complexes can build up in the bloodstream. If the kidneys cannot adequately excrete them, they accumulate in the soft tissues, causing inflammation and symptoms such as hives, joint pain, headaches, fatigue, and even arthritis. It is estimated that approximately 80 percent of food allergies are Type III reactions.<sup>21</sup>

In Type IV, Cell-Mediated Allergies, symptoms typically appear 2 to 3 days following exposure. The main triggers of such allergies are various plants, including poison ivy, and some

pharmaceutical drugs. These allergies can result in allergic contact dermatitis, allergic colitis, Crohn's disease, and graft-transplant rejections. In such Type IV reactions, T cells directly attack an antigen. Since it takes about a day for the body to amass adequate T cells in the affected area, allergic symptoms (usually allergic contact dermatitis) are experienced some 1 to 3 days after exposure. Approximately 3,000 substances are known to be able to cause this type of allergy, ranging from mercury and nickel, through rubber and plastic, hair dyes, cosmetics, and latex. Various foods, such as pineapples, bananas, papaya, kiwi, and avocado, are also contact allergens in some sensitive individuals.<sup>22</sup>

It is quite likely, therefore, that a schizophrenic is oxidizing adrenaline to adrenochrome as the result of one or more of these types of allergic reactions.<sup>23</sup> A Bau-Biologie clinic may greatly reduce exposure to such allergen(s), resulting in a decline in psychotic symptoms. If not, there appear to be two necessary treatment steps. The first of these is fasting, in a manner similar to that used by Nickolayev at the Moscow Psychiatric Institute.<sup>24</sup> This will allow the body to recover from diet-related allergies. Foods should be returned to the diet one at a time after the fast is over. When eating a food to which they are allergic, a schizophrenic's symptoms may quickly reappear. Other symptoms may take several days to reoccur, as, for example, in the case of certain grains. Once a patient has been shown to be allergic to a particular food, it should be permanently avoided, although it may be possible to develop less sensitivity to it with treatment.<sup>25</sup>

In addition to fasting, there are a multiplicity of available ways to identify allergens. The simplest of these is taking a patient history including the circumstances surrounding original symptoms. Others include the scratch or prick skin test, the patch test, serial endpoint titration (SET), the radio allergosorbent

test (RAST), ELISA Test, cytotoxic testing, the ALCAT, provocative neutralization, and electrodermal screening (EDS). This is not the place to review the merits and drawbacks of such tests, but all are discussed in *Allergy Free: An Alternative Medicine Definitive Guide*.<sup>26</sup> What is important here is the need to identify what, if anything, an acute schizophrenic is allergic to and then to treat them by completely removing, when possible, this allergen from their environments and/or diet. It should be no surprise to find that some patients are very allergic to a wide variety of foods. Jackson and colleagues,<sup>27</sup> for example, reported on the case of an 11 year old boy who suffered greatly from agitation, asthma, attention deficit disorder, diarrhea, fatigue, sleep problems, and muscle aches. He was found to be positive in 49 out of 90 cytotoxic food/chemical sensitivity tests. He recovered on a carefully controlled diet and natural thyroid, mineral, and vitamin supplements.

#### Low Sugar Diet: Step Four

Not only are specific food allergens of concern in the schizophrenic diet, but so too is sugar. It may be recollected that many of the recovered schizophrenics felt that they had formerly suffered from hypoglycemia. The western diet has been increasingly dominated by sugar. The per capita consumption in the US, for example, has increased by roughly a factor of 20 since 1822.<sup>28</sup> Hypoglycemia, as a result, is now rampant. This elevated dietary intake of sugar stimulates the body to release insulin which in turn drives the blood sugar levels down, encouraging the adrenal glands to release adrenaline.<sup>29-30</sup> It follows, therefore, that anyone suffering from the large blood sugar swings that characterize hypoglycemia is going to over-produce adrenaline. In individuals with one of the genetic aberrations seen in schizophrenia, this may result in psychosis, caused by adrenaline's oxidation to adrenochrome and other toxic metabolites.

It follows, therefore, that the schizophrenic diet should be designed to avoid any foods to which the patient is allergic, while simultaneously greatly reducing sugar consumption. It should be remembered that, as early as 1924, Harris<sup>31</sup> discovered that the best way to control hypoglycemia was through small, high protein, low-sugar meals, eaten frequently.

### Adrenochrome Reduction: Step Five

The orthomolecular physician treating schizophrenia is faced with two basic, yet distinct challenges. Firstly, they must quickly reduce the destructive impacts of excess adrenochrome and its derivatives. Secondly, they must address the other biochemical anomalies that are directly related not to such indoles, but to the genetic aberration encouraging their overproduction. In schizophrenics with the MTHFR C 677TT variant, for example, the patient will also be suffering from depressed methionine and elevated homocysteine.

There appear to be several avenues for lowering excess adrenochrome levels. Hoffer,<sup>32</sup> for example, uses high doses of niacin or niacinamide, up to 32 grams daily, to reduce adrenochrome. This goal can also be achieved by the use of the other natural methyl acceptors thiamine (vitamin B<sub>1</sub>), riboflavin (vitamin B<sub>2</sub>), and ubiquinone (Coenzyme Q<sub>10</sub>). Niacin is usually the treatment of choice. The oxidation of adrenaline to adrenochrome occurs in two steps. Initially, adrenaline loses one electron to form oxidized adrenaline, a highly reactive molecule. In the presence of nicotinamide adenine dinucleotide, which is created in both oxidized (NAD) and reduced forms (NADH) from niacin, oxidized adrenaline recaptures one electron to reform adrenaline. If NAD and NADH are in short supply, however, oxidized adrenaline loses another electron and is converted to adrenochrome. This second reaction is not reversible. Adrenochrome, therefore, cannot be converted back to adrenaline.

High levels of niacin, therefore, help prevent the formation of adrenochrome.

There is another good reason for giving niacin to schizophrenics. On average, the human body requires 60 milligrams of tryptophan to manufacture one gram of niacin.<sup>33</sup> Tryptophan is also needed to metabolize serotonin, another adrenochrome antagonist. It follows, therefore, that if the schizophrenic patient is being supplied with high doses of niacin, then more tryptophan is likely to be converted to serotonin, also lowering adrenochrome levels. It should be recalled, however, that serotonin has a Jekyll and Hyde relationship with adrenochrome, only reducing its production when present at levels that exceed those of the indole.

Another adrenochrome antagonist, triiodothyronine, appears to be very effective in treating schizophrenia. As reported by Danziger,<sup>34</sup> every one of the 80 schizophrenics who had been ill for 6 months or less, who took between 120 to 1,200 milligrams of desiccated thyroid daily for at least 100 days, recovered, suffering relapses only if they later discontinued their medication. These doses may seem high, but it should be remembered that schizophrenics are known to be very resistant to thyroid medications.

Treatment might also involve attempts to directly raise body levels of another adrenochrome antagonist, serotonin. If serotonin is not provided as a supplement, its metabolism could be encouraged by the consumption of foods that are high in tryptophan,<sup>35</sup> for example, beans, cod, pork, soybeans, and cheese (provided that the patient is not allergic to them). In addition, every effort should be made to repair the antioxidant defence system, increasing glutathione peroxidase, catalase, and superoxide dismutase activity. In *What Really Causes AIDS*,<sup>36</sup> a detailed discussion is provided on how the body's

glutathione peroxidase production can be stimulated with supplements and a diet enriched with tryptophan, glutamine, cysteine, and selenium. A small number of orthomolecular physicians are reporting a dramatic improvement in schizophrenics treated with injected glutathione.<sup>37</sup> This can not be taken orally because it is broken down in the digestive tract. However, this adrenochrome antagonist appears to be very effective when injected.

### Mitigation of Other Biochemical Abnormalities: Step Six

Many of the biochemical “dominoes” in schizophrenia are part of the cascades that occur as adrenochrome and its metabolites interfere with normal levels of serotonin, triiodothyronine, glutamine, and other components of the antioxidant defence system. It seems reasonable, therefore, to anticipate that orthomolecular treatments, designed to reduce levels of the toxin adrenochrome, will automatically correct many of these abnormalities. Some, however, are not due directly to excess adrenochrome, but accompany the genetic abnormalities that help create it. This is why step two, genetic screening, is so important.

To illustrate, schizophrenics with the GSTM1\*0 allele are very likely to overproduce adrenochrome.<sup>38</sup> The treatments just described, for example triiodothyronine, niacin, and injected glutathione, may be capable of correcting this problem. However, it is still possible that this genetic aberration may result in deficiencies or excesses of other catecholamines. This is an issue that needs to be explored further in such patients if a reduction of adrenochrome alone does not result in a complete return to health.

Similarly, schizophrenics with the MTHFR C677T variant of the gene encoding for methylenetetrahydrofolate will suffer from

an excess of homocysteine and a deficiency of methionine,<sup>39</sup> even if treatment reduces adrenochrome levels. Clearly, since these imbalances will have major adverse impacts separately, they also need to be corrected. It seems likely that such schizophrenics would have been classified as suffering from histadelia by Pfeiffer,<sup>40</sup> whose treatment for this mental illness included 500 milligrams of methionine. Such treatment would help to elevate methionine levels but might also result in more homocysteine production. Since the remethylation (or detoxification) of homocysteine requires folic acid, vitamin B12, zinc, and trimethylglycine,<sup>41</sup> it is likely that schizophrenics with this genetic aberration will require high doses of these nutrients. Choline is a further methyl donor that can help to lower homocysteine levels, but largely in the liver and kidney. Folic acid, vitamin B12, and the other cofactors are still needed to protect the brain and heart.

Many schizophrenics have a low activity associated COMT-L allele that may cause epinephrine and metanephrine abnormalities<sup>42</sup> which may need to be addressed, in addition to any adrenochrome imbalance. It would appear that Pfeiffer's<sup>43</sup> protocols would be a good place to begin when searching for treatments for remedies for biochemical abnormalities above and beyond those due to excess adrenochrome and its metabolites. His treatments are described in detail in *The Schizophrenias: Ours to Conquer—Nutrition and Mental Illness* and in *Mental Illness: The Nutritional Connection*.<sup>44-45</sup>

### Repairing the Damage: Step Seven

Adrenochrome excess and the other biochemical abnormalities that occur in schizophrenia can eventually cause serious damage to the thyroid gland as well as the brain itself.<sup>46</sup> Long term chronic patients are, therefore, much more difficult to treat successfully. This task might not be impossible, but it

will almost certainly require higher doses of orthomolecular nutrients, taken for longer periods, before improvement becomes apparent.

One of the major problems in chronic schizophrenia is the development of brain atrophy, associated with large fluid filled spaces known as ventricles. Buckman and coworkers<sup>47</sup> provided evidence that blood levels of the selenoenzyme glutathione peroxidase have a strong negative correlation with computer tomography scan measures of such brain damage. Simply put, the less blood glutathione peroxidase, the greater the brain damage in chronic schizophrenics. Obviously, one treatment strategy worth trying is supplementation with the four nutrients, selenium, cysteine, glutamine, and tryptophan, that the body requires to produce glutathione peroxidase.<sup>48</sup> Injected glutathione may be of value.

Rudin and colleagues<sup>49</sup> reported some success in the treatment of schizophrenics with linseed oil, although they pointed out that the amount given was critical. Overdosing can apparently make the illness worse. Unheated linseed oil, of course, contains high levels of alpha linolenic acid, which is necessary for prostaglandin production. Interestingly, Rudin and coworkers<sup>50</sup> have argued that supplementing the diets of schizophrenics with essential fatty acids is only successful when the patient's selenium levels are optimum. To quote them directly,<sup>50</sup> "If a primate is deficient in the antioxidant element selenium, providing supplemental essential fatty acids will only make the selenium deficiency worse. Whatever selenium stores are in the body will be used up the much sooner in an attempt to protect the EFA (Essential Fatty Acids) from oxidative damage." Clearly, if essential fatty acids are going to be given to schizophrenics in attempts to reduce ventricle damage, they should be preceded by high levels of selenium supplementation.

There is growing evidence that eicosapentaenoic acid can repair ventricle damage in chronic schizophrenics, leading to an improvement in their mental health.<sup>51-54</sup> Horrobin<sup>55</sup> argues that there is excess activity of phospholipase A2 in schizophrenia. This is thought to remove highly unsaturated fatty acids, such as arachidonic acid, from nerve cell membranes. Excess phospholipase A2 activity has been identified in the plasma, red cells, and brains of schizophrenics and low arachidonic acid has been found in the brains of people with this illness. Eicosapentaenoic acid (EPA) is a natural intermediate in human metabolism that will inhibit phospholipase A2 production, so helping to preserve highly unsaturated fats such as arachidonic acid. EPA occurs naturally in fish oils, but so do other substances that antagonize it. However, certain fish oils, such as Kirunal, are particularly high in EPA and low in its antagonists. Pure EPA (LAX-101) is also available.<sup>56</sup> Several studies have shown that EPA can cause substantial improvements in schizophrenics, without adverse side effects. In about 40 percent of unmedicated schizophrenics, EPA (by itself) can control symptoms with the use of antipsychotic drugs. In chronic patients who had been unresponsive to normal treatment, EPA also was associated with more improvement than could be produced by conventional drugs.<sup>57</sup> In one of Horrobin's presentations that I attended, he showed slides of a patient's brain scans, taken at various times while they were receiving EPA. When these scans were superimposed, it was very obvious that treatment with this essential fatty acid was repairing brain ventricle damage. It seems likely that EPA would be even more effective if it was given together with supplements, including selenium, which were designed to elevate glutathione peroxidase activity.

It is clear that damage is not restricted to the brain in chronic schizophrenics. All of these patients also appear to suffer from extensive thyroid abnormalities.<sup>58</sup> I do not know how to repair

a damaged thyroid gland. If this is impossible, significant behavioural improvements can only be expected when using a protocol that includes continuous desiccated thyroid gland supplementation.

### Repairing the Soul: Step Eight

A society can best be judged by the way in which it treats its weakest and most vulnerable members. Traditionally, the mentally ill were ejected from the main stream and isolated in badly run, inhumane asylums. Considered “crazy,” “insane,” and “nuts,” they were society’s victims. In movies they played the role of monsters.<sup>59</sup> They appeared in the news as perpetrators of murders or bizarre crimes. Recovering schizophrenics are still one of the few groups that society feels free to abuse, ostracize, and discriminate against.<sup>60</sup> While it is socially acceptable to admit to cancer, heart disease, multiple sclerosis, or Parkinson’s disease, to admit to schizophrenia is to invite fear and derision.

To recover, schizophrenics need orthomolecular treatments, vitamins, minerals, essential fatty acids, and hormones. These are rarely covered under medical plans and because of their illness, most schizophrenics are too poor to afford them. To recover, schizophrenics need stress free environments. Many are now on the streets, in prison, or in overcrowded wards. To recover, schizophrenics need low sugar diets that are free of allergens. Many are in prison eating junk foods, in hospitals eating what passes for food there, or on the streets rummaging around in garbage cans looking for their next meal. To recover, schizophrenics need employment, respect, and compassion. All too often they receive rejection, abuse, and derision.<sup>61</sup>

## SUMMARY

This chapter presents an eight step approach to improving the cure rate for schizophrenia. The approach includes treatment in clinics designed using Bau-Biologie principles, genetic screening to identify the aberration involved, and allergy testing. Treatments should provide diets free of allergens and low in sugar. Patients should also receive orthomolecular antagonists of adrenochrome and its metabolites and of the other biochemical abnormalities seen in this mental illness. Brain repair can be encouraged by glutathione peroxidase and eicosapentaenoic acid, while desiccated thyroid is required to compensate for the poorly functioning thyroid glands which are characteristic of schizophrenia. Recovering schizophrenics need peaceful, low stress environments, respectable shelter, meaningful work, and respect. They do not need abuse, derision, and social abandonment.

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*Science changes one funeral at a time.*

Harvey Weiss (2002)

Roughly 1 out of every 400 Black Americans develop sickle cell anaemia.<sup>1</sup> In those with this chronic hereditary disease, many of their red blood cells form rigid crescent or sickle shapes that cannot pass through capillaries. Affected children often die during adolescence of strokes, heart disease, and infections. Sickle cell anaemia also causes sufferers painful, unpredictable health crises. Those children that survive are underweight and slow to mature.<sup>2</sup> How is it that a genetic, highly damaging disease can be so widespread amongst the Black population in the USA? What's in it for Darwin? Or more correctly asked, what is the evolutionary advantage that this mutation gives to Blacks that make its obvious disadvantages worthwhile? After all, as McElroy and Townsend<sup>3</sup> point out, "It is only the phenotypic characteristics that give some advantage of degree of Darwinian fitness that are subject to selective action."

At first glance, the sickle cell anaemia trait appears to provide Blacks with the very reverse of Darwinian fitness. After all, those with this genetic disorder tend to die in adolescence. Even if they don't, they are usually underweight, slow to develop, and often sick. These are not the type of people who might be anticipated to have larger families than the norm and so have a disproportionate effect on the human gene pool.

As anticipated, the differential reproduction and mortality linked to this genotype in the US are both negative, sufferers reproduce less and die younger. One might expect that, as a result, over time the mutation responsible for sickle cell anaemia would have disappeared. This has not been the case. Why?

Malaria has plagued humanity for thousands of years.<sup>4</sup> Even now it affects an estimated 200 million people every year, causing some 2 million deaths. In tropical Africa, for example, it kills about 1 million people annually, most of those being children.<sup>5</sup> The disease also contributes to death from other causes including pneumonia, anaemia, and kidney failure. The anaemia associated with malaria is linked to miscarriage, still-birth, and low birth weight.<sup>6</sup>

Malaria is caused by a protozoan parasite of the genus *Plasmodium*, which infects red blood cells. These protozoans cannot live outside their hosts and depend completely on the glucose, enzymes, and metabolism of such cells to survive.<sup>7</sup> This parasitic relationship eventually destroys the red blood cells, usually at 2 or 3 day intervals. The release of associated waste products and pigments causes the intermittent fever and chills seen in malaria sufferers. *Plasmodium* protozoa are spread from one human to another by four species of mosquitoes.

At some time in the past, a point mutation occurred in one of the human DNA base pair codes for the hemoglobin protein chains.<sup>8-9</sup> Instead of glutamic acid at the sixth position, as is usually the case, valine was produced. This substitution affected hemoglobin's level of oxygen affinity and led to the distortion of the cell membrane into an irregular, sickled shape. *Plasmodium* do not appreciate this abnormality. As a result, people with this sickling trait are unlikely to suffer as much from malaria. They are not completely immune but, if infected, the disease is less severe. In heterozygotes, who usually do

not exceed 30 to 40 percent of the population living in areas where malaria is commonplace, the sickling trait provides both normal and abnormal hemoglobin in every blood cell. This is a characteristic that increases their chances of surviving malaria to reproduce.<sup>10</sup> In those who are homozygous for sickle cell anaemia, this characteristic still helps to resist malaria, but their cells have nothing but abnormal hemoglobin. As a consequence, they develop sickle cell anaemia, which, as described, is often fatal. The offspring of two parents who carry the trait (heterozygotes) have a 25 percent chance of being born with sickle cell anaemia (homozygotes).<sup>11</sup> In West African populations, this occurs in roughly 4 percent of children, most of whom die before they can reproduce. The sickle cell trait has survived in Blacks, therefore, because despite the high toll sickle cell anaemia takes, the trait is counterbalanced by the benefits of reduced susceptibility to malaria that it provides.

Interestingly, in regions where malaria has been wiped out and where the sickling trait only brings disadvantages, its prevalence begins to decline. In the US, for example, it is now found in only 8.5 percent of Blacks. As a result, sickle cell anaemia occurs in a fraction of 1 percent of the Black population,<sup>12</sup> causing roughly 350 deaths annually.<sup>13</sup>

This brings us back to schizophrenia. Schizophrenia is usually first diagnosed in early adulthood or late adolescence. Suicide is far more common than usual in those who suffer from it. Its symptoms often cause long-term hospitalization, and prevent employment or meaningful relationships. Given all these evolutionary disadvantages, one might have expected schizophrenia's associated genetic aberrations to have disappeared long ago from the human gene pool. Nevertheless, schizophrenia occurs in roughly one out of every 100 people. As Torrey and Miller<sup>14</sup> have demonstrated, rather than dying out, schizophrenia has been increasing steadily. There seems

to be only one logical conclusion to be drawn from this reality. Just as the sickle cell trait helps protect against malaria at the cost of losses to sickle cell anaemia, schizophrenia traits must provide some benefits to the human gene pool that outweighs the ravages of this mental illness. How then do schizophrenia's genetic traits increase Darwinian fitness? What's in it for Darwin?

I have argued elsewhere in this book that there are at least four genetic traits that predispose those who carry them to the development of schizophrenia. These include the low enzyme activity variant of the catechol-O-methyltransferase gene, the GSTM1\*O allele (required to produce a form of glutathione S-transferase) and possibly the C677TT variant of the gene for methylenetetrahydrofolate reductase.<sup>15-17</sup> What these three genetic aberrations appear to have in common is that they all result in higher than normal exposure to adrenochrome, a metabolite of adrenaline, or an abnormal susceptibility to its negative impacts. Since all three of these variants are quite widely distributed in the human populace, it seems likely that abnormal levels of adrenochrome must carry some evolutionary advantage(s). That is, there appears to be not one, but at least three and maybe four balanced genetic morphisms. The suggestion that there is a balanced morphism in schizophrenia is not new. Sir Julian Huxley and colleagues,<sup>18</sup> for example, argued in *Nature* in 1964 that, since the fertility of schizophrenics was only about 70 percent of normal, the genetic aberration causing this illness must also carry with it some unrecognized evolutionary advantage. They suggested that this may be resistance to surgical and wound shock (including burns) associated with rapid recovery, or partial immunity to epidemic diseases such as smallpox and bubonic plague. It was also suggested that heterozygote females, who did not develop schizophrenia, might be unusually fertile, although no firm evidence could be provided to support this possibility.

The balanced morphism idea has reappeared in the literature at various times. Hoffer,<sup>19</sup> for example, has argued that the family members of schizophrenics who do not develop the disease tend to be unusually intelligent. This concept underlies Horrobin's<sup>20</sup> book *The Madness of Adam and Eve*, in which he argues that:

*Schizophrenia can affect people of all abilities in all strata of society, but it does with surprising frequency seem to affect the families of the great, the good, the clever, the rich, the ambitious, the intellectual and the creative.*

This belief is not new. Galton's eugenic ideas were rejected by Henry Maudsley,<sup>21</sup> the greatest psychiatrist in London in the second half of the 19th century, because he knew that schizophrenia occurred repeatedly in the great families of Victorian Britain. Maudsley recognized that an eugenic programme, designed to eliminate schizophrenia, would inevitably prevent the birth of some of Britain's future most creative and dynamic individuals. Myerson and Boyl<sup>22</sup> came to the same conclusion in the US where they found that US presidents, philosophers, writers, scientists, and physicians all had schizophrenic relatives that had been treated at McLean Hospital, near Boston. Anyone wanting more details about the close link between brilliance and psychosis should read *The Madness of Adam and Eve*.<sup>23</sup> Suffice it to say that a recent Scandinavian study has established that children of university graduates are almost twice as likely to develop schizophrenia than the children of non-graduates.<sup>24</sup> Similarly, Karlsson<sup>25</sup> has shown that Icelandic males, with psychotic family members, seem to have more skills and abilities and contain higher achievers in a variety of fields than do those with families without those who have this illness. Healthy relatives of psychotic patients, for example, publish more books of fiction and poetry and perform better in school, particularly in mathematics.<sup>26-27</sup>

There is quite good evidence, therefore, that one or more of the genetic aberrations that increase susceptibility to schizophrenia also appear to encourage intelligence and creativity. The last word on the topic is left to Horrobin,<sup>28</sup> who wrote:

*What I have suggested in this book [The Madness of Adam and Eve] is that the genes for schizophrenia, which are likely to include genes for bipolar disorder, dyslexia, high intelligence and schizotypy, are responsible for most of the religious sense, most of the technical and artistic creativity, and most of the leadership qualities in modern humans.*

The suggestion by Huxley and coauthors<sup>29</sup> that the gene associated with schizophrenia might give family members greater immunity to infectious disease was supported also by Eliot Slater.<sup>30</sup> However, the available evidence does not seem compatible with this idea. Torrey and Miller,<sup>31</sup> for example, have documented that epidemics have frequently caused major life loss amongst institutionalized schizophrenics. This has been true of typhus, cholera, pneumonia, tuberculosis, and syphilis, which appear to have been the major causes of death in English asylums in the 19th century. Indeed, the number of patients in such mental hospitals fell by 17 percent between 1915 and 1920, largely because of the enormously high death rates associated with the Spanish Lady influenza pandemic.<sup>32</sup> The evidence, therefore, seems clear. Schizophrenic genetic aberrations give very little protection, if any, against the infectious diseases that have been common, in the Developed World, during the past two centuries.

This does not mean that such aberrations provide no protection against disease. It has been argued previously that adrenochrome is protecting schizophrenic smokers from developing lung cancer.<sup>38</sup> Beyond this, it has been shown that the drug IntraDose, which contains the powerful oxidant Cisplatin and

adrenaline, is a very effective treatment for melanoma and cancers of lung, liver, breast, head, and neck. This drug is injected into the tumour mass where it almost certainly creates elevated adrenochrome. It would appear, therefore, that one of the major reasons that the genetic aberrations that are linked to schizophrenia are so widespread is because they provide a reduced risk for the development of cancer. As the environment altered during the past three centuries, the cost of such genetic aberrations has risen, filling the mental asylums with schizophrenics. Simultaneously, the benefits of such genetic variants have also increased as carcinogens have become more widespread and diverse and the cancer mortality rates associated with them have risen rapidly, particularly amongst families that do not carry genes that encourage above normal adrenochrome production.

## SUMMARY

Any economist will tell you that every strategy carries with it benefits and costs. The genetic aberrations increasing the risk of schizophrenia appear to promote religious sense, technical and artistic creativity, and leadership. They also seem to provide a greater resistance to a wide range of cancers, especially that of the lung. Whether you consider this Darwinian exchange with the Devil to have been worthwhile will probably depend on how you and your family fared in the distribution of its associated costs and benefits.

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## The Author

The author lives with his wife Sarah and cat McNuff in Victoria, British Columbia. A Canadian by choice, he was born in Tunstall, Yorkshire, England where he was educated at the Hull Grammar School and University College London. While at university, he specialized in geology and geography, earning a B.Sc. in 1964 and Ph.D. in 1968 from London University.

He has been a faculty member in the Department of Geography, University of Victoria since 1967. A tenured professor, he has authored or edited some 230 publications, the majority of which focus on reducing disaster losses or identifying the causes of chronic disease or longevity. He has published hypotheses on the origins of numerous diseases including myocardial infarction, SIDS, cancer, diabetes, schizophrenia, multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's and Parkinson's diseases, stroke, and AIDS.

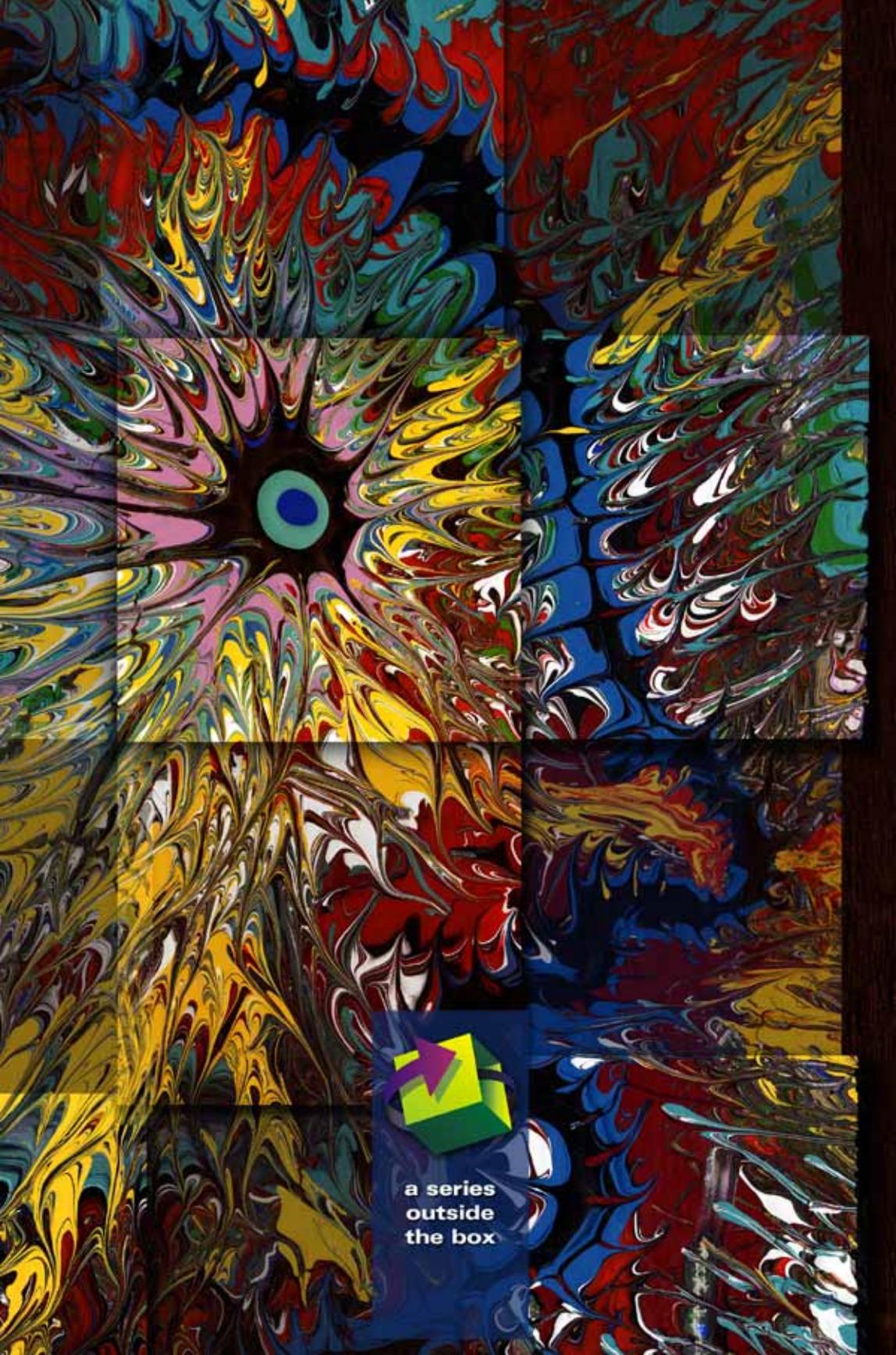
His many books include *Disaster Planning: The Preservation of Life and Property*, Springer Verlag, New York; *Reducing Cancer Mortality: A Geographical Perspective*, Western Geographical Press, Victoria; and *The Ozymandias Principles*, Southdowne Press, Victoria. Further books by the author include *Health, Disease, and the Environment*, Bellhaven Press (now John Wiley), London, and *What Really Causes AIDS*, Trafford Publishing, Victoria.

He is a member of the Explorers Club and several academic organizations including The New York Academy of Sciences, The Royal Geographical Society, and The Royal Society of Literature. In addition, he is the editor of both the International and Canadian Western Geographical Series and is a member of the boards of the Journal of Orthomolecular Medicine and the International Schizophrenia Foundation. He has been a

consultant to numerous organizations, including the United Nations, NATO, and the governments of Canada, Ontario, and British Columbia. Every day he takes at least the recommended daily allowance of the known essential nutrients, in the belief that this will slow the aging process. As a consequence, most of his salary is spent in health food stores. His other bad habits include providing treats to all the neighbourhood dogs; losing at chess to his computer; being regularly beaten by his stepson Dan at video games; and, with the assistance of @Derby and various computer models, failing to correctly predict the outcomes of horse races. For a more complete curriculum vitae visit <http://www.hdfoster.com>. A free copy of this book and “What Really Causes AIDS” can be downloaded at this website.

*The man who discovers a new scientific truth has previously had to smash to atoms almost everything he had learned, and arrives at the new truth with hands blood-stained from the slaughter of a thousand platitudes.*

José Ortega y Gasset  
*The Revolt of the Masses*, 1930



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