The Potential Relationship of Mental Illness, Oxidative Stress and Evolutionary Pressure Applied via Sexual Selection

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Abstract *Humanity can be distinguished from the rest of the animal kingdom by the prevalence of mental illness. One might wonder, given that mental disorder may affect 1 in 4 during adolescence/adulthood, why the brain should be so afflicted while other organs such as liver and kidney are not. This paper proposes two main biochemical explanations: (1) The brain relies mainly and precariously on a single metabolic channel for energy production whereas other organs have more channel; (2) In the face of metabolic stress, much of the metabolic activity of the human brain apparently prioritizes damage limitation over the metabolic needs of healthy mental function. This prioritization derives from an inability to synthesize vitamin C, caused by an ancient mutation. Consequential oxidative stress triggers a protective biochemical switch from glycolysis to the pentose phosphate pathway, resulting in critically diminished neuronal energy production and predisposition to impaired mental function and aggression. At the time of that mutation, this aggression increased successful mating and reproduction in our ancestors. However, the mutation's damaging effect on human neurochemistry has led to the current pattern of psychiatric and behavioral disorder.*

1. The Challenge of Mental Illness

The impact of psychiatric disorder is massive; this is reflected in prevalence rates reported between 0.4%-3.25% (**Table 1,** p.26).[1] In the USA, in 2003, there were 30,559 suicides[2] and there are 8-25 attempted suicides for every successful suicide.[3] These suicides and attempted suicides are strongly associated with mental disorder.[4,5] Approximately 25% of all people have a lifetime experience of some form of psychiatric or behavioral disorder.[1] These data probably underestimate the prevalence of psychiatric disorder because personality disorders (which in some cases share, with major psychiatric disorders, the sort of changes seen on positron emission tomography) may not always be identified.

Behavioral disorders are widespread, e.g., violence against women is a major issue involving women of all ages, cultural backgrounds, and income levels.[1] Domestic violence against women has been reported to have a lifetime prevalence of 16%-50%, whilst the lifetime risk for females of rape or attempted rape has been estimated to be 20%,[1] 80%,[6] and 97%[7] in different populations. Risk factors for sexual offence and other violence are almost identical.[8] There are two situations in psychiatric disorder: organic psychiatric order where there is an identifiable and specific underlying cause and non-organic psychiatric disorder where no underlying cause is obvious.

There is a crucial question here: evolution has made an excellent job of, for example, the human eye. Why has evolution let us down when it comes to brain function? This psychiatric and behavioral data may be taken to represent a tragic aspect of the human condition (corresponding to expressions of inadequate brain function) ingrained in hu-

Table 1. Prevalence Rates of Some Psychiatric Disorders.[1]

Unipolar Depression:	
Males	1.9%
Females	3.2%
Schizophrenia	0.4%
Bipolar Disorder	0.4%

man predecessors perhaps for eons and destined to be expressed forever.[9]

This paper challenges the view that such behavior in human predecessors through Eocene and perhaps Paleocene periods was always thus. It asserts that (i) psychiatric disorder, (ii) violent behavior and (iii) assault on females are all connected to a critical and pivotal point in evolution for humans and other primates about 60 million years ago and will be examined later through the lens of neurochemistry.

Conclusion

The facts that non-organic psychiatric disorder is common and relatively common compared to other causes of major disability are both puzzles.

2. Neurochemistry of Mental Illness

Mental illness tends to be associated with oxidative stress.[10-12] Oxidative stress is simply described as occurring when there is imbalance between, on the one hand, potentially toxic by-products of metabolism sometimes referred to as reactive oxygen species (ROS), e.g., superoxide (a free radical) and hydrogen peroxide (a non-radical oxidant)[13] and on the other hand the antioxidant system, which opposes or at least, tends to oppose, this toxic potential.

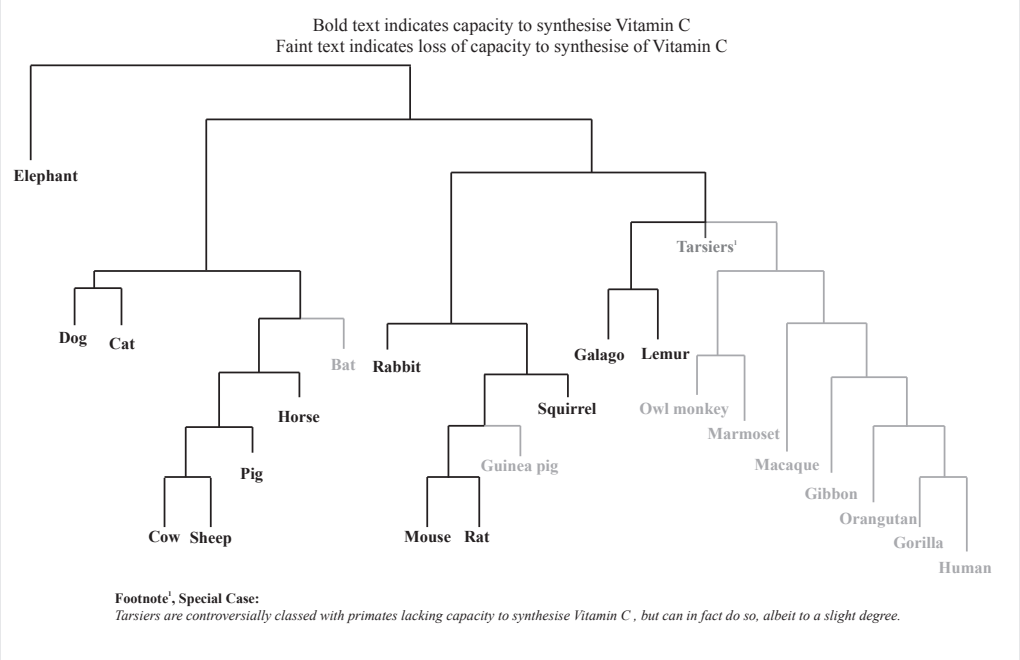
The antioxidant system comprises (but is not restricted to) protective enzymes: superoxide dismutase and catalase and other components such as glutathione (in oxidised and reduced forms), glutathione peroxidase, glutathione reductase, thioredoxin (TRXSH2) systems and vitamin C. These comprise a highly integrated network[14,15] whereby the ROS are normally safely converted into e.g., water and carbon dioxide. Oxidative stress occurs when there is an imbalance between the level of ROS and the capacity of the antioxidant system to inactivate them. Vitamin C, recognized for a long time as an important antioxidant, has recently come to be seen as exercising an even more important part in the operation of the antioxidant system, than previously understood and this role will be described in more detail later. The significance attaching to the close integration of parts of the antioxidant system becomes apparent when variation of the antioxidant status of the cell comes to be considered.

When oxidative stress is expressed by the imbalance mentioned, biochemical switches are tripped in such a way as to oppose the accumulation of these reactants. In this way the liability for structural damage is diminished. As and when the antioxidant system is overwhelmed by free radicals, the switching system fails and there is damage to cell structures (e.g., cell membranes) and interference with fundamentally important cellular functions.[13,14] For this reason, the antioxidant system plays a key role in protecting the structure and function of the cell.

3. Vitamin C Metabolism in Humans Compared to Non-primates

The key role of vitamin C in the antioxidant system was mentioned in the previous section. Humans, other primates and a few other species (including hamsters) cannot synthesize vitamin C.[16] Primate ancestors lost the capacity to synthesise vitamin C because of a mutation, some 60 million years ago[17] which suppressed the gene expressing gulonolactone oxidase (GLO), an enzyme situated on the walls of the endoplasmic re-

Figure 1. Distribution of the capacity for Vitamin C synthesis in selected species



ticulum.[18] The distribution of species which possess the capacity to synthesise vitamin C and those which have lost it, is displayed in **Figure 1** (above). Out of over 4,000 mammalian species, only a handful have lost the capacity to synthesise vitamin C. GLO is the penultimate enzyme on the metabolic pathway leading to vitamin C synthesis (the uronal acid pathway). In the face of the loss of GLO activity, affected species must rely on dietary sources of vitamin C.

What impact, if any, has there been on the antioxidant system resulting from this mutation? (1) There is currently evidence of vitamin C deficiency in the human diet.[19] Probably in the face of the historical hazard of deficient vitamin C in the diet, the antioxidant system in humans and other primates is boosted by greater expression of a key protective antioxidant enzyme, mentioned before: superoxide dismutase.[20] The specific activity of superoxide dismutase was found to be much less in species capable of synthesising vitamin C. However, superoxide dismutase activity was found to be greater in humans than in all mammals tested[20] suggesting that the biochemical impact in mammals of the loss of GLO activity has had its greatest expression in humans. (2) Vitamin C economy is boosted by reabsorption from the kidney. (3) As with other species, vitamin C is recycled by an antioxidant, NADPH. (4) Vitamin C is pumped into cells and mitochondria.[21]

Are these refinements sufficient to compensate for the loss of capacity to synthesize vitamin C? To answer this question it is necessary to assess the effectiveness of vitamin C-related metabolism in humans as expressed in both laboratory and clinical studies.

Gross metabolic consequences of inability to synthesise Vitamin C

a) Humans have significantly lower vitamin C levels in blood compared to non-primates,

such as the dog.[22]
b) Stressed rats (and other non-primates) can boost vitamin C metabolism (in rats 20-fold).[23] Humans and other primates cannot synthesize, let alone boost vitamin C synthesis in the face of metabolic stress and, in contrast, humans experience a diminution in vitamin C status in the face of stress.[24] Such acceleration of vitamin C metabolism in non-primates is via the uronic acid metabolic pathway. The trigger for this boosted metabolism of vitamin C in non-primates may be the accumulation of ROS, particularly superoxide,[15] seeing as barbitol both accelerates vitamin C synthesis in non-primates[23] and inhibits Complex 1 of the electron transfer system[15] This suggests that in non primates, mitochondrion activity is reciprocally related to flux in the uronic acid pathway with the effect of (respectively) diminishing ROS production (a normal accompaniment of mitochondrion activity) and strengthening the antioxidant system (by way of vitamin C synthesis), a two-fold means of countering oxidative stress. As stated, the antioxidant resource, expressed by the uronic acid pathway, is not available to humans and other primates because of loss of the gene expressing GLO, a critical enzyme on the uronic acid pathway for vitamin C synthesis.
c) In humans, oxidative stress varies inversely with vitamin C status.[25]
d) The U.S. Third National Health and Nutrition Examination Survey indicated that vitamin C may reach low levels due to dietary deficiency.[19] At such levels defective changes in cognitive function start to occur (and occur before measurable physical signs).[26]

Over all, the evidence indicates that human reliance on diet as a source of vitamin C is a hazard to biochemical efficiency and healthy cognitive function, particularly if the dietary supply of vitamin C is suboptimal.

Clinical Correlations
a) Oxidative stress varies directly with the severity of depression.[27]
b) Schizophrenics tend to have lower vitamin C status compared to controls.[28,29]
c) Vitamin C tends to remit schizophrenia and depression.[28,30]

4. Potential Metabolic Consequences for Neurones Resulting from Mutated Loss of Capacity to Synthesize Vitamin C

Reference was made earlier to a report that one in four is likely to experience psychiatric symptoms during adolescence and adult life. Other organs do not fail so commonly in such a way as to cause disability. This suggests that brain cells are rather more metabolically vulnerable compared to other types of cell.

The following questions are posed:
1. What might explain the vulnerability of brain cells?
2. Where does the ROS-antioxidant balance fit in the context of brain cell metabolism, given the connection between psychiatric illness and oxidative stress and against the background of the potential of ROS to interfere with effective metabolism?

Neurones face a particular metabolic hazard for four reasons:
a) They rely mainly (and precariously) on a single metabolic channel for energy production[31] (glucose oxidation) thereby lacking significant redundancy for generating energy, (beta oxidation also provides some energy especially in such circumstances as fasting, strenuous exercise, low carbohydrate and ketogenic diet).[32]
b) That main reliance on a single metabolic channel is hazarded by the accumulation of ROS, which can inhibit sulphydryl enzymes such as glyceraldehyde-3-phosphate on the glycolytic pathway.
c) Neurones cannot up-regulate energy production by their own glycolytic channel.[33]
d) Neurones possess limited antioxidant reserves compared to astrocytes.[34]

Neurones possess the pentose phosphate pathway (PPP)[35] as well as glycolysis, so, in that specific respect, the metabolism of neurones is similar to that in other cells. Activity of the PPP contributes to the antioxidant

system by means of synthesising NADPH and this role is described in more detail below. Accordingly, neurones appear to have similar mechanism, within limitation as mentioned above, to combat ROS as other cells. An understanding of the strength and weakness of the PPP in its role of combating ROS is central to understanding the challenge faced by neurones in the situation of accumulating ROS and will be considered in more detail later.

Other cells can more reliably meet energy needs by metabolising breakdown-products of fat and protein to create energy. Clearly, if the prioritised metabolic channel in neurones for energy production (glucose catabolism) is obstructed in some way, energy production is hazarded and such obstruction will be considered shortly.

In Part 2 of this paper ("Neurochemistry of Mental Illness"), the association of oxidative stress and mental illness was mentioned. What happens at a biochemical level when neurones are exposed to the effects of oxidative stress?

Re-Routing of Biochemical Pathways: a Key Safety Feature in Neurones to Protect the Cell Against Oxidative Stress

Oxidative stress can be induced experimentally in neurones by a variety of means but whatever the means, the cells protective response is similar. Rat cortical neurones exposed to the oxidised form of ascorbic acid (Dehydroascorbic acid) display increased flux in the PPP and diminished flux in the glycolytic pathway.[36] Dehydroascorbic acid is not an antioxidant and stresses the antioxidant system. Nitrosative stress[34] and hydrogen peroxide.[37] similarly promote metabolism via the PPP. These switches seem to be determined by the following enzymic responses to oxidative stress (**Figure 2**, p.30):[34]

1. Down regulation of phosphofructokinase – this causes a build-up of metabolites proximal to Phosphofructokinase on the glycolytic pathway; and
2. Up-regulation of glucose-6-phosphate dehydrogenase – this promotes the diversion of the built up metabolites via the PPP.

Switching between these metabolic pathways can be demonstrated in different ways. For example, inhibition of the PPP causes an increase in flux via glycolysis.[38] Contrariwise, inhibition of glycolysis at the phosphofructokinase stage results in up-regulation of glucos-6-phosphate dehydrogenase causing increased flux in the PPP.[34]

The key enzymes here are phosphofructokinase and glucose-6-phosphate dehydrogenase. In this context of neuronal defence against oxidative stress, they are gatekeepers and determinants of flux in glycolysis and the PPP respectively.

Protective results of the biochemical switches

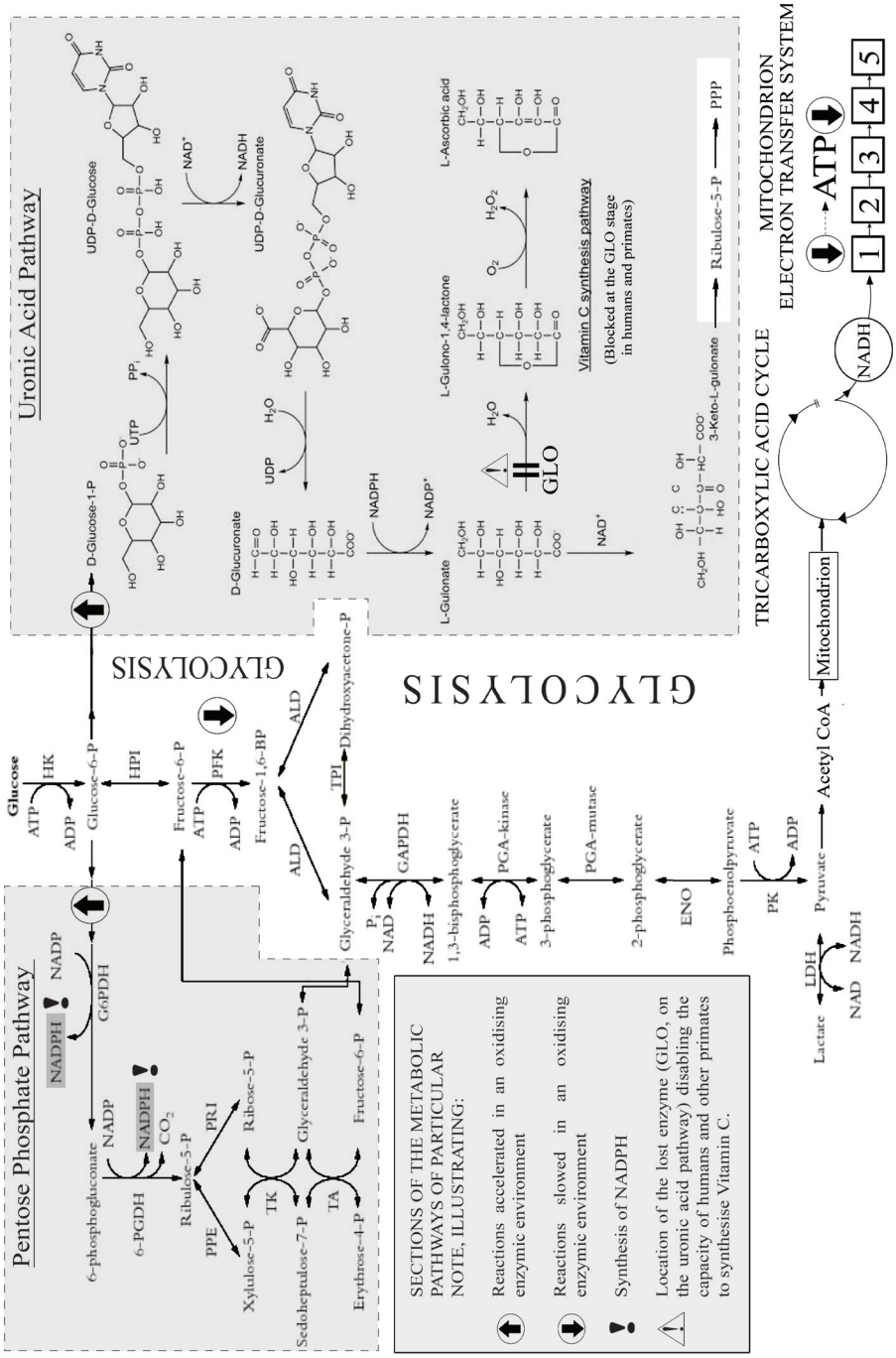
In consequence of these switches, specifically by prioritisation of the PPP, increased quantities of NADPH become available. By recycling vitamin C and glutathione, NADPH multiplies the effect of these antioxidants, tending to conserve structure but seemingly at the risk of impairing function. The process of switches described here suggests that in the situation of antioxidant weakness, the antioxidant system is strengthened at the expense of suppressing glycolysis and effective energy production.

Amount of flux in the neuronal PPP in rats.

The PPP amounts to about 14% of glucose metabolism in rat neurones[38] where both the oxidative and non-oxidative stages of the PPP operate. The final products of the PPP are glyceraldehyde-3-phosphate, which can enter the glycolytic pathway, and fructose-6-phosphate (Figure 2). The fate of fructose-6-phosphate, as an end product of the PPP, is determined by whether antioxidant strengthening or energy production are prioritised in the cell. Accordingly, the following trends occur: in the situation of oxidative stress, glycolysis is diminished at the phosphofructokinase stage, as described above. Consequently, fructose-6-phosphate is recycled via the glycolytic pathway, (via conversion to glucose-6-phosphate) back into the PPP (Figure 2). When phosphofructokinase is not restricted, (as in the situ-

Figure 2. **Simplified Diagram of Glycolosis, the Pentose Phosphate Pathway (PPP) and the Uronic Acid Pathway (UAP).**

a) The accelerated and slowed biochemical reactions which occur in response to an oxidising enzymic environment.
b) The location of the enzyme GLO which is present in most species but absent in humans and closely related primates.



ation where oxidative stress has not tripped the biochemical switches referred to here) fructose-6-phosphate is preferentially introduced into the glycolytic pathway for conversion to fructose-1,6-biphosphate for onward catabolism and energy production (Figure 2).

Diminished energy production when the PPP is used.

However, despite the advantage of the PPP strengthening the antioxidant system by means of synthesising NADPH, the PPP, even when operating at maximum energy production capacity, is only capable of generating 85%* (*=per unit of glucose metabolised) of the energy created via the glycolytic pathway.

Progressive drop in energy production in the face of increasing diversion to the PPP

In contrast to the 85% situation described above, in the situation of significant oxidative stress, the PPP tends to recycle fructose-6-phosphate (otherwise usable for energy production via glycolysis) into another circuit of the PPP, (via transformation into glucos-6 -phosphate) so as to further enhance NADPH production. In the notional situation, where all the fructose-6-phosphate is being recycled to secure maximum production of NADPH, energy production via the PPP is only 15%* of that achieved by glycolysis.

Oxidative stress in neurones results in rerouting of metabolic channels with the result of less energy production.

The account of the biochemical switches just described, apply to neurones. Other ways in which other cells may be affected by ROS and the metabolic resources available to those cells to counter them have been described.[13,15,39-42] It is clear from these studies that metabolic pathways can be switched and slowed in a variety of ways. Notably, thyroid hormone can uncouple oxidative phosphorylation, a process which diminishes superoxide production[15] thereby tending to diminish oxidative stress. However, the potential contribution of the greater thyroid system to the control of oxidative stress (though important on account of hypothyroidism being a fairly common condition) is beyond the scope of this paper.

Seeing as it appears that, in the face of oxidative stress, the metabolic pathways supporting the antioxidant system are preferred over glycolysis and energy production, what outcome is to be expected? In the case of brain cells, the hazard of diminished energy production includes potential impairment of the means of neuronal signalling,[43] which is considered in more detail in Part 9.

Diminished neuronal energy production therefore provides one explanation of the biochemistry of non-organic psychiatric disease, starting with ROS accumulation in the situation of oxidative stress[10, 12] and, leading through protective biochemical pathway switches, ending with impairment of neurotransmitter function and impaired/ distorted mental performance.

From the perspective described in this section, the view expressed by others that psychiatric disease is a metabolic disorder,[11] is supported. However, if so, what is the origin of the metabolic disorder? In other words, if ROS are associated with psychiatric disease, what accounts for the inordinate accumulation of ROS and the development of oxidative stress in the first place? The critical role of vitamin C in preventing ROS accumulation will be considered first, followed by a consideration of how the loss of capacity to synthesize vitamin C has come about and what critical consequences have ensued.

5. The Critical Role of Vitamin C in the Antioxidant System

The enzyme superoxide dismutase was mentioned earlier as playing an important part in the operation of the antioxidant system. To understand vitamin C's critical role in the antioxidant system, it is necessary to understand the way in which vitamin C interacts with the protective enzyme, superoxide dismutase, the most powerful enzyme in the human antioxidant system. Some accounts of the function of vitamin C as an antioxidant, refer to its capacity to accept and donate electrons. However, recent research into the actions of vitamin C in the face of

oxidative stress has moved vitamin C to centre stage as a key conductor of the way that the antioxidant system functions, operating in some ways more like a hormone than a vitamin. *In vitro* study of vitamin C supplemented cells, has shown that vitamin C induces superoxide dismutase and catalase (by transcriptional and post-transcriptional processes), roughly doubling their activities and thereby diminishing markers of oxidative stress.[44] Other studies confirm vitamin C induction of superoxide dismutase.[45-48] and the role of superoxide dismutase in protecting neurones against oxidative stress.[49] Seemingly, these enhanced changes in antioxidant performance speak to us from millions of years ago when the cells of human ancestors were replete with vitamin C, before the capacity to synthesize vitamin C was lost.

Cells abundantly supplied with vitamin C are less likely to sustain oxidative stress than those which are not and this effect is mediated by the multiplying effect of vitamin C on the activity of superoxide dismutase, the cells strongest antioxidant enzyme.

The metabolic handicaps (relative to non-primates) which humans and other primates face in relation to Vitamin C metabolism involve:

1. The inability to synthesize vitamin C;
2. The reliance on dietary sources for vitamin C
3. The effects of dietary deficiency of vitamin C
4. The lack of ability to boost vitamin C metabolism in the face of stress; and
5. The lack of induction of antioxidant enzymes: superoxide dismutase and catalase, whereby the antioxidant system is strengthened. In contrast, in species capable of synthesising vitamin C, induction of these protective enzymes results.

Summary of Parts 1-5

As stated, there is a known association between psychiatric disorder and oxidative stress. The interaction between ROS and the ROS-responsive trigger points of the cell just described, prioritises the strengthening of the antioxidant system at the expense of energy production. It is proposed that these biochemical events (particularly diminution in energy production) are factors in the pathogenesis of a range of psychiatric disorders,[10,11] expressed fundamentally by diminution in neuronal signalling,[43] leading to impaired mental functioning manifesting as psychiatric disorder.

6. Evolutionary Setting of the Biochemical Battle between Vitamin C and ROS

The evidence suggests that much psychiatric and behavioral disorder stems from ROS accumulation interfering with brain metabolism and cognitive processes, and there is circumstantial evidence that much of this is due to the broken antioxidant system.

What has gone wrong here? Surely the process of evolutionary pressure should have removed oxidative stress as a metabolic, behavioral, social and ultimately species-wide liability. This is an apparent paradox.

It is necessary to introduce, as a preamble, two topics which contribute to providing an answer to this question. These preambles are:

Topic i) Common manifestation of severe psychiatric illness; and

Topic ii) Common misconceptions about how evolution operates.

Topic i) of Preamble: Psychiatric Disease Manifestation:

The account of psychiatric and behavioral disorder described in Part 1 illustrates the scale of the contemporary challenge of these disorders. In contrast, the following description of psychiatric and behavioral disorder, characterized partly by aggression, serves to place them in the context of the behavior of human ancestors at the time when the gene expressing GLO was lost, many millions of years ago.

Aggression is a relatively frequent manifestation of bipolar disorder, schizophrenia and other psychiatric illnesses. US and European studies assessed the risk and manifestation of aggression in these disorders at 21% and 52% respectively.[50,51] The associa-

tion of oxidative stress with psychiatric illness therefore implies, in a clinical context at least, an association between oxidative stress and aggression. The overlap of risk factors for aggression and sexual violence was mentioned in Part 1 of this paper.

The important part played by aggression (resulting, it would seem, from the hazard of oxidative stress in vitamin C–depleted neurones) in human ancestors who had undergone the mutation depriving them of capacity to synthesize vitamin C, will be considered in the next section. In the meanwhile, the schizophrenia-oxidative stress-aggression relationship should be remembered.

Topic ii) of Preamble: Evolutionary Pressure

The survival of the GLO mutation, asserted here as resulting in major rates of psychiatric and behavioural disorder, is counter-intuitive, indeed, appears not to make sense at all. However, to understand this, it is necessary to accept that the following commonly-accepted beliefs about evolution (listed below), are incorrect and are so because they are at variance with sound principles which partly determine the process and outcome of evolution, namely sexual selection, comprising: i) male competition and ii) female selection. These commonly held, but inaccurate beliefs are: 1. Humans have progressed from inferior to superior versions according to an evolutionary process, which enhances humans in all respects with every change; 2. Mutational changes disadvantageous to the species are always eliminated by evolutionary pressure.

It is more accurate to describe the evolutionary process as follows: evolutionary pressure dictates that when a mutation has benefit for reproduction which strongly outweighs any downside, the mutation may survive. Darwin's assertion that sexual selection works to improve population fitness has been contradicted by studies indicating that the outcome of co-evolution between sexes through sexual conflict may actually decrease the fitness of populations[52-54] as well as creating exaggerated male characteristics.[55] Briefly, such studies have led to the conclusion that:

"The idea that mating interactions might cause the evolution of decreased fitness (present authors' italics) in a population has been particularly difficult for people to entertain: public and scholars alike…."[56]

But what about the mutation which deprived human ancestors of the capacity to synthesize vitamin C? Where does this mutation sit in all this? Counter intuitively, the GLO mutation (associated as it appears to be with extensive current psychiatric morbidity) must have invoked strong evolutionary advantage (disadvantageous as the mutation would seem). What strong evolutionary advantage has attached to oxidative stress, stemming from relative vitamin C deficiency? This question is addressed in the next section.

Conclusion

1. Hostility is a common feature of major psychiatric disorder; and
2. Evolution may promote the survival of mutations which are disadvantageous to the species.

7. Behaviour of Human Ancestors 60 Million Years Ago

Introduction

In the text which follows discussion will include alternation between species such as humans, chimpanzees and orang-utans (belonging to the Primate suborder Haplorhinni) which cannot synthesize vitamin C and Primate species which can (the Primate suborder Strepsirrhinni). As stateed eaelier the loss of the gene expressing Gluconolactone Oxidase (GLO) determines species which cannot synthesize vitamin C, in the text which follow, they will be tabbed Gluconolactone negative, abbreviated to GLO-ve. Contrariwise, speices which can syntesize vitamin C will be tagged GLO+ve.

The clue to answering this paradox is provided by studying the behavior of non-human primates. The description of primate behavior which follows is concerned with orangutans and chimpanzees, neither of which possess GLO activity (i.e., are GLO-ve just as humans are). In orangutans, the male aggressively forces approximately

50% of copulations. In the case of adolescent orangutans, the frequency is greater. In chimpanzees, males use aggression towards females to increase the chances that females will mate with them and to diminish the chance that the females will mate with other males, thereby promoting successful reproduction. Thus, male on female aggression, particularly for the purpose of coercion to copulation (in mainly estrous situations but also in anestrous) is an important determinant of successful reproduction for the male. This connection between aggression and reproductive success applies in chimpanzees even though the aggression tends not to take place at the actual time of copulation. In contrast, orangutans tend to express aggression at the actual time of copulation.

Importantly, research has provided an example of the least aggressive chimpanzee in a troop being totally unsuccessful at procreating in the face of competition from more aggressive chimpanzees. Astonishingly, male on female aggression in, for example, mountain gorillas, has been observed at a rate of approximately once every three hours per female.[57] Male on male aggression is usually commoner than male on female aggression.

Thus, in terms of this paper, the emergence of neuronal oxidative stress in a mutant, caused by loss of expression of GLO activity, predisposed that mutant to aggression. A parallel here is drawn with the situation at the present time in which mental illness (schizophrenia), oxidative stress and aggression tend to occur together. This ancestral aggressive coercion to copulation was perhaps amplified by testosterone-induced suppression of superoxide dismutase,[58] thereby adding to ROS accumulation with the hazard of even greater aggression. The evidence suggests that biochemically–induced aggression in the mutant would soon eclipse the efforts of unmutated peers at reproductive performance and reproductive success (without specification of effect on fecundity).

Darwin described the two components of sexual selection in evolution mentioned earlier: i) competition between males, and ii) selection by females. The process described here conforms to Darwin's classification of sexual selection in evolution: namely competition between males. In the context described here, female selection may be totally eclipsed.

Importantly, strange as it may seem, evolution is driven by success at reproduction, regardless of whether that success creates disadvantage in other respects.[56] At the time of this mutation, which determined reproductive success, more was possibly less, for the species as a whole, raising the question as to just how effective the process of evolution actually is.[59]

The somewhat alarming process described here, which appears to have critically conditioned primates, has been described as follows: "*Whatever features* (present author's italics) assisted individuals in their efforts to survive and reproduce would come to characterize the population."[60] It appears that the characterisation of primates and their ancestors, after the loss of GLO, has been to display the effects of oxidative stress.

Conclusion

Regarding the emergence and survival of the GLO-ve mutation in human ancestors, we can state the following:

1. That exaggerated aggression arose as a consequence of impaired brain function stemming from oxidative stress caused by relative deficiency of vitamin C in neurones, prioritising the PPP over glycolysis, leading to diminished neuronal energy production; and
2. Male on female aggression was a behavioural consequence of this, which survived as a result of a quirk of evolution because it favoured reproductive success for the mutant male, compared to males not possessing the mutation.

8. Predictions Attaching to the Proposition of a Link Between GLO-ve Status on the One Hand and Aggression and Psychiatric Disorder on the Other

Prediction 1: Study of non human primates should show that GLO–ve primates should dis–

play more aggression than GLO+ve primates

As described, some Primates (the suborder Strepsirrhini can synthesize vitamin C whereas primates in the suborder haplorhinni cannot. The former includes new world monkeys, old world monkeys, gibbons, orangutans, gorillas, chimpanzees and humans. If the loss of GLO (the GLO-ve situation) has indeed predisposed humans to psychiatric illness (and through that, to aggression), then it follows that GLO-ve primates should express more aggression than GLO+ve primates. A study of the literature devoted to promate behaviour[1,2,7,61-75] and relating this to primate GLO status[76-81] reveals considerable variablility. Furthermore the data is scanty and not of sufficient quality to enable the task. Notwithstanding this, indices of aggression have been measured in a few speices. The greatest frequency of male on female aggression (and the greatest intensity of male on female agression versus male on male aggression) have both been reported in a GLO-ve species (Mountain gorilla[57] and Magabeys[82] respectively).

Prediction 2: Vitamin C deficiency (scurvy) should be associated with mental disorder

The association between deterioration in cognitive function and vitamin C deficiency (but not advanced clinical scurvy) has been reported in an experimental study[26] mentioned in section 3. Advanced scurvy should be associated with notable psychiatric disorder, according to this paper. In this connection, a study of experimental scurvy was undertaken in the UK during world war two (in conditions which would not be allowed today). In that study, despite classical signs of scurvy which appeared in the test subjects, mental disorder was not reported, so presumably not observed.[83] Sudden death has been reported to be associated with scurvy, so this consideration was an obvious constraint which limited the scope of this study. That absence of report of mental disorder in scurvy is at variance with other observations, particularly in the situation of epidemic scurvy where clinical signs such as skin and gum changes have consistently tended to occur early in individuals displaying features of what we would probably recognise today as signs of depression.[84] Those reports did not draw the conclusion that these selected individuals were possibly already displaying depression as a sign of scurvy, which, drawing on modern data,[26, 27, 30] is likely to have been the case. Historical reports of scurvy in ships crew members have described hallucinations as a feature.[84] There has been debate about the possible role of scurvy in determining the fatal outcome of Scott's Terra Nova expedition to the South Pole (embarked 1910), in which disorientation was a feature in one member of the sledge party, prior to his tragic death. However, early descriptions of what has been described as scurvy are possibly, at least, descriptions of combined dietary deficiency (e.g., deficiency of folic acid, which, as in the case of vitamin C, is heat-labile and subject to destruction during cooking). Other cases, reported as scurvy with severe mental disorder may have resulted from lead poisoning due to the primitive process of sealing tinned food with lead solder, as was the case in the early 19th century.[84]

According to the proposal in this paper, namely that mental illness is associated with defective vitamin C metabolism, it appears that scurvy should be associated with more dramatic signs of mental disorder than those which have been reported.

8. Conclusion

In relation to the hypotheses put forth in this paper, it should be clearly understood that:

1. The data in relation to primate behaviour and GLO status (+ve/-ve) is not of sufficient quality to ascertain whether aggression is commoner in GLO-ve primates (as predicted by this paper, but should not be used to support or refute the association proposed); and
2. The data in relation to mental disorder in scurvy, points to depression as a complication; however, more florid manifestation of psychiatric disease is predicted than most reports relate.

9. The Theory that Evolution has Adversely Affected Human Neurochemistry Leading to Psychiatric Disorder

How, if at all, does this account of biochemical changes in the face of oxidative stress (ROS accumulation) sit with explanations of psychiatric disease, proposed and described by others? Many factors have been identified as being associated with psychiatric disorder/disordered perception (e.g., genetic factors, stress, hypothyroidism, organic brain disease, nutritional factors, and sociocultural factors). In addition neurotransmitter and psychodynamic theories have been proposed.

1) Neurotransmitter theory of psychiatric disease

Defects in neuronal signalling[43] and neurotransmitter metabolism[85,86] have been proposed as (at least intermediate) causes of psychiatric disorder. The process described in this paper (Figure 2) has it that neurones prioritize protection over production in the face of oxidative stress, associated as it is with a range of psychiatric disorders.[10, 11] Consequently, as described earlier (Part 4), it seems probable that biosynthetic pathways not connected with antioxidant activity (including the synthesis of neurotransmitters for neuronal signalling) are marginalized in terms of ATP supply, to meet their energy needs as follows.

2) Neurotransmitter synthesis is an ATP-dependent process.

The connection between defective energy production and impaired neuronal signalling is illustrated by the biochemistry of glutamate, the most common neurotransmitter in the brain. Entry of glutamate into cells is dependent on the sodium/potassium (Na+/K+) concentration gradient across the cell membrane[87,88] This concentration gradient is maintained by a Na+/K+ pump, which in turn is powered by ATP, generated in the mitochondria. In the situation of critically diminished availability of ATP, it follows that the availability of glutamate is diminished with resultant impairment of glutamate-determined signalling.

3) Psychodynamic theory of psychiatric disease

Freud identified aggressive impulse in what he described controversially as the Oedipus Complex thereby placing thoughts of violence linked to sex in the setting of psychiatric disorder.[89] According to the account given here, the link between the GLO gene suppression, male on female aggression in a sexual context, and current patterns of mental ill health, reflect genetically determined biochemical damage to brain cells which has been repeated in successive generations of primates for millions of years. For Freud to suggest in his penetrating way, that much psychiatric/behavioral illness presents clinically in the context of aggressive feelings is thus reflected at neurochemical and evolutionary levels.

4) Proposal of a connection between schizophrenia and deviant glucose metabolism, particularly enzymatic activity on the glycolytic pathway at the point of phosphofructokinase.

The switching of glycolysis to the PPP brought about by down regulation of phosphofructokinase was considered in Part 4. Others have proposed a distinct role for deviant glucose metabolism in the aetiology of psychiatric disorder. In particular, a link has been reported between schizophrenia and the gene (Pfkfb2) expressing the enzyme 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase(PFK2)[90] a bifunctional enzyme involved in both the synthesis and degradation of fructose-2,6-bisphosphate, a key regulatory molecule that controls glycolysis, by strongly influencing the activity of phosphofructokinase. An abundance of fructose-2,6-biphosphate stimulates phosphofructokinase (and glycolysis) whereas a relatively low concentration inhibits phosphofructokinase and also glycolysis.

Phosphofructokinase is influenced by a variety of entities and is located at an important metabolic crossroads on the glycolytic pathway (Figure 2). Glucose, insulin, fructose-2,6-biphosphate, citrate, PH, ATP and AMP can all influence its activity. Slowing, restoration, reversal and redirection of glucose metabolism can all be triggered at

this point. That complexity is reflected in the remarkable structure and dynamism of phosphofructokinase, which changes shape, rather like an ultramicroscopic sculpted jelly, according to which of several entities, at which level of intensity, is impacting on it at any given moment. Although the activity of the enzyme PFK1 is infulenced by a large number of entities, for purpose of simplification these entities can be regarded as a servo system in which ROS accumulation slows it and the emergence of a small ATP:AMP ratio accelerates it (indices of oxidative stress and energy requirement, respectively). Their importance in the clinical context will be discussed below. This enzyme, before the GLO mutation, had possibly reached the limit of the range of activity that an enzyme could do and still perform a reliable and effective function.

The state of equilibrium at the phosphofructokinase stage of glycolysis determines how much of the glycolytic flux is devoted to energy production and how much to strengthening the antioxidant system via NADPH, synthesised on the PPP. The genetic study referred to here (pointing to a potential role for Pfkfb2 in schizophrenia[90]) accords with the biochemical view expressed here (Figure 2) that events at the phosphofructokinase stage of glycolysis can influence the level of oxidative stress, a level known to be elevated in psychiatric disorder.

It is useful to consider the operation of phosphofructokinase before and after the loss of GLO activity in human ancestors ("pre" and "post' loss). In the pre-loss situation, the flexibility of phosphofructokinase enabled, for example, short term local recovery of neurones, say, in the situation of brain contusion, arguably the sort of situation for which it had evolved. In this situation of cerebral contusion, it is easy to imagine local promotion of the PPP to strengthen the antioxidant system in the hypoxic and oxidatively stressed region of the brain, thereby promoting survival and recovery. In contrast, the post-loss situation for phosphofructokinase is notably different. The metabolic role of the enzyme changed dramatically because it then had to compensate for permanent, relative, global loss of vitamin C and a variable loss at that, determined by variation of dietary intake of vitamin C with the potential for significant and sustained oxidative stress.

Compensatory mechanisms, which apparently evolved to overcome this situation in the GLO-ve situation of primates, have been described earlier: the capacity for pumping vitamin C into cells and greater specific activity of superoxide dismutase (none greater than in humans, amongst mammals which have been studied). However, pre-loss, phosphofructokinase was already highly sophisticated and geared to respond to a variety of biochemical variables in its milieu, against the background of a substantial concentration of vitamin C, arising from GLO activity and the uronic acid pathway. The existing pre loss sophistication and complexity of this enzyme was possibly an impediment to the challenge it faced in adjusting to, what had become (post-loss), relatively low and highly variable levels of vitamin C. It is proposed that phosphofructokinase, because of its sophistication and complexity, made an incomplete adjustment post-loss and failed (and continues to fail) to consistently meet the challenge of diminished vitamin C levels. According to this view, the failure of phosphofructokinase to meet that challenge is represented by three hazards:

a) The result of too much glycolysis and not enough of the PPP: Phosphofructokinase, at one time, diverting too much flux down the glycolytic pathway (At the expense of the PPP) resulting in sufficiently energised neurones but neurones without proper antioxidant defence. Result? Apoptotic death of unprotected neurones. This hazard may explain why dehydroepiandrosterone (DHEA), known to block the PPP in neurones,[91] has been reported not to prevent deterioration in Alzheimer's disease.[92]

b) Too much of the PPP and not enough glycolysis: Conversely, if phosphofructokinase diverts too much flux into the PPP, neurones are protected from antioxidant damage but have insufficient energy to function properly.

This may explain why, in contrast to the Alzheimer's disease situation, DHEA tends to remit depression.[93,94]

c) First too much glycolysis and not enough PPP, alternating with the reverse: This picture of challenging and ambivalent phosphofructokinase choice at the fructose-6-phosphate step in glycolysis, provides a model for (at least) rapid cycling bipolar disorder based on the following:

i) Phosphofructokinase prioritisation of the PPP pathway at one time, giving rise to depression (because of insufficient neuronal energy, resulting from inadequate glycolysis);

ii) At another time, phosphofructokinase switching priority to the glycolytic pathway because of a diminishing energy production (diminishing ATP:AMP ratio) which attaches to PPP metabolism. This gives rise to adequate neuronal energy but insufficient antioxidant defence from the PPP, causing disrupted neuronal signalling, resulting clinically in confusion, aggression (i.e., with enough build-up of ROS, the switch to the PPP recurs and so on).

In summary, certain biochemical studies in psychiatric disorders, plus psychodynamic and neurotransmitter theories, represent various explanations to account for non-organic mental illness. Incomplete as these theories may be, they fit within the framework of the biochemical account of the origin of much non-organic psychiatric disorder, put forward in this paper.

It appears that the unfortunate outcome of the loss of GLO in primate ancestors was to ensure reproductive success at the price of positioning man at the edge of insanity.

10. Is There Sufficient Reason to Trial the Restoration of GLO Activity to the Genome of Species Lacking it, and Is there the Technology to Do so?

It has been proposed that overexpression of antioxidant enzymes could be successful in enhancing antioxidant defences.[15] Enhancement of antioxidant defences is relevant to humans lacking GLO and consequently tending to express effects of insufficient antioxidant defence. The remarkable effect of vitamin C in inducing the antioxidant enzymes has been described, thus vitamin C is an obvious resource to meet the need of this proposal. But how pressing is the need to address mental illness by this approach?

The introduction to Jung's work "The Psychology of the Unconscious: A Contribution to the Evolution of Thought"[95] contains the following criticism of human mental function: "It is hardly too much to say that all the important errors of conduct, all the burdens of man or of societies are caused by the inadequacies in the association of the primal animal emotions with those mental powers which have been so rapidly developed in mankind."

The thrust of this paper clearly has been to look at evidence that impairment of vitamin C metabolism predisposes to deficient brain metabolism with resultant deficiency in mental function and psychiatric disease. If this paper contributes to an understanding of "Primal animal emotions" referred to in the Jung text, there is an argument for addressing this defect with whatever technology has to offer. If that is the case, what then, must we do? Recent experimental work, in the field of applied genetics, has restored the capacity for vitamin C synthesis to cells lacking it. In particular, gene therapeutic HDAd-mCMV-Gulo vectors can mediate the expression of GLO and endogenous production of vitamin C in human cells and in transgenic mice totally lacking GLO activity.[96] These findings indicate a technological way forward to trial the effect of boosting endogenous vitamin C synthesis by restoring, in vivo, GLO to a species lacking it, such as the hamster.

Male hamsters, when confined, tend to attack and kill each other. Possibly, a trial of repair of the hamster genome by restoring the gene expressing GLO to see if this lethal behavior becomes moderated, is a worthwhile scientific objective.

Are there dangers attaching to interference with the primate genome in this way? ROS effects are not all deleterious. In certain situations, ROS have a signalling and other

function in cells as described earlier.[13,15] Effects of boosting superoxide dismutase and catalase activity (albeit in non-primates) have been associated with some damaging as well as beneficial results. ROS take part in an apoptotic (i.e., cell killing) mechanism to eliminate faulty cells and this process contributes to embryonic development. Overexpression of superoxide dismutase, 6-10 fold, caused reduced fertility and abnormal development in mice,[97] nor did it prolong the life span in mice.[98] On the other hand, overexpression of the antioxidant enzyme catalase in mitochondria, increased median life span in mice by five months.[99] However, these studies are of limited relevance to species lacking GLO activity. This is because an analogy cannot be drawn here between overexpression of these enzymes in species which have a capacity to synthesize vitamin C (mice) and species which do not.

Overall Conclusion

It is proposed that psychiatric illness is predisposed by oxidative stress as a result of species-wide genetically determined loss of the capacity to synthesise vitamin C. To compensate for this deficiency, a metabolic switch is activated in neurones at the phosphofructokinase stage of glycolysis to support the defective antioxidant system. This prioritises the relatively inefficient pentose phosphate pathway over glycolysis, resulting in inadequate supply of energy for proper mental function. A quirk of evolution allowed this mutation to persist.

Competing Interests

The author declares that he has no competing interests.

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