Schizophrenia: is the potato the environmental culprit?

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Summary   The pathology and aetiology of schizophrenia are reviewed in the light of the most recent research into the genetic/sporadic occurrence of this disease complex of world-wide distribution but of variable incidence. Although the aetiology is still unknown, numerous hypotheses have been postulated including dietetic factors but never has the potato (*Solanum tuberosum L.*) been suspected. However, a strong case can be advanced incriminating this widely, in fact almost universally, consumed vegetable tuber with its variable content of steroidal glycoalkaloids (SGAs) with known toxic action on both animals and humans, including possible teratogenic and cell membrane-damaging properties, as a very likely aetiological contender in most but possibly not all cases.

INTRODUCTION

In the grave affliction of schizophrenia, which appears to occur world-wide as indicated by an extensive WHO Survey by Jablensky et al. (1) there are basic problems with diagnosis, there being no specific confirmatory laboratory tests as, for example, in the case of syphilis or AIDS. Hence schizophrenia may be a symptom complex with multiple causes.

Nevertheless, it would appear that highly experienced psychiatrists can differentiate a disease entity first described a century ago by Kraepelin (2) in 1896 under the term 'dementia praecox' and now mostly but not entirely, defined almost world-wide by DSM-111-R criteria, many phenotypes of which occur in the 18–35 year age group with a peak incidence about 3–5 years earlier in males than in females, but now suspected to have first arisen in childhood and manifested then by unusual behaviour and only culminating with a diagnosis of schizophrenia frequently, but not entirely, in the late second and early third decades (3,4). The question of stability of diagnosis in schizophrenia has been studied in considerable detail over time and has been reported to be high (5,6) notwithstanding the absence of confirmatory laboratory tests.

As regards the pathology of schizophrenia, there does

appear to be general consensus that there are abnormalities in the temporolimbic region with anatomic anomalies in the mesiotemporal structure (7) and structural or functional abnormalities of the frontolimbic system (8). The regional neuropathology in schizophrenia has been extensively reviewed by Shapiro (9) and neuroimaging, in particular, by Travis and Kerin (10).

In addition to cerebral damage in schizophrenia most likely occurring in the middle trimester of pregnancy, other extra-cerebral congenital anomalies of development also known to arise in the middle trimester are changes in dermatoglyphics (ridge dissociation) of only the affected twin in MZ twins discordant for schizophrenia (11,12). (Epidermal ridge configurations are completed shortly after 4 months gestation, i.e. in the mid-trimester (11,13). Also, faulty clockwise scalp hair patterning determined during weeks 10–16 of fetal development has been reported (14). Red blood cell dynamics have also been found to be abnormal (15).

There also appears to be an interweaving of genetic and environmental factors in which approximately 40% of cases have a genetic component and 60% occur sporadically with no family history of schizophrenic siblings, parents or other family members. However, its genetic mechanism of inheritance appears to be multilocular and so far has not been elucidated with certainty (16,17). As evidence of a possible environmental effect, both monozygotic twins are affected in at most only 50% of cases (18).

Of the non-genetic factors, ante-natal obstetric complications, season of birth, maternal nutrition and infections,

particularly viral, have all been incriminated to a greater or lesser extent (19). Also postulated have been dietetic factors including sensitivity to wheat gluten (20–22), gestational zinc deficiency (23) gut abnormalities resulting in abnormal intestinal permeability (24–26) and auto-immune mechanisms (27–29). However, in the case of the last-mentioned, Rix et al. (30) suggest that immunological findings may represent consequences of the illness or its treatment, rather than the cause. More recently, Phillips et al. (31,32) have demonstrated higher concentrations of carbon disulphide in the expired air of schizophrenics. Many other hypotheses have been forthcoming – in particular the dopamine hypothesis, reviewed by Reynolds (33). More recently, there have been general update reviews, including course, chronicity and outcome (34,35). Biological factors in this disease have been reviewed by Syvälahti (36). There would appear to be general agreement in a multitude of reviews that both genetic and environmental factors are involved.

Furthermore, there is still doubt as to whether the pathomorphology in schizophrenia is progressive and represents a neurodegenerative condition or a neuro-developmental lesion (37). Nevertheless, even if either of the above, it is difficult to envisage an intermittent course, not to mention possible recovery, without an important fluctuating environmental contributory factor as in the case of gluten in coeliac disease.

The subject of chronicity has been reviewed by Harding et al. (34) who, in their meta-analysis of the results of long-term follow-up series, found that over 50% of subjects recovered and/or improved significantly – hardly the pattern of a neurodevelopmental or neurodegenerative disease.

ENVIRONMENTAL FACTOR

On the assumption that the majority of cases conforming to DSM-111-R criteria comprise a single disease entity, then the causative environmental factor or factors acting alone or superimposed on the genetic background must satisfy the following criteria if it is an external toxin to which the patient reacts:

1. The toxin must have world-wide distribution but be of variable potency in order to account for some variations in incidence and prevalence as in certain areas of Ireland (38,39), Croatia and elsewhere as reviewed by Torrey (40,41).
2. It must be absent or have minimal action in areas where schizophrenia has been reported to be rare or absent before the inroads of Western civilization to these areas, for example the New Guinea Highlands and Northern Ghana (41).
3. Temporal variation in which there appears to have

been a reduction in incidence in the latter half of this century and particularly in rural Ireland referred to below.
4. The variable clinical course with recovery and/or significant improvement at least in some cases, albeit superimposed on a pre-existing premorbid personality believed by many to be present since childhood, would suggest the intermittent action of a toxin possibly acting for many years prior to the onset of florid schizophrenia (42).

POTATO: THE POSSIBLE CULPRIT?

To the best of the writer's knowledge, the potato (*Solanum tuberosum L.*) has never been suspected as a possible dietetic culprit, although many other foods have (30,21,22,43–45).

The potato would satisfy the above criteria, as it has been consumed in almost every country including Third World countries over the last century or more. However, it is unlikely to have been consumed in Third World countries which have not been Westernised, e.g. Highlands of New Guinea and other areas referred to by Torrey (40,41) where schizophrenia was rare or non-existent before the advent of Western civilization as mentioned above. Furthermore, there are many varieties of potato, in fact more than 60, all of which contain a variable quantity of steroidal glycoalkaloids (SGAs), mainly the two toxic alkaloids a-solanine and a-chaconine and their breakdown products, a subject extensively reviewed by Jadhav et al. (46). The alkaloid content has been estimated in a number of potato varieties (cultivars) in various countries – Sweden (47), India (48), Australia (49) and by other groups in the USA, Great Britain, New Zealand and elsewhere. In all these countries, great variations in SGA content of the tubers have been reported, not only in different cultivars but also influenced by a considerable number of other factors including season of growth (early or late potato varieties), weather conditions, the variety of soil type, (including magnesium content), cultivation practices and handling before eating including damage of the tubers and improper storage. These factors affecting the chemistry, toxicology and occurrence of steroidal glycoalkaloids in potatoes have been extensively reviewed by Van Gelder (50). In fact one cultivar (Lenape) has been banned in the USA because of its high SGA content (51).

Of still greater significance implicating the potato are the findings by Waddington's group of pockets of variable incidence and prevalence of schizophrenia in Ireland within the counties of Cavan and Roscommon in 1991 and 1997 respectively (38,39). They emphasize that these are 'predominantly rural counties with a substantial agricultural economy where little migration of families

has occurred over generations'. This is important, as the type of potato and the above-mentioned cultivation practices would tend to remain static in individual areas or possibly improve only slowing over time. An explanation to account for such specifically localized variations within certain intra-county districts would point to local factors and, of these, variable agricultural practices especially as applied to the potato, which in Ireland is widely consumed as the staple diet, would seem to merit high priority for investigation, particularly as these workers have shown meticulous care in eliminating other variables as far as possible. The findings of Torrey et al. (52) in western Ireland where 'psychosis seems to be endemic in some rural lower socioeconomic areas' would support this contention. It may be more than coincidence that the highest SGA content in the 8 varieties investigated by Hallenas et al. (47) was in Ulster Chieftan which, one must assume, is an Irish variety. Aforementioned local variations in soil nutrients, agricultural and even storage practices could account for differences in the alkaloid content of even one variety of potato (49) not to mention the possibility of different cultivars being employed as best suited to local agricultural conditions. Furthermore, improved agricultural practices in recent years, particularly in the aforementioned lower socioeconomic areas, could account for the fall in alkaloid content of potatoes not only in Ireland but world-wide, thus offering an explanation for the fall in the incidence of schizophrenia in rural Ireland (53) and elsewhere referred to below.

TOXICOLOGY OF POTATO STEROIDAL GLYCOALKALOIDS (SGAS)

The clinical effects in animals produced by SGAs are due to their triple pharmacological function as reported by Morris and Lee (54), namely, direct toxic, teratogenetic and, most importantly, saponin-like action on cell membranes.

Toxic actions

The toxicity of potato glycoalkaloids is far greater in man than for other animals studied… there appear to be a considerable variation in response between people to high levels of glycoalkaloids. Toxicity is due to both the anticholinesterase activity on the central nervous system and membrane disruption activity which affects the digestive system and also general body metabolism (54).

Furthermore the toxic action can be:

a. either acute, as in the boys' school reported by McMillan and Thompson (55) following ingestion of stale potatoes; or
b. chronic; but unfortunately, as Van Gelder (50) states: the 'literature on chronic effects of SGAs is not

available, thus the no-adverse effect level is unknown. Consequently an acceptable level of solanine glycosides in household potatoes cannot be derived from data on SGA toxicity'. However, we do know that in susceptible people prone to develop coeliac disease, mere traces of gliadin are adequate to produce clinical symptoms.

The same could equally well apply to SGA ingestion in subjects susceptable to develop schizophrenia.

Teratogenicity

Poswillo et al. (56) found behavioral defects in Marmoset monkeys born to mothers fed from a batch of defective potatoes with a high level of glycoalkaloids indicate possible neurological defects. Congenital lesions have also been produced in other animals (57).

Saponin-like action on cell membranes

The SGAs could thus impair the neuronal membranes in the higher cerebral centres as well as cell membranes elsewhere in the body – thus supporting the 'membrane hypothesis' of schizophrenia (58).

DISCUSSION

In the following discussion, the triple actions of SGAs will be correlated with the known findings in schizophrenia particularly in relation to aetiology.

The increased incidence of schizophrenic births in late winter and early spring might be affected by potato consumption by the mother in the second trimester of pregnancy 3–6 months before birth in view of the possible toxic and teratogenic actions of SGAs. Early spring potatoes vary in glycoalkaloid content depending, inter alia, on weather conditions.

A number of independent workers have reported the apparent increased incidence of schizophrenia in the UK in first-generation and still more so in second-generation Afro-Caribbeans who have migrated from the Caribbean to the UK. This aspect has been reviewed by Harrison et al. (59) and still more recently by Hickling and Rodgers-Johnson (60) and Hutchinson et al. (61). Also, a similar increase in Afro-Caribbeans migrating to The Netherlands from the Netherlands Antilles has been reported (62). Whilst this phenomenon has been attributed to the increased risk of exposure to viral infections in their adopted country it could quite as easily be explained by alterations in diet whereby a toxin acquired anew or in greater concentration in the adopted country would have longer time to act in the second generation after birth as well as acting pre-natally in a supplementary

teratogenic and/or toxic capacity on the higher cerebral centres undergoing maturation in the fetal brain. Equally, this would afford a more rational explanation for the three- to six-fold rise in the incidence of schizophrenia in foreign-born migrants (first generation) living in the UK and an even higher incidence in the second generation (UK-born) than would viral infections acquired in pregnancy. Sugarman and Craufurd (63) exclude genetic differences and strongly favour an environmental factor or factors in the land of adoption as being responsible for the increased frequency in the Afro-Caribbean community as compared with the general population.

So far, there has been no satisfactory explanation for the possibility that schizophrenia is a relatively recent disease as suspected by Ellard (64) and Hare (65). The latter contends that 'the hypothesis that schizophrenia is a recent disease can explain why descriptions of schizophrenia-like disorders were rare before 1800, why the prevalence of insanity in the Western World increased during the 19th century but remained low in the non-Western World until the 20th century'. Hare further states that the 'recency hypothesis' asserts that some 'change of a biological kind occurred about 1800 such that a particular type of schizophrenia thereafter became more common'. Both Hare's and Ellard's comments would broadly fit the facts regarding potato consumption as reported by Van Gelder (50), namely that about 70% are consumed in developed and 30% in developing countries. Furthermore, it would appear that potato consumption on a significant scale spread gradually from the Western world to which it was introduced from South America to the non-Western world, thus explaining Hare's contention regarding the later increase in prevalence of the latter.

There has now been an apparent reduction in the recent incidence of schizophrenia in England, Wales, Scotland, Denmark, Australia and New Zealand and other Western countries as reviewed by Der et al. (66) and Geddes (72). A declining incidence in a rural Irish population since 1940 has also been reported (67). The subject of a widespread decline has been reviewed in a series of papers edited by Angst (68). However, such conclusions are dogged by methodological problems occasioned partly by the ever-changing diagnostic criteria and, even more so, by the absence of laboratory confirmation. Nevertheless, constant improvement in the choice of cultivars resulting in the commercial production of new potato varieties and better handling and merchandising could explain the 'apparent' reduction as being real. In fact, a vast amount of research has been devoted to the reduction of potato SGA content world-wide (54).

Even the report by Wagemaker and Cade (69) claiming that their dialysed patients 'are in a better state of remission than patients who are being treated with neuro-

leptics' would be entirely consistent with elimination of a toxin such as an SGA.

If the findings of O'Callaghan et al. (70) that the 'season of birth effect' may be most evident among patients without a family history of the disorder can be generally substantiated then that is still further evidence in favour of a variable environmental factor acting alone affecting the pregnant mother in the sporadic cases. This could also involve ingestion of potatoes if their SGA content showed a seasonal variation which in fact they do (50) and particularly if SGAs have a supplementary teratogenic as well as toxic action, however mild, in the human species. In further support of an environmental factor it might be noted that although most reports in the literature – in fact by far the majority – do not distinguish between familial and sporadic cases, nevertheless when such a distinction is made clinical differences indicating distinct neurobiology and earlier age onset for familial cases become apparent (71), as would be expected with an environmental factor supplementing a genetic component. Damage by SGAs would not mutually exclude viral infections in the mother during pregnancy nor obstetric complications but could further enhance the damage.

The slightly greater incidence of schizophrenia reported in urban as opposed to rural communities could be attributed to a more variable mixture of potato varieties purchased in city markets where as many as 60 different varieties may be available for sale, thereby increasing the risk of ingesting potatoes with a high SGA content. Furthermore, likely longer periods of storage under unsuitable conditions in urban areas could augment the SGA content even further.

Schizophrenia may not of course be a specific single disease entity but a heterogenous disorder involving toxins from other food sources in the diet such as maize. In South Africa, as reported by Campbell and Daynes (73) mycotoxins in uncovered stored maize 'may contribute to the epidemic of schizophrenia or organic brain disease that is being encountered in young rural blacks living upon toxin-infected maize supplies'. Dramatic changes in patterns of brain neurotransmitters induced by mycotoxins have been reported in experimental animals (74). However, practically all work on toxic steroidal glyco-alkaloids and mycotoxins has related to acute episodes and not chronic intermittent intoxication. Hemming (26) cited P.S. Guth (personal communication) as stating that neuroleptic drugs are known to stabilize membranes. Thus, the therapeutic action of these drugs could well be explained as counteracting the destabilizing action on membranes by SGAs due to their saponin-type properties referred to above (54). If it subsequently transpires that schizophrenia has a multiple aetiology, as appears likely, then other potential SGAs such as a-Tomatine in tomatoes

must be excluded (Jadhav et al. 46). Nevertheless, Morris and Lee (54) emphasize that humans are particularly sensitive to intoxication by potato SGAs occasioned by their now-known triple action. Hence such alkaloids, now very widely consumed throughout the world, could be the missing precipitating environmental factor emphasised by Kety (75), who states, inter alia, 'the evidence that exists for the operation of genetic factors in schizophrenia does not diminish the importance of environmental influences, which may be physical as well as psychological'; or, as expressed by Wyatt et al. (76) 'the plateauing in symptoms and the possibility of long-term improvement however, indicate that schizophrenia is not produced by a continuous process, but that the insult is time-limited as precipitating the onset and variable course of schizophrenia'. Furthermore, periodic ingestion of a toxin particularly one known to act on cell membranes would be consistent with the report by Mason et al. (77) that, after the initial episode, the course of schizophrenia is relatively stable. Also their 'data support neither concepts of progressive deterioration nor progressive amelioration', finally adding that there was no evidence of a 'late recovery' in their 67 patients diagnosed with ICD-9 schizophrenia over a 13-year follow-up study. These findings are consistent with a premorbid underlying diathesis aggravated by an environmental factor.

CONCLUSION

It is suggested that the above considerations certainly point to a very strong possibility that schizophrenic symptomatology could be explained as a chronic intermittent toxemia which is most likely, in the majority of cases, caused by glycoalkaloid poisoning following potato ingestion both in subjects genetically predisposed to schizophrenia and also in subjects not so genetically vulnerable but more sensitive to glycoalkaloids. In particular, their action on membrane permeability would not only harmonize with the 'membrane hypothesis' elaborated by Horrobin et al. (58) but could also account for the apparent variable Irish regional geographic incidence – a phenomenon very difficult to explain other than by the intervention of a variable environmental factor, most likely in the diet.

Despite a vast amount of research into epidemiology and aetiology culminating in a plethora of hypotheses, the writer can find no reference to the potato (*Solanum tuberosum L.*) as the major causative environmental factor but possibly not the only one – in this disease of theories.

It may be more than a coincidence that in Ireland, where the potato has been very widely consumed – virtually the staple diet – schizophrenic prevalence rates 'have been amongst the highest in the world for over a century' (79).

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