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William Hogarth, Unwitting Neurochemist?*

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William Hogarth's famous etching *Gin Lane* is often used to illustrate the debilitating results of alcohol addiction. Less well known is the companion etching *Beer Street* in which death, murder and squalor are replaced by health, orderliness and joy. Some 250 years later, the rise of science, and specifically of neurochemical research, has defined how the malnutrition, including avitaminosis, resulting from addiction to distilled spirits (rather than more judicious use of less potent alcoholic beverages) disturbs brain metabolism and function. These two etchings, which have survived for their historical and artistic value, continue to have sociological and clinical relevance.

KEY WORDS: Alcoholic malnutrition; thiamine.

One of William Hogarth's most famous etchings is *Gin Lane* (Fig. 1A), which dramatically depicts the untoward effects of gin on its users. Catastrophe and death are everywhere: a child is falling from the arms of its drunken mother; murder and suicide are rampant; a hanged man dangles from his noose. Buildings in disrepair are crumbling. Only the pawn and gin shops are thriving. *Gin Lane* is a vivid tableau which still appears from time to time in newspaper and magazine articles having to do with the deleterious outcomes of alcohol abuse. Much less well known is a companion Hogarth etching entitled *Beer Street* (Fig. 1B). Here, all is order and conviviality. The criminals and victims of Gin Lane are replaced by amicable lovers. A happy artist paints; new buildings are under construction; a butcher hoists a tasty viand. We are offered a picture of thriving prosperity, except for the pawnshop, which is defunct.

In order to assure wide distribution of these etchings, Hogarth specified that they be sold in pairs at a reduced price (1,2). Historians speculate that he likely was not decrying the evils of alcohol, but specifically of gin, and that the message to be gained from comparing the two etchings might have been as much social and/or political as humanitarian (1,2). Gin was the drink of the lower classes, and its disastrous impact was a result of its low cost and easy availability. So while Hogarth's message could have been compassionate, he may also have been expressing the concern of the upper classes regarding the dwindling availability of healthy and sober servants to allow them to pursue their more fortunate lifestyles. Also, gin was of foreign origin (Dutch *genever*) and was the declared scourge of the British underclass, while beer was considered to be thoroughly English and compatible with a happy and proper existence.

As indicated by the title, for the purpose of this essay I facetiously attribute this pair of eighteenth century etchings to Hogarth's prescient insight, presaging our eventual understanding of the nature of the ravages of alcoholic malnutrition, specifically of beriberi and its prevention by thiamine, which was present in beer but not in distilled spirits such as gin. Brewer's yeast

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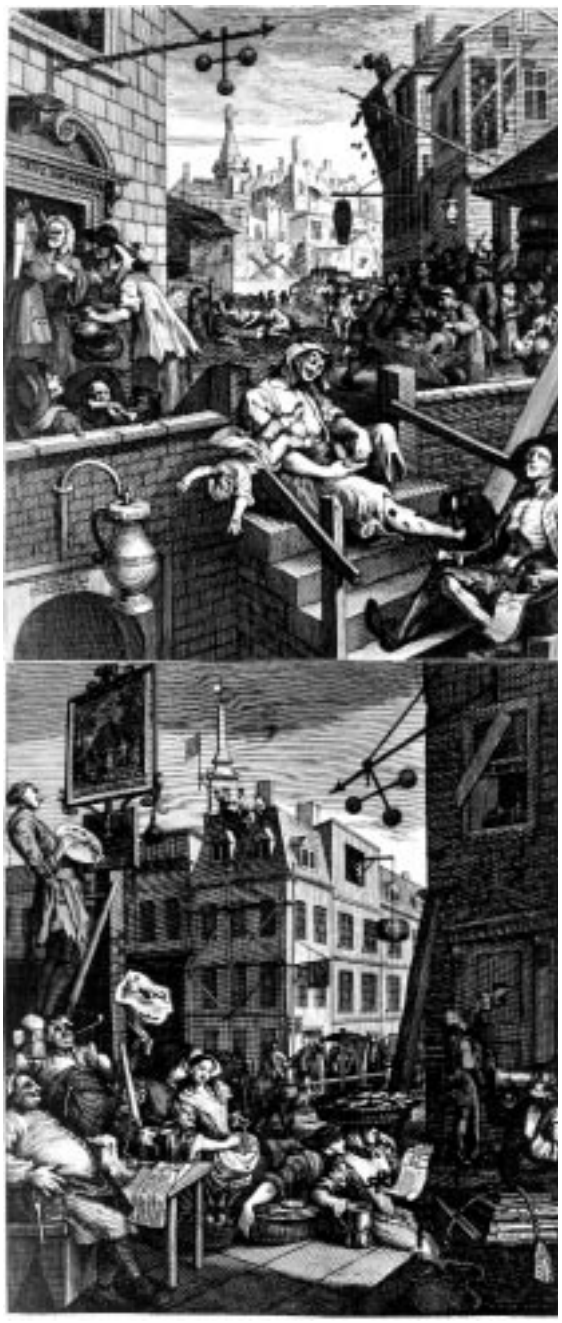

Fig. 1. Two etchings by William Hogarth (1697–1764). **A.** *Gin Lane* **B.** *Beer Street*

is a rich source of thiamine and other vitamins, and was undoubtedly present in the ale consumed on Beer Street. [Present-day beers are for the most part thiamine-deficient (3)]. As is discussed below, deciphering the role of thiamine in brain function nearly two hundred years later was to be a milestone in neurochemistry. Of course, in Hogarth's time (1697–1764), too little was known about chemistry, let alone biochemistry, to think of the brain in biochemical or neurochemical terms. A contemporary of Hogarth was Johann Thomas Hensing (1683–1726), who found that brain tissue contained phosphorus (4), then a mysterious substance which, when purified, glowed in the dark and could spontaneously burst into flame. Later chemists further characterized the composition of the brain, among them Vauquelin (1763–1829), who found that the phosphorus in brain was not aqueous, but complexed in a whitish matter. This finding was refined by Couërbe (1807–1867), who further purified the phosphorus-laden material, which he named "cérébrote," and reported that it was reduced in the autopsied brains of mentally retarded subjects. Others claimed that phosphorus was increased in the brains of the insane (4,5). J. L. W. Thudichum (1829–1901) performed by far the most comprehensive chemical analysis of the brain of his time and is recognized by many as the father of neurochemistry (6,7). In his 1884 treatise on the chemistry of the brain (8), he characterized a number of phospholipids that largely account for its high phosphorus content. A contemporary of Thudichum, Jakob Moleschott (1822–1893), was a professor of physiology in Switzerland and later in Italy, who, perhaps impressed by these earlier findings, espoused his materialistic orientation in regard to the unity of brain structure and function with the provocative dictum, "Ohne Phosphor kein Gedanke" ("Without phosphorus, there is no thought") (9). It has been said that it was this phrase that led the Harvard biologist Louis Agassiz to state that fish, being rich in phosphorus, make good brain food (for humans), and to comment further that fishermen are more intelligent than farmers because they eat so much more fish (10). William James challenged the entire hypothesis on the basis that there is not increased phosphorus excretion by the brain during thought processing (10). While neither Moleschott nor James had much basis for their remarks, both would undoubtedly have been amazed by the central role of phosphate compounds in biology and in brain metabolism as we understand it today.

Whatever the origin of the fish-brain food myth, it has enjoyed a rebirth on the basis of the high content of ω-3 (omega-3) fatty acids in fish. Both the ω-3 and ω-6 families of fatty acids are essential, i.e., they cannot be synthesized by animals and must therefore come from plant sources or from the flesh and viscera of animals that have eaten plants. Furthermore, the brain is highly enriched in essential fatty acids (EFAs) (11). Eggs enriched in EFAs are available in many countries, and EFAs are added to baby formulas in

some (12,13). Because of the reductive environment of the bovine rumen, cow's milk is deficient in EFAs. In Korea, milk fortified with EFAs is known as "Einstein" milk (registered trademark of Namyang Dairy, Korea). It has been rumored, possibly as part of an advertising campaign, that Albert Einstein was himself weaned at a relatively advanced age.

Returning to the Hogarth etchings, it should be noted that whether or not the dwellers of Gin Lane suffered from thiamine deficiency, it remains a fact to the present day that thiamine deficiency, particularly in alcoholics, can be disabling, even life-threatening. The discovery of a dietary deficiency as the cause of beriberi in the late nineteenth century and the eventual elucidation of the biochemical role of the vitamin thiamine are intertwined with the development of the discipline of neurochemistry in the twentieth century, which turned its emphasis from the investigation of brain composition to brain metabolism.

While there is evidence that beriberi occurred as far back as prehistoric times, dramatic evidence of its importance emerged only in the last part of the nineteenth century, when polished rice replaced dietary brown rice, resulting in beriberi epidemics throughout the Far East (14). It was soon discovered that an ingredient in the rice hulls, eventually termed thiamine, could restore health to patients suffering from beriberi, but its chemical structure was not elucidated until 1937 (15).

The importance of thiamine in brain metabolism was dramatized in the laboratory of Sir Rudolph Peters, who examined the neurological and biochemical consequences of thiamine deficiency. Starting with the observation that a diet deficient in thiamine fed to pigeons caused opisthotonos, a spastic arching of the back that could be quickly relieved by injection of thiamine, Peters examined the biochemical effects of added thiamine on incubations of minced brain tissue (brei) from thiamine-deprived pigeons. He found a linear relationship between the amount of thiamine added and the increase in the rate of oxygen consumed in the presence of a glucose substrate (16). This finding indicated that the opisthotonos was of CNS rather than of neuromuscular origin as had previously been thought, and importantly, that for the first time an in vitro biochemical observation of metabolic disturbance could be directly correlated to a pathological neurological finding (17). The brain's requirement for a vitamin and the importance of intermediary metabolism to understanding in vivo brain function were thus at once dramatically demonstrated—a milestone in defining the experimental horizons of neurochemistry. Soon to follow was the identification of thiamine pyrophosphate as cocarboxylase (18,19), a cofactor for pyruvate decarboxylase and somewhat later, the involvement of thiamine pyrophosphate (TPP) in the decarboxylation of other α-ketoacids, α-ketoglutarate and branched chain amino acid metabolites. TPP was also demonstrated to be required for the action of transketolase (20,21).

Thiamine deficiency, particularly in alcoholics, gives rise to an acute encephalopathy involving a number of CNS deficits, including a confused mental state and, like opisthotonos in pigeons, can be dramatically reversed within minutes of administration of thiamine. On autopsy however, there remain diffuse regions of glial proliferation in the myelin and periventricular regions (22). Korsakoff's syndrome is an irreversible deficit in memory formation and storage and is accompanied by bilateral lesions of the dorsal medial nucleus of the thalamus (23). There are indications that the combination of alcoholism and thiamine deficiency produce the disease. The diagnostic term "Wernicke-Korsakoff syndrome" reflects the frequent difficulty of distinguishing the two encephalopathies clinically. It is likely that in each instance the observed toxic effects of thiamine deficiency in the brain are attributable to accumulation of cerebral pyruvate and lactate. Thiamine deficiency seen in starvation is less destructive of the brain than that seen in the presence of otherwise adequate nutrition. The reason for this is not completely clear, but it should be noted that in starvation, half or more of the brain energy needs can be met by ketone bodies, primarily acetoacetate and β-hydroxybutyrate, which can give rise to acetyl CoA, thereby bypassing pyruvate decarboxylase in the Krebs cycle. As an important practical matter, it is the case that administration of glucose in the presence of thiamine deficiency can aggravate CNS symptoms and outcome. Acute alcoholics or otherwise severely malnourished patients brought to hospital emergency rooms are often dehydrated and are administered intravenous fluids, usually containing glucose. Emergency room physicians now know that the administration of glucose without simultaneous or pretreatment with thiamine can bring on brain pathology characteristic of the Wernicke-Korsakoff syndromes. It is curious that in earlier times, a presumptive test for thiamine deficiency was elevation of plasma pyruvate. It was found that administration of a glucose challenge would evoke elevated pyruvate in cases of a marginal thiamine deficiency (24). One wonders how many iatrogenically induced cases of Wernicke-Korsakoff syndrome occurred inadvertently before the hazards of this diagnostic procedure were recognized.

Hogarth and his contemporaries could not have known about the devastating effects of thiamine deficiency. Nevertheless, these two etchings could well serve today as a reminder of the possible disastrous effects of the administration of glucose to malnourished patients, alcoholic or otherwise, who could also be suffering from a thiamine deficiency, and might well be included in emergency room manuals for today's physicians.

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