Hypersusceptibility to chemicals: risk factors for neurological disease?

Neurotoxicology has taken on a new lease of life as it becomes clear that chemicals may be responsible for more than the occasional epidemic caused by unusually high exposure to a dietary toxin, such as lathyrysm and cassava poisoning, or from industrial accident, substance abuse or the pharmaceutical industry. The role of the clinician in recognising unusual cases and clusters where there is a clue to the chemical trigger cannot be over-emphasised. Easily dismissed coincidences, can be important because they may establish the relevance of current hypotheses or even generate new ones. The N-methyl-4-phenyl tetrahydropyridine (MPTP) and Domoic acid outbreaks of neurotoxin mediated damage are recent examples of this.1-3

The interaction between chemical exposure and genetically determined hypersusceptibility may be crucial to understanding a number of poorly understood neurological diseases and is worthy of further consideration.

The importance of dose
Paracelsus (1493–1541), who first expressed views that remain the basis of the science of toxicology,4 emphasised the toxic agent as a chemical entity and antedated Paul Ehrlich’s ‘Magic Bullet’ in proposing a degree of specificity for both therapeutic and toxic effects. Paracelsus considered that nearly all substances were potential poisons and that the difference between a therapeutic or toxic response was often the dosage. Argument continues about whether certain natural chemicals are toxins without understanding that the dose in the vicinity of the target cell or subcellular organelle may be crucial. Recent reminders are glutamate and related compounds, toxic at certain concentrations and locations, but vital neurotransmitters at others. Discussion of the potential toxicity of dopamine sometimes has the same basic flaws.4 Conversely chemicals may be toxic in cell culture or in animal experiments but only at doses that would not be reached in vivo.

Neurotoxins: specificity and mechanism of neuronal damage
Natural (and synthetic) toxins have been used extensively as tools in helping to understand the workings of the nervous system, such as, the studies on strychnine, emetine and carbon monoxide by Magendie and his pupil Claude Bernard. Later studies on botulinus, tetanus and spider toxins were landmarks and demonstrate the specific dysfunction of certain neurons after a particular exposure sometimes due to a single biochemical lesion. Claude Bernard’s treatise on Experimental Medicine5 was essentially a toxicology thesis and the whole concept of homeostasis and the ‘milieu interior’ re-emphasises that many compounds are toxic once they stray outside physiological limits.

In recent years there has been intense interest in investigating the biochemical mechanisms of cell death in sub-populations of neurons, in both the peripheral and central nervous system, after a variety of insults. These include the disruption of brain energy metabolism and the failure of adequate ATP synthesis by cutting off the supply of nutrients. More recently there has been interest in intraneuronal calcium homeostasis, production and quenching of oxygen and other toxic radicals, the effect of inhibition of the mitochondrial electron transport chain, activation of proteolytic pathways and excitotoxic damage.6-13 These and other mechanisms are often inter-related producing a cascade of biochemical events. Future therapeutic options to rescue cells may depend on intervening before a hypothetical point of no return is reached. Separating early from late biochemical changes on diseased tissue can be difficult, even before ante- and post-mortem artefacts are addressed. Distinguishing the catastrophic biochemical changes of death from factors within the cell that may have predisposed to their premature demise is fraught with problems.

Selective neuronal death
In 1937 Vogt and Vogt14 expounded the important concept of selective neuronal death recognising that the brain was capable of reacting to generalised forms of trauma, such as hypoxia, in a non-uniform manner and suggested that specific intrinsic properties of certain nerve cells were responsible for their selective vulnerability. "Pathoclisis", which largely replaced previous theories, related to the degree of vascularity. Initially differential energy failure was thought to be responsible until it was realised that incomplete ischaemia could cause more cell loss than complete ischaemia. In the early 80’s the role of synaptic transmission was investigated and it was subsequently shown that innervation by excitatory amino acid neuronal systems15-16 (glutamate was already known to have toxic potential17) was the key element in a vulnerability to hypoxia, convulsions and
hypoglycaemia. Thus the excitotoxic hypothesis was born. Other mechanisms that include differences in active transport and channelling systems that concentrate the toxin will be important, as may differences in mitochondrial function and free radical defence mechanisms, and a whole host of other factors that will emerge to explain selective vulnerability amongst populations of neurons or glia exposed to particular stresses.

Xenobiotics—exposure, safety margins, delayed effects and hypersusceptibility

Percival Pott (1775) is credited with the role of xenobiotics (foreign chemicals) in human disease. Although illness due to hypersusceptibility to the fava bean (now known to be secondary to defective glucose-6-phosphate dehydrogenase) was known at the time of Pythagoras. There are many other examples of "ecogenetic" diseases whereby inheritance of an unusual protein leads to extreme sensitivity to an environmentally derived chemical trigger, for example, α-antitrypsin deficiency, malignant hyperpyrexia, suxamethonium apnoea and other pharmacogenetic disorders. The role of xenobiotics in precipitating migraine has been known from ancient times and still remains a common and notable example of an acute idiosyncratic response to chemicals found in our diet. Pott's main contribution was recognising that such xenobiotic exposure could result in a long latency illness such as cancer. Slow poisoning of a nervous system that regenerates with difficulty and has large functional reserves could quite easily lead to the late onset of clinical illness even though the process had been active over decades; this lack of close temporal relationship leads to difficulties in recognition of a causal association.

The number of xenobiotics in our environment is enormous but rarely has toxicity, particularly long term, been adequately tested. Testing remains difficult as many xenobiotics are not toxic in their own right but are substrates for the formation of endogenous toxins and thus are protoxins. Animal experimentation has been used for detecting adverse responses and much useful information has been obtained. The problem has been in assessing their relevance for humans and that extrapolation of such experimental findings is not an easy exercise even on the rare occasions when the biological mechanisms involved are understood. The idea of safety limits to exposure is however flawed when it ignores long term effects or the likelihood of the rare hypersusceptible individual.

Xenobiotic metabolism

Biotransformation of virtually all xenobiotics that are absorbed occur rapidly, chiefly in the liver during first pass metabolism and often differs dramatically, both quantitatively and qualitatively between individuals. Absorption requires a degree of lipid solubility whereas excretion via the biliary tract or kidney requires a more polar water soluble compound. Normally the first step is an oxidation reaction, often by Cytochrome P450, and largely occurs in the liver and the second a conjugation. Usually these steps reduce the biological half life enormously but they should not be thought of as simple detoxification reactions for two reasons. Firstly, the compartment in which the reaction takes place can be important, such as, on which side of the blood-brain barrier or in which subcellular compartment; toxins can get trapped just where you do not want them. Secondly, the oxidation step, or more rarely conjugation can produce a toxic metabolite.

The term "lethal synthesis" was first used by Peters in 1952 in his Croonian lecture describing the transformation of fluoroacetic acid within CNS tissue to the toxic fluorocitric acid. Many other reactions will take place, not as in this case in the tissue in which the damage occurs, but sometimes distinctly by the xenobiotic metabolising enzymes, of which the cytochrome P450 subfamily of enzymes is an example. These phenomena are by no means unique to xenobiotics and it is equally possible that lethal synthesis can take place from endogeneous substrates. Despite some caveats, Cytochrome P450 and other xenobiotic enzymes systems are an important defence mechanism to cope with our varied and changing chemical environment and is likely to have been an important evolutionary step as the enzyme machinery seems to be able to cope with an extremely wide range of substrates, including new challenges, and in some instances is inducible which has obvious adaptive significance. The evidence is in favour of this complex system being tuned to cope with most environmental chemical hazards that produce acute and life threatening damage but may not be so efficient in protecting neurons or avoiding mutagens particularly as the effect may not occur until after the age of biological uselessness.

Slow and fast metabolisers of xenobiotics are well described particularly from studies on isoniazid and debrisoquine (in both instances the slow metaboliser is associated with neuropathy after exposure to isoniazid and pergolide respectively). Pharmacogenetics has shown that much of this variation is genetically determined, with many other polymorphisms already described, for example, for monoamine oxidase B and thiol methyl transferase. It is equally clear that environmental influences have an effect on enzymic function, most dramatically when there is an increase in enzymic activity after exposure to the relevant substrate or when it is induced or repressed by drugs such as phenobarbitone or cimetidine.

Hypersusceptibility may reside in variation in the handling of xenobiotics

The stresses that a neuron may find itself under may be subject to enormous individual variation and not just related to the degree of environmental exposure. Susceptibility may lie at the level of the cell destined to die and could include genetically determined or acquired defects in any of the defence systems involved or the mechanisms of cell death already alluded to, for example, mitochondrial, antioxidant and cellular buffering functions. The recent discovery of mutations in one of the superoxide dismutase gene in familial motor neuron disease is a dramatic example of this phenomenon. There is, however, considerable evidence that in some cases hypersensitivity to chemical injury resides in those enzymes involved in the initial metabolism of the compound that influence the dose of toxin delivered to the cell. This arena is now a growth industry in general toxicology. A rapidly increasing number of such genetic traits are being identified and becoming linked with disease states, particularly cancer, and all carry the liability of a higher susceptibility to chemical injury. It is also probable that physiological regulatory systems including the cytokine network and the immune system will be found to modify the expression of chemically induced toxicity with interindividual variations in response. Genetic factors may also determine the chemical environment that
the individual seeks. Xenobiotic enzyme systems are active in olfactory tissue\textsuperscript{32} which may provide a feedback mechanism signalling to the individual which compounds suit their particular metabolism. Dysfunction and then destruction of the olfactory pathway, as in several neurodegenerative diseases, may influence this relationship and cause a vicious cycle of increasingly inappropriate exposure.

The MPTP story has taught us that a chemical is capable of causing such selective neuronal death that it can mimic Parkinson's disease. Since there is so much overlap with other degenerative diseases of the nervous system, chemicals could cause others similar disorders. It was only a series of coincidental steps that led to the uncovering of MPTP-like neurotoxins. If chemicals can cause such damage it is a plausible logical progression to suggest that individual susceptibility may reside in either a failure to detoxify neurotoxins or that lethal synthesis of toxins can take place in certain individuals. Migraine and some diet- or drug-sensitive neurobehavioural diseases are obvious candidate examples of acute conditions but mounting evidence suggests that delayed toxicity in the hypersusceptible individual could be responsible for some neurodegenerative disorders.

**Evidence to date in neurodegenerative disease**

Defective xenobiotic enzymes may be a significant risk factor for the development of Parkinson's disease, an exacerbating element, and one that influences drug responsiveness and side effects. For instance, although phenotypic studies were unimpressive the poor metaboliser debrisoquine genotype is over-represented, at least in hospital based populations of Parkinson's disease.\textsuperscript{33, 34} It also appears that N-methylated pyridines not too distantly related to MPTP-like compounds, are excreted in high concentration in patients with Parkinson's disease\textsuperscript{35} and this increased production, or decreased catabolism that may involve cytochrome P450, could lead to a rise in compounds potentially toxic to dopaminergic neurons. There may also be alterations in function of monoamine oxidase B (MAO-B) in Parkinson's disease\textsuperscript{36-38} which could be of importance as MAO-B converts the protoxin MPTP to the toxin MPP\textsuperscript{+} and that blockade of this enzyme may retard the progress of the disease.\textsuperscript{39} Thus a series of largely genetically determined alterations in enzymic function could act alone or in concert to produce a biochemical endophenotype that, if provoked by an environmentally derived chemical trigger, is hostile to the substantia nigra in the long term. The recent evidence that fetal implants do rather better in MPTP Parkinsonism than in Parkinson's disease\textsuperscript{40} is compatible with this as in the latter case exposure to the putative toxic atmosphere persists.

Decreased activity of the enzyme cysteine dioxygenase in Parkinson's, motor neuron and Alzheimer's diseases has also been found\textsuperscript{41-43}; this raises the level of the excitotoxin cysteine and simultaneously decreases sulphate availability,\textsuperscript{44} which is important for several detoxification steps. Although this finding is not specific for any one disease it may represent a necessary biochemical component for damage to occur or relate to disease severity; this mirrors many other findings in the neurodegenerative diseases where a mix of specific and non-specific changes is found, emphasising the overlap between them. Disease specific abnormalities that may relate to mechanisms of selective neuronal death rather than severity are a decreased acetylation capacity\textsuperscript{44} and altered capacity to methylate sulphur compounds in motor neuron and Parkinson's disease. The latter is due to differences in activity of thiol methyl transferase\textsuperscript{45} best known for its role in detoxification of hydrogen sulhide, which may be deficient in Parkinson's disease. This enzyme is also known to methylate mercury to more toxic derivatives which may be a factor in motor neuron disease where the enzyme is overactive. Potentially the sulphur equivalent of the N-methylated pyridines could be produced from other substrates though nothing as yet is known about the toxicity of such substrates or whether or not they are preferentially concentrated in motor neurons in a similar way that MPP\textsuperscript{+} is avidly taken up by the dopamine transporter.

**The potential**

If this hypothesis about the importance of hypersusceptibility to chemical factors is true, we have an interesting and hopefully remediable interaction between genetically determined traits that act as an Achilles' heel if exposed to some crucial chemical stress. Such individuals could in turn be identifiable and technological advances will make this a testable and refutable proposition. Enzymic machinery may then be modified towards greater safety and the pharmaceutical industry should explore these possibilities, alternatively critical environmental toxins or protoxins could be avoided by a preemptive manipulation of metabolism. A new dawn of preventive approaches towards some neurological diseases will be an exciting prospect. Identifying the environment trigger may not be easy. However, once we know the chief metabolic pathways, we will be able to make an educated guess as to the likely substrates. The proposed culprits may then be sought in epidemiological studies which would have greater power as sub-populations of the disease groups could then be identified. In the 'good' metaboliser group the accumulative environmental dosage would have to be greater and so more prominent in a combined biochemical/epidemiological survey.

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Neurological stamp

Philippe Pinel (1745-1826)

When Philippe Pinel was physician to the Hospice de Bicêtre, the Paris asylum for men, he authorised removal of the chains that restrained the patients. The uncontrolled behaviour of the men, that others had predicted, did not occur.

Pinel was convinced that insane people needed treatment and were not possessed by a devil. His theory that insanity was a mental illness was not received favourably by the medical profession. His influence, however, led to a far more enlightened approach to the treatment of those that were mentally ill.

In 1801 Pinel published a full account of his new techniques in his Traité Médecino-Philosophique sur l’aliénation mentale ou la manie (Medico-Philosophical Treatise on Mental Alienation of Mania). Three years earlier he had published Nosographie Philosophique which was an attempt to classify diseases in the way Linnaeus had earlier classified animals.

This stamp was issued in 1958 as part of a set honouring French doctors (Stanley Gibbons 1367, Scott 865).

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