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JOHN JEYES LECTURE*

Environmental Chemical Influences on Behaviour and Mentation

By Derek Bryce-Smith
DEPARTMENT OF CHEMISTRY, UNIVERSITY OF READING, WHITEKNIGHTS PARK, PO BOX 224, READING, BERKSHIRE

1 Introduction

It was C. P. Snow who first clearly identified what he termed the 'two cultures' problem. By this, he meant the paradox that our modern scientific and technological society is largely controlled by people educated in the humanities who are, to put it bluntly, and with a few exceptions, scientifically illiterate. He gave much offence in some quarters by suggesting that a person without knowledge of the Second Law of Thermodynamics could not really be regarded as well-educated.

I propose to follow in Snow's footsteps, though I hope without giving offence, by pointing out another important example of the 'two cultures' dichtomy, namely the beliefs that have grown up about factors which influence behaviour and the social phenomena to which human behaviour gives rise.

The subject of behaviour is of course relevant to all human affairs, and is therefore of interdisciplinary importance. Yet within the political and social sciences, psychiatry, and to a lesser extent psychology, behavioural and social phenomena are conventionally assumed to result mainly from social influences, or disorders of mind and thought. The *causation* of such phenomena is not normally seen as relevant to a 'hard' science such as chemistry despite the widespread medical use of neuroactive drugs to treat behavioural symptoms. Thus, while it would be patently absurd to suggest that neurosis is a symptom of, say, Valium deficiency, little thought seems to be given to the possibility that real nutrient deficiencies affecting brain function, or other influences from the chemical environment, could be playing a part.

In contrast, chemists and biologists would tend to see behaviour as an output from brain function following inputs to the brain from the physical senses. Since brain function itself largely, if not wholly, involves chemical and electrical processes occurring within complex physiological structures which are themselves ultimately chemical in nature and which develop by chemical mechanisms, it is indisputable that behavioural outputs from the brain (or more strictly the central nervous system, CNS) should be regarded as intrinsically subject to chemical influences. Such chemical factors can be either endogenous or exogenous, and constitute a

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dimension to our understanding of the causes of behavioural and social phenomena that is at present virtually ignored.

Endogenous chemical influences on behaviour can include chemical changes induced by social factors, *e.g.* changes in the metabolism of cortisol, adrenaline, and zinc induced by stress. Exogenous factors can include deficiencies of some B vitamins, the abuse of neuroactive drugs such as ethanol, amphetamines, *etc.*, and neurotoxic pollutants, a category that includes most pesticides, mercury, and lead.

Biologists have of course long known that many insects and other animals are powerfully influenced by sex attractant chemicals termed pheromones: it has been reported that some insects can respond behaviourally to a single molecule. There is nothing controversial about the principle that exogenous chemical influences can powerfully influence behaviour: it is the extension of this principle to the human condition that now needs to be discussed.

I shall be concentrating on those environmental chemical influences on behaviour to which exposure is *involuntary* because these have been almost wholly ignored in the social sciences, and because these factors raise some important moral questions about the extent to which an individual involuntarily exposed to behaviour-modifying chemical influences is truly responsible for any anti-social actions that may result. I shall be considering the evidence that a wider recognition of the neglected chemical dimension in our understanding of behavioural and social phenomena can provide, in fact is already providing, new approaches towards abating some of the currently most intractable social problems such as educational under-achievement, aggression, and the rising crime rate. This lecture therefore has a marked inter-disciplinary character, and I venture to hope that the present written version of it will come to the attention of people in the behavioural and social sciences who do not normally read *Chemical Society Reviews*.

Before I go further, I need to define some terms. By 'social' influences on behaviour, I largely mean those influences from other persons received through the senses, including the written word, television, *etc.* The connection between some traditional social factors such as poverty and disturbed behaviour is actually more correctly described as an indirect association than a direct causal relationship. Thus, while poverty *per se* does not necessarily cause crime, violence, educational under-achievement, *etc.*, and among the religious is often regarded as an aid to a better life, it can sometimes be associated with increased exposure to behaviour-disturbing social stresses and/or adverse non-social factors such as dietary deficiencies and chemical pollutants.

By 'chemical' influences, I refer to those which essentially arise from our chemical/nutritional environment. Genetic influences on behaviour have their origin in our genetic inheritance, and being chemically mediated are also susceptible to features of the chemical/nutritional environment. Certain infectious diseases that affect the brain, *e.g.* meningitis, can leave a legacy of effects on behaviour and intelligence, but I shall not be considering these further on the present occasion. In principle, all these influences can interact.

2 Interactions between Social and Chemical/Nutritional Influences on Behaviour, Intelligence, *etc.*

The social sciences have long taught, largely following Émile Durkheim (who died in 1917), that social phenomena result largely from social causes. This essentially circular thinking has undoubtedly encouraged social scientists to turn their eyes more to the fascinating arena of politics than to relevant 'hard' sciences such as biology and chemistry; with the result that many would now regard sociology for example as an area of study which subscribes more to political than scientific ethics. Politicians of most persuasions aim to use the levers of power for 'social engineering' of one sort or another to produce a society where everyone can be more fulfilled and happy. But these usually well-intentioned efforts are bound to fail unless both social and non-social factors are taken into account. For example, a person with mental depression caused by, say, a disorder of zinc or 5-hydroxytryptamine metabolism (as may well be the case) will not be happy even in a socioeconomic Utopia. Similar restricted thinking is found in psychology and psychiatry, professions more directed towards individual behaviour than social phenomena. I have the impression that psychiatry in particular is currently in a state of dichotomy between on the one hand the apparently non-material concepts of conscious and unconscious mind, thought, ego, body image, *etc.* stemming from the teachings of Freud and his followers, and on the other hand the growing recognition among those who study the biochemistry of behaviour that many if not all types of mental illness and lesser disorders of perception, adaptation, *etc.* result from physical disorders in the structure and/or biochemistry of the brain. In practice, psychiatry now largely involves the administration of synthetic neuro-active organic chemicals to patients: some 30 million prescriptions for tran-quillizers, anti-depressants, and other behaviour-modifying chemicals were issued in the U.K. in 1983. As already noted, the idea that mental disorders could be *caused* by chemical agents has been slow to take root in mainstream psychiatry. The emphasis is still on frequently ill-defined social factors such as poverty or familial influences as the main causes of aberrant behaviour, and few appear to perceive any inconsistency between the assumption of non-chemical causation on the one hand, and the widespread adoption of chemical remedies or palliatives on the other.

The division between social and chemical influences on behaviour is in fact less sharp than might be supposed. Figure 1 illustrates the ways in which such influences tend mutually to interact, using as examples the neurotoxins ethanol and lead, and nutritional deficiency of zinc—all of which can modify behaviour, personality, and other aspects of mentation through effects on brain chemistry, and also act synergistically with each other. Thus the chains of cause-and-effect tend to be cyclic, or parts of complex matrices, rather than linear, although in particular cases one particular factor may be dominant, and attention to it may relieve the situation. I shall be describing later our successful application of this approach to develop a rapid cure for many cases of *anorexia nervosa*, a hitherto intractable and sometimes fatal behavioural disorder which we believe to be usually caused by a combination of social and chemical/nutritional factors, the latter being dominant.

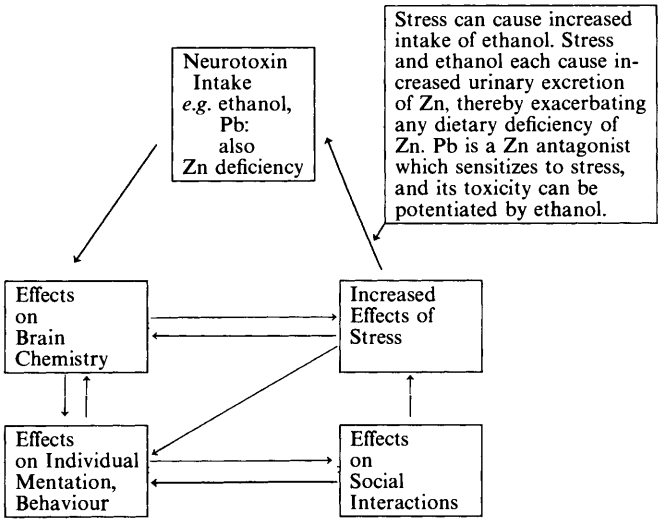


Figure 1 *Neurotoxin–behaviour interactions*

Most of the relatively few previous cases where researchers have sought to evaluate both social and chemical environmental influences on mentation and behaviour have involved studies of the effects of environmental lead on children's intelligence and learning ability. (These are not always closely related in children who have been overexposed to lead, apparently owing to disturbance of cerebral inhibitory functions and the resulting difficulties in concentration associated with a tendency to over-react to sensory stimuli, *i.e.* hypoinhibition.[1]) In the statistical analysis of data, it has mostly been tacitly assumed that 'social' and 'lead toxicity' effects can be treated as independent variables, and that while 'lead' effects on IQ *etc.* can be confounded by social factors, effects that apparently correlate with social factors cannot be confounded by lead.* The statistical bias thereby introduced causes the contribution from lead neurotoxicity to be underestimated—as for example in the following recent investigation of several thousand London schoolchildren.[2] Various measures of intelligence and scholastic ability were studied in relation to lead levels in shed teeth categorized as 'low', 'medium', and 'high'.[2] The results before and after 'controlling' for largely social variables are shown in the Table. The data show clear indications of a lead-related IQ deficit of some 5 points—a serious matter when it occurs throughout a major section of the

* 'Low level' lead has in fact been shown to alter social interactions: see P. J. Bushnell and R. E. Bowman, *Neurobehav. Toxicol.*, 1979, **1**, 207: J. M. Donald, M. G. Cutler, M. R. Moore, and M. Bradley, *Neuropharmacol.*, 1981, **20**, 1097.

[1] R. K. Byers and E. E. Lord, *Am. J. Dis. Child.*, 1943, **66**, 471.

[2] M. Smith, T. Delves, R. Lansdown, B. Clayton, and P. Graham, *Dev. Med. Child Neurol. Suppl. 47*, 1983, **25** (5), 1.

population—and a dose–effect relationship: the uncontrolled relationships with tooth-Pb are statistically significant ($p < 0.05$). For the reason given above, such amendments to the data tend to under-estimate the contribution arising from the neurotoxin. Thus it is known that the toxicity of lead tends to be enhanced by poor diet[3] and stress,[4,5] both of which tend to be related to social class. Exclusion of social differences in the statistical analysis thereby excludes part of the contribution due to the neurotoxin and leads to underestimates of the hazard. Similarly dubious 'corrections' for social factors have been made in many of the numerous other studies of lead and mentation which are reviewed in reference 6. However, the authors of one very recent study of London children do appear to have recognized the problem of over-correcting for social factors and report numerous correlations between blood-lead levels and various measures of impaired educability and behavioural control.[7]

Table *Tooth lead levels in relation to mean intelligence and reading scores*[1]

Tooth Pb *Category*	*Full-scale IQ*	*Verbal IQ*	*Performance IQ*	*Reading Ability*
Low	108.7 (107.1)	106.6 (105.1)	109.0 (107.8)	45.9 (44.6)
Medium	104.9 (104.9)	102.6 (102.8)	106.4 (106.1)	43.2 (42.4)
High	103.7 (104.8)	101.6 (102.9)	104.7 (106.0)	38.7 (40.4)

NOTE: The figures in parentheses are those after 'controlling' for social factors

I view these adverse effects of environmental lead on brain function and development as the most serious effects of any individual chemical pollutant so far demonstrated, but as I am seeking to paint a rather broad canvas on this occasion, and also because the hazards from environmental lead have already been acknowledged as sufficiently well-proven to require Government legislation and/or other official action to control lead pollution in the United States, Russia, Japan, Australia, and the EEC, *inter alia*, I do not propose to enter into a detailed discussion of the matter here.* It would however be a serious omission not to mention the extremely important contribution made to the debate by Needleman and his colleagues, and in particular their celebrated study of 2146 schoolchildren

* Readers who wish to study the effects of lead on children in further depth, together with the methodological problems involved in such work, may consult the recent critical survey by Neeledman and Bellinger.[8] Refs. 3, 6. 9, and 10 also provide coverage of this topic together with associated information on studies with experimental animals, and the neurochemical and neuroelectrical effects of lead at contemporary exposure levels.

[3] D. Bryce-Smith and R. Stephens in 'Trace Elements in Health', ed. J. Rose, Butterworths, London, 1983, p. 83, and references therein.
[4] American Academy of Pediatrics, *Pediatrics*, 1969, **44**, 291.
[5] J. P. Filkins and B. J. Buchanan, *Proc. Soc. Exp. Biol. Med.*, 1973, **142** (2), 471.
[6] D. Bryce-Smith, *Nutrition and Health*, 1983, **1** (3/4), 179.
[7] W. Yule, M.-A. Urbanowicz, R. Lansdown, and I. B. Millar, *Br. J. Dev. Psychol.*, 1984, **2**, 295.
[8] H. L. Needleman and D. Bellinger, 'The Developmental Consequences of Childhood Exposure to Lead' in 'Advances in Clinical Child Psychology', Vol. 7, ed. B. J. Laney and A. E. Kazdin, Plenum Publishing Corp., 1984.
[9] 'Lead versus Health', ed. M. Rutter and R. R. Jones, Wiley, Chichester, 1983.
[10] 'Low Level Lead Exposure', ed. H. L. Needleman, Raven Press, New York, 1980.

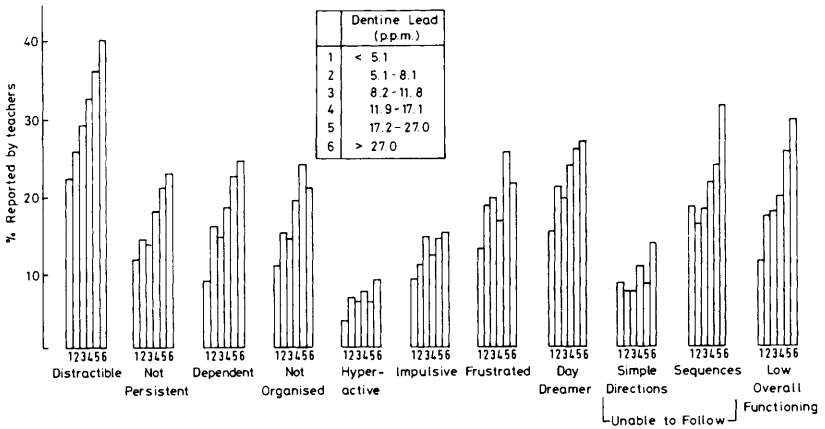
published in 1979.[11] This is widely regarded as the most methodologically sound and convincing of all studies so far published, and its results have been substantially confirmed in a subsequent smaller-scale study of London children: see *ref.* 7 and *ref.* 9, p. 267. Figure 2 shows the 'forced-choice' questionnaire answered by teachers who were blind to the dentine lead levels, and the results obtained when the frequency of negative assessments was related to six categories of increasing dentine

Figure 2 *Children's behavioural ratings in relation to dentine lead levels.*[11]
The teacher of every child who gave a tooth was asked to fill out an 11-item forced-choice behavioural rating scale scoring the child as 'yes' or 'no' on the following questions.

1. Is this child easily distracted during his/her work?
2. Can he/she persist with a task for a reasonable amount of time?
3. Can this child work independently and complete assigned tasks with minimal assistance?
4. Is his/her approach to tasks disorganized (constantly misplacing pencils, books, *etc.*)?
5. Do you consider this child hyperactive?
6. Is he/she over-excitable and impulsive?
7. Is he/she easily frustrated by difficulties?
8. Is he/she a daydreamer?
9. Can he/she follow simple directions?
10. Can he/she follow a sequence of directions?
11. In general, is this child functioning as well in the classroom as other children his/her own age?

This form was completed by the teachers (who were blind to the lead level) after at least two months of classroom experience with the child. Sum scores (11 = good, 0 = poor) and item analyses were computed. The scale was obtained for the 2146 subjects who submitted at least one tooth. These 2146 subjects were then divided into six groups according to dentine lead level.

In the parallel comparison between smaller but carefully matched groups, the higher lead group showed a significant IQ deficit of some 4—5 points, deficiencies being most marked in verbal tests, on three measures of auditory and verbal processing, on attentional performance, and on most aspects of classroom behaviour covered by the above list of questions.



Classroom behaviour in relation to dentine lead concentration; results for 2146 *children* (Needleman *et al.*)[11]

[11] H. L. Needleman, C. Gunnoe, A. Leviton, R. Reed, H. Peresie, C. Maher, and P. Barrett, *N. Engl. J. Med.*, 1979, **300**, 689.

lead levels. A dose–effect relationship is clearly apparent for all the measures, and in most cases there is no indication of any threshold of effect. In another part of the study, Needleman *et al.* investigated some 39 non-lead (mostly medical and social) factors that might have influenced the outcomes, but none of these accounted for the findings as convincingly as the dentine lead levels. I do not need to labour the enormous social implications of such findings.

3 Behavioural Toxins, Teratogens, and Genotoxins

The foregoing effects of the neurotoxin lead occur in the absence of any of the classical signs and symptoms of poisoning. They thereby exemplify a general principle discovered originally by Russian workers who were following up Pavlov's classic work on conditioned reflexes. It was observed that acquisition of such reflexes or responses (a type of learned behaviour) was surprisingly sensitive to exposure to neurotoxins,[12–14] in general producing behavioural and learning disorders as some of the earliest observable effects, and at levels well below those at which more obvious symptoms of poisoning are liable to occur. The phenomenon appears to be general for all neurotoxins so far studied: in the case of Pb^{2+}, subtle behavioural effects in fish have been observed at levels approaching 1000th of the incipiently lethal level (LD_1).[15] The study of these chemically induced effects on mentation, behaviour, intelligence, adaptability, personality, stress sensitivity, *etc.* now forms the subject of *behavioural toxicology*.[16,17] Ethanol provides the best known example of a behavioural neurotoxin. It is common experience that alcoholic beverages induce subtle changes in behaviour, personality, *etc.* at levels well below those liable to cause symptoms of clinical poisoning. The cause-and-effect connection between alcohol and some types of criminality is very well established, and provides an excellent example of a chemically induced social effect. Oddly enough, alcoholism is still widely seen in the social sciences as exclusively a social problem—a classic oversimplification, and to some extent a confusion of cause and effect: the effects are social and medical, and the primary cause chemical, sometimes with secondary social influences. Heroin, cannabis, amphetamines, LSD, and other drugs of abuse also act as behavioural toxins and, like ethanol, generate social problems. Exposure to these is of course voluntary, at least until addiction sets in.

A particularly instructive example of involuntary (*i.e.* guiltless) exposure to an environmental neurotoxin is provided by the behavioural disorder termed *mercurial erethism*. This was once common in hat makers who used mercuric nitrate in the felting of fur, and it gave rise to the saying 'Mad as a Hatter'. The following description of symptoms is taken from a standard textbook of

[12] (*a*) L. I. Medved, E. I. Spynu, and Iu. S. Kagan, *Residue Rev.*, 1964, **6**, 42; (*b*) L. I. Medved, and Iu. S. Kagan, *Ann. Rev. Pharmacol.*, 1966, **6**, 293; (*c*) A. Bokina, N. Eskler, and A. Beresina, *Adv. Pharmacol. Therap.*, 1979, 179.

[13] D. Bryce-Smith, *Chem. Br.*, 1972, **8** (6), 240, and references therein.

[14] (*a*) A. P. Silverman in 'Chemical Influences on Behaviour', ed. R. Porter and J. Birch, Churchill, London, 1970, p. 25; (*b*) A. P. Silverman, *New Sci.*, 1974, (31 Jan.), 255.

[15] P. A. Weir and C. H. Hine, *Arch. Environ. Health*, 1970, **20**, 45.

[16] B. Weiss, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, 1978, **37** (1), 22.

[17] D. M. Warburton, *Br. Med. Bull.*, 1981, **37** (2), 121.

toxicology,[18] and provides a good indication of the range and subtlety of the behavioural effects that can be induced even by such a chemically simple neurotoxin as Hg^{2+}. 'The physical or emotional disturbance is characterized by self-consciousness, timidity, embarrassment with insufficient reason, anxiety, indecision, lack of concentration, depression or despondency, resentment of criticism, irritability or excitability; these appear sometimes to cause a complete change of personality.'

Hunter has described an almost equally bizarre range of behavioural symptoms induced by exposure to the environmental neurotoxin tetraethyl-lead (present at low levels in air, especially near traffic and petrol filling stations[19]).* These include restlessness, talkativeness, illusions, mania, over-anxiety, aggression, suicidal tendencies, and even symptoms of schizophrenia. Some cases have been mistaken for drunkards and lunatics:[20] see also the important review by Grandjean and Nielsen.[21]

Although it is not suggested that the foregoing behavioural quirks or mental illnesses are always caused by mercury or tetraethyl-lead, the fact that so many common variants of individual behaviour and personality can be induced not by the social environment or genetic inheritance, but by exposure to simple chemicals present in the general environment, provides an excellent illustration of my central thesis. There are good grounds for regarding neurotoxins as potentially the most dangerous of all chemical pollutants since they can affect our most critical organ, the brain, and thence even the way we think. Partial lists of environmental neurotoxins to which exposure is (a) voluntary and (b) involuntary are given in Figures 3 and 4 respectively. Some such as alcohol and, I submit, lead are evidently already producing behavioural effects at present levels of exposure. Others such as organochlorine pollutants clearly have the potential to modulate, agonize, or even possibly antagonize such effects, but conjoint phenomena of this type as yet remain largely uninvestigated.

It is also important to recognize that both general malnutrition[22] and certain specific nutrient deficiencies before and/or after birth can produce disordered mentation and behaviour. The mental effects tend to be substantially irreversible when the deficiencies occur before birth or in infancy. Examples include deficiencies of vitamins B_1 (thiamine), B_6 (pyridoxal), and B_{12} (cyanocobalamin), and iodine, iron, and zinc. Deficiencies of iron and zinc appear to be very common in the U.K., and the W.H.O. have estimated that some 200 million people, mostly in less

* The main toxic entity is believed to be Et_3Pb^+ formed by dealkylation in the liver, rather than Pb^{2+}, although further slow dealkylation leading eventually to Pb^{2+} appears to occur *in vivo* over a period of weeks or months.

[18] E. Browning, 'Toxicity of Industrial Metals', 2nd Edn., Butterworths, London, 1969, p. 234.

[19] D. M. Colwill and A. J. Hickman, Department of the Environment, TRRL Report LR545, Transport and Road Research Laboratory, Crowthorne, 1973.

[20] D. Hunter, 'The Diseases of Occupations', 4th Edn., English Universities Press, London, 1969, p. 283.

[21] P. Grandjean and T. Nielsen, *Residue Rev.*, 1979, **72**, 97.

[22] (*a*) J. Dobbing, *Br. Med. Bull.*, 1974, **30** (2), 164; (*b*) M. B. Stock and P. M. Smythe, *Arch. Dis. Child.*, 1963, **38**, 546; (*c*) R. S. Illingworth, 'The Normal Child', 8th Edn., Churchill Livingstone, London, 1983; (*d*) R. S. Illingworth, 'The Development of the Infant and Young Child', 7th Edn., Churchill Livingstone, London, 1980.

Figure 3 *Some behavioural neurotoxins of social abuse, or to which exposure is voluntary*

Ethanol
Nicotine, Cigarette smoke (see Note 2)
Cannabis (tetrahydrocannabinols, *etc.*)
Toluene (in 'glue-sniffing', a growing cause of juvenile crime)
Cocaine
Heroin
LSD (lysergic acid diethylamide)
Oral contraceptives (*e.g.* progestogens can induce depression and loss of libido)[a]

Note 1 Tranquillizers, sedatives, anti-depressants, lithium, and neuroleptic agents in general are mostly medically prescribed, and all produce mainly benevolent short-term alterations in behaviour through chemical effects on the CNS. Many are now considered to pose a hazard to the foetus if taken in pregnancy. Prolonged use of benzodiazepine tranquillizers, *e.g.* Valium, Librium, can lead to addiction with serious behavioural symptoms on withdrawal. It is extremely interesting that anti-monoamine oxidase drugs, widely prescribed as antidepressants, can produce in some individuals surprising adverse effects on the *moral* sense, in that they lose any awareness of the emotions of others and become very self-centred.[b] In general, psychopaths are moral defectives, and were so described prior to the 1959 Mental Health Act.
[a] E. C. G. Grant and J. Pryse-Davies, *Br. Med. J.*, 1968, **3**, 777; E. C. G. Grant in 'Biological Aspects of Schizophrenia and Addiction', ed. G. Hemmings, Wiley, London, 1982, p. 263. [b] S. P. Wright, *Lancet*, 1978, i, 284: see also D. Bryce-Smith, *Zygon*, 1977, **12**(3), 212 for a discussion of the physical aspects of moral deficiency.
Note 2 Many, though probably not all, of the behavioural effects of smoking are due to nicotine, an alkaloid which tends to accumulate in the hippocampus: this brain organ is thought to play an important part in learning ability and the establishment of long-term memory (and is also a target organ for Pb^{2+}). Smoking produces adverse short-term effects on learning and memory, though long-term memory may be improved.[c] Smoking produces decreased hostility and aggressiveness in the short-term, whereas these are *increased* after cessation of smoking.[d]
[c] K. Anderson, *Psychopharmacologica*, 1975, **41**, 1, and references therein. [d] M. D. Schechter and M. J. Rand, *Psychopharmacologica*, 1974, **35**, 19, and references therein.

Figure 4 *Some environmental neurotoxins (behavioural toxins) to which exposure is mostly involuntary*

Organophosphorus pesticides (residues are now present in flour and bread)[a,b]
Organochlorine compounds *e.g.* DDT, CCl_4, trichloroethylene, polychlorinated biphenyls (PCBs)[b,e]
n-Hexane (→ hexane 2,5-dione *in vivo*)[c]
Carbon monoxide (also voluntary exposure through tobacco smoking)
Carbon disulphide (occupational exposure)
Manganese (heavy occupational exposure)
Mercury vapour and salts: $MeHg^{+}$ [d]
Organotin compounds[d]
Lead salts: organolead compounds[d]
Vanadium (?)
Aluminium[f]

[a] D. R. Wilkin and F. B. Fishwick, Proceedings 1981 British Crop Protection Conference--Pests and Diseases, p. 183. (Copies available from Ministry of Agriculture, Fisheries, and Food, Slough Laboratory, London Road, Slough, Berks.) [b] Report of the Working Party on Pesticide Residues (1977—1981), Ministry of Agriculture, Fisheries, and Food, H.M.S.O., London, 1982. [c] R. J. Anderson and C. B. Dunham, *J. Toxicol. Environ. Health*, 1984, **13**, 835. [d] Can also act as behavioural teratogens. [e] Human maternal exposure to PCBs from contaminated fish during pregnancy has been reported to correlate significantly with reduced birth weight and head circumference. [G. G. Fein, J. L. Jacobson, S. W. Jacobson, P. M. Schwartz, and J. K. Dowler, *J. Pediatr.*, 1984, **105** (2), 315]; so if PCBs can impair development of the foetal brain they probably also act as behavioural teratogens. [f] For excellent reviews see S. Brusewitz, 'Aluminium', University of Stockholm Institute of Physics, (USIP Report 18—11), Vanadisvägen 9, Stockholm, 1984, and M. R. Wills and J. Savory, *Lancet*, 1983, ii, 29.

developed countries, suffer from iodine deficiency. For details, see references 23—27. Vegetarians are at particular risk of vitamin B_{12}[23] and zinc deficiencies.[27]

The concept of *behavioural teratogens* is of more recent origin but is no less important.[28] It stems from research on teratogens, *viz.* substances which tend to cause physiological deformities in the developing embryo and foetus. The drug thalidomide is probably the best-known example. For some teratogens the developing CNS is a target organ, and in the exteme case of anencephaly the neonate may be born almost literally brainless, or with only rudimentary amounts of ill-developed brain tissue (yet often with the facial features and limbs almost normal). The cause in man is not yet definitely known, but Elwood and Elwood list some 30 exogenous agents that can cause this serious maldevelopment of the foetal brain in various animals, including *X*-rays, sulphonamides, excess of Vitamin A, mercury, cadmium, and deficiencies of B vitamins and zinc.[29] The behavioural importance of these findings lies in the fact that agents for which the foetal brain is a target organ tend at lower levels of exposure to act as behavioural teratogens. The neonate may appear normal at birth, but defects in intelligence, personality and behavioural control are liable to appear in later life. One may reasonably suppose that at these lower levels of exposure to the teratogen, the foetal brain suffers more subtle developmental disorders which are not visible at birth. In animal studies, these have in some cases appeared as biochemical abnormalities, or been revealed by detailed histopathological studies of brain structure. For example, prenatal exposure to the behavioural teratogen lead, *via* the mother, causes delays of synaptic development in the rat pup brain associated with blood-lead levels of only about 36 $\mu g\ dl^{-1}$ (0.36 μgg^{-1}):[30,31] levels above this are sometimes found in city children. Even much lower lead levels, throughout the range now regarded as 'normal' (upwards of *ca.* 3 $\mu g\ dl^{-1}$ at birth) are reported to correlate negatively with postnatal development of children in a dose-related manner.[32] For a discussion and further references, see references 3, 6, and 33.

[23] CRC Handbook Series in Nutrition and Food, Section E: Nutritional Disorders, Vol. III, ed. M. Rechcigl, CRC Press, West Palm Beach, Florida, U.S.A., 1978.
[24] Y. S. Shin, R. Rasshofer, and W. Endres, *Lancet*, 1984, **i**, 870.
[25] C. C. Pfeiffer, 'Mental and Elemental Nutrients', Keats Publishing, New Canaan, Connecticut, U.S.A., 1975.
[26] H. Wieck, W. Pribilla, and B. Heerklotz, *Dtsch. Med. Wochenschr.*, 1969, **94**, 1473.
[27] Ministry of Agriculture, Fisheries, and Food, Food Surveillance Paper No. 5 (1981), H.M.S.O., London; T. D. B. Lyon, H. Smith, and L. B. Smith, *Br. J. Nutr.*, 1979, **42**, 413.
[28] C. V. Vorhees, R. L. Brunner, and R. E. Butcher, *Science*, 1979, **205**, 1220.
[29] J. M. Elwood and J. H. Elwood, 'Epidemiology of Anencephalus and Spina Bifida', Oxford University Press, 1980, p. 23.
[30] K. M. Crofton, D. H. Taylor, R. J. Bull, D. J. Sivulka, and S. D. Luckenhoff, *Life Sci.*, 1980, **26**, 823.
[31] P. T. McCauley, R. J. Bull, and S. D. Lutkenhoff, *Neuropharmacol.*, 1979, **18**, 93.
[32] H. L. Needleman, D. Bellinger, A. Leviton, M. Rabinowitz, and M. Nichols, *Pediatr. Res.*, 1983, **17**, 179A.
[33] D. Bryce-Smith and R. Stephens, 'Lead or Health', 2nd Edn., Conservation Society, London, 1980.

A. The Foetal Alcohol Syndrome (FAS).[34]—Ethanol acts as a behavioural teratogen. Yet although a clear allusion to the foetotoxicity of alcohol (ethanol) can be found in the Bible,[35] the damage to the unborn child resulting from maternal consumption of alcohol during pregnancy only appears to have been generally recognized by the medical profession since the mid-1970s—not exactly a triumph of medical diagnosis. Yet by 1983, over 800 papers on the teratogenic effect of ethanol had appeared. The effects on the neonate can range from mild (*e.g.* low birthweight) to severe (*e.g.* death, heart damage) and certainly include mental defects and disorders of behavioural control (hyperactivity) in later life which are highly relevant to the theme of this article. The FAS child has such a characteristic appearance—small head, broad retroussé nose, thin upper lip,[36]—that it is difficult to understand why recognition of the condition was so long delayed. Even now, it may be doubted whether many of those faced with persons of sub-normal intelligence and/or impaired behavioural control consider the possibility that these stem from foetal brain damage due to maternal ethanol—for which the affected person is in no way to blame.

There has been considerable dispute about the amount of maternal ethanol intake associated with foetal damage, but recent evidence suggests that as little as one alcoholic drink every three days can increase the risk of miscarriage, itself a recognized indicator of toxic effects on the foetus.[37,38] The toxic effects of ethanol are exacerbated by smoking, lead, and by zinc deficiency.[39] Indeed, alcohol increases the urinary excretion of zinc, and the mental disorders associated with severe alcoholism (hepatic encephalitis) can be successfully abated by zinc sulphate.[40]

Ethanol therefore joins lead as a common behavioural teratogen of special importance. Vorhees and Butcher list references to numerous others to which pregnant women are liable to be exposed, including phenobarbital, the anaesthetics halothane ($CF_3CHClBr$) and phencyclidine, various benzodiazepine tranquillizers and anti-depressants, marijuana, nicotine, heroin, various food colorants and phenolic food anti-oxidants, anabolic steroids, polychlorinated biphenyls, salicylates, carbon monoxide, *X*-rays, methylmercury, and excess of iron.[41] Maternal cigarette smoking during pregnancy has been reported to correlate significantly with educational under-achievement, and behavioural and psychological deficiencies in the offspring.[42] It is not yet known which of the various toxic constituents of tobacco smoke are responsible.

[34] M. W. Holland, *Int. J. Environ. Stud.*, 1981, **17**, 67; G. Edwards, *Br. Med. J.*, 1983,, **286**, 247.
[35] The Bible, Judges 13.
[36] J. O. Beattie, R. E. Day, F. Cockburn, and R. A. Garg, *Br. Med. J.*, 1983, **287**, 17.
[37] J. Kline, B. Levin, Z. Stein, M. Susser, and D. Warburton, *Environ. Health Perspect.*, 1981, **42**, 119.
[38] K. Hemminki, P. Kyyrönen, N. Marja-Liisa, K. Koskinen, M. Sallmen, and H. Vains, *Am. J. Public Health*, 1983, **73**, 32.
[39] R. E. Ruth and S. K. Goldsmith, *J. Nutr.*, 1981, **111** (11), 2034.
[40] P. Reding, J. Duchateau, and C. Bataille, *Lancet*, 1984, ii, 493.
[41] C. V. Vorhees and R. E. Butcher in 'Developmental Toxicology', ed. K. Snell, Croom Holm, London, 1982, p. 247.
[42] A. G. Dunn, A. K. McBurney, S. Ingram, and C. M. Hunter, *Can. J. Public Health*, 1977, **68** (1), 43; but *cf.* M. M. Lefkowitz, *Dev. Psychol.*, 1981, **17**, 192.

Pre-natal chemical effects on behaviour are not, however, restricted to those which follow exposure during pregnancy or postnatally. The critical exposure can even occur before conception.[43] It usually involves malformation of sperm (teratospermia) and/or chromosomal abnormalities and/or abnormalities in seminal fluid. The female ovum appears to be better protected from environmental toxins. Such chemically induced genetic effects or genotoxicity should not be confused with the natural genetic variability of brain development, and thence personality, behaviour, *etc.* which stems from the combination of male and female chromosomes at conception whereby sperm and ovum each contributes 23 chromosomes to the fertilized ovum (zygote). A number of environmental genotoxins for male sperm have been identified, leading to malformation and/or low birthweight of the offspring: these include ethanol,[44] 2,3,7,8-tetrachlorodibenzo-*p*-dioxin,[45] nicotine,[46] ethylene dibromide,[47] 2,3-dibromo-1-chloropropane (a soil fumigant),[48] and lead.[49] Of these, ethylene dibromide and lead also act as *behavioural genotoxins.* By a bizarre coincidence, both of these pollutants are used as petrol additives. Concerning lead, in 1978 the U.S. Occupational Safety and Health Administration (OSHA) issued an official warning about the genetic damage from occupational exposure of either parent. They referred to conclusive evidence of miscarriage and stillbirth in women exposed to lead or whose husbands were exposed, and noted that children born of parents, *either* of whom had been exposed to lead, are at increased risk of birth defects, early death, mental retardation, and behavioural disorders.[50]

So to summarize thus far, chemically induced behavioural disorders can result (a) prior to conception from the action of behavioural genotoxins on sperm, (b) between conception and birth by the action of behavioural teratogens, and (c) after birth by exposure to behavioural toxins. Categories (b) and (c) include certain nutrient deficiencies, particularly of zinc. One of the many reasons for special concern about environmental lead is that it falls into all three categories. And in view of the known correlation between male sub-fertility and low semen-zinc,[51] there are grounds for suspecting that zinc deficiency may come to join lead exposure in all categories. Toxicologically, lead and cadmium act as zinc antagonists *inter alia*, so the effects of zinc deficiency are liable to be exacerbated by exposure to these environmental toxins.

[43] S. Brenner, *Br. Med. Bull.*, 1973, **29**(3), 269.
[44] R. W. Klassen and T. V. N. Persaud, *Exp. Pathol.*, 1976, **12**, 38.
[45] T. Cairns, L. Fishbein, and R. K. Mitchum, *Biomed. Mass Spectrom.*, 1980, **7**, 484.
[46] B. N. Hemsworth, IRCS Medical Science: *Anatomy and Human Biology; Biochemistry; Developmental Biology and Medicine; Drug Metabolism and Toxicology; Pathology; Pharmacology, Physiology, Reproduction, Obstetrics and Gynaecology*, 1981, **9**, 728.
[47] D. Fanini, M. S. Legator, and P. M. Adams, *Mutat. Res.*, 1984, **139** (3), 133; R. F. Smith and L. Goldman, *Neurobehavioral Toxicol. Teratol.*, 1983, **5**, 579.
[48] Anon., *Chem. Eng. News*, 16 Jan., 1984, p. 36.
[49] K. Brady, Y. Herrera, and H. Zenick, *Pharmacol. Biochem. Behav.*, 1975, **3**, 561; I. Lancranjan, H. I. Popescu, O. Gavanescu, I. Klopsch, and M. Serbanescu, *Arch. Environ. Health*, 1977, **30**, 396; H. D. Stowe and R. A. Goyer, *Fertil. Steril.*, 1971, **22**, 755.
[50] J. Peterson, *Ambio*, 1979, **8** (5), 226; *Fed. Reg.*, 1978, **43** (220), 52952.
[51] J. Piesse, *Int. Clin. Nutr. Rev.*, 1983, **3** (2), 4.

The operation of these environmental factors means that the behaviour, personality, and general mentation of an individual at a particular time will arise from the effects of natural genetic heredity modulated by the foregoing genetic and post-conception nutritional and toxic influences on brain development and function acting in conjunction with past sensory information stored as memory, and contemporary sensory information from the physical and social environments. All these influences are chemical, or are mediated by chemical mechanisms.

Some, including myself, would add spiritual influences to this list, but these are not yet susceptible to the present type of analysis.

B. Biochemical and Physiological Mechanisms of Chemically Induced Behavioural Effects.—In general, the effects on behaviour *etc.* that I have been discussing appear to stem mainly from disturbances of physical brain development and/or function, since the brain, or more strictly the CNS, mediates all aspects of mentation and behaviour, usually in co-operation with other organs, particularly the adrenal glands which synthesize and secrete steroid hormones, adrenaline, and noradrenaline. The factors which determine and control brain development and function are still very imperfectly understood, especially the role of that mysterious entity termed mind, but the following brief and somewhat over-simplified account of some salient features may serve as a framework for better understanding. (Much fuller accounts of the chemistry of brain function will be found in specialist textbooks, *e.g.* references 52 and 53).

We may start with the female ovum and male sperm, or gametes. These develop separately and contain genetic information coded in the chemical form of the DNA 'double helix' molecules which comprise genes. Chromosomes in turn are composed of connected strands of hundreds or even thousands of longitudinal assemblies of genes. Each gamete has 23 chromosomes, and the union of ovum and sperm produces the zygote containing the 46 chromosomes in which are encoded the genetic information required for development of the new individual, including his or her brain. Since zinc is a constituent of many enzymes involved in the metabolism of DNA and RNA (about 20 zinc-dependent DNA and RNA polymerases are now known), and is also required to stabilize the structure of these genetic molecules,[54] it is not surprising that nutritional zinc deficiency, now quite common,[27] and zinc antagonists such as cadmium and lead, can disturb genetic expression at the most fundamental molecular level. When this disturbance involves those genes which control development of the physical brain, and remains uncorrected by genetic repair processes, it can be expected to hinder the expression of a future individual's true mental potential.

These considerations may at least partly account for the observed behavioural genotoxicity of lead, and the adverse genetic effects of zinc deficiency, to which I have previously referred. It is hard to envisage how social factors as such could have any significant direct causative influence on the genetic expression of behaviour,

[52] S. Reinis and J. M. Goldman, 'The Chemistry of Behavior', Plenum Press, London, 1982.
[53] H. L. Meltzer, 'Chemistry of Human Behavior', Nelson-Hall, Chicago, 1979.
[54] 'Zinc Enzymes', ed. T. G. Spiro, Wiley-Interscience, Chichester, 1983.

though there could well be indirect effects arising from associations between, say, poverty and genotoxic pollutants and/or dietary deficiencies.

Let us now consider how environmental chemical factors can influence brain development between conception and birth, and thereby influence postnatal behaviour *etc.* The following account is of necessity brief: sources of fuller information are provided in *refs.* 22 and 55. Thus Illingworth lists over 50 non-social pre- and peri-natal influences that can disturb an infant's mental development.[22d]

The brain develops much more rapidly than most other organs in the embryo, and by about the twentieth week of pregnancy contains most of the *ca.* 10^{10} neurons present in the adult brain (excluding the cerebellum which is initially slower to develop, but quicker to mature). Maternal malnutrition during the first half of pregnancy permanently reduces the number of neurons formed in the foetal cerebrum, reduces the DNA content, and alters succinate dehydrogenase and other enzyme systems in the brain.[22d] Whereas each neuron in the mature brain has on average *ca.* 10^4 of the interneuronal connections required for normal adult mentation,* only a minor proportion of these connections has developed by birth, sufficient no doubt for the relatively undemanding mental needs of the neonate.

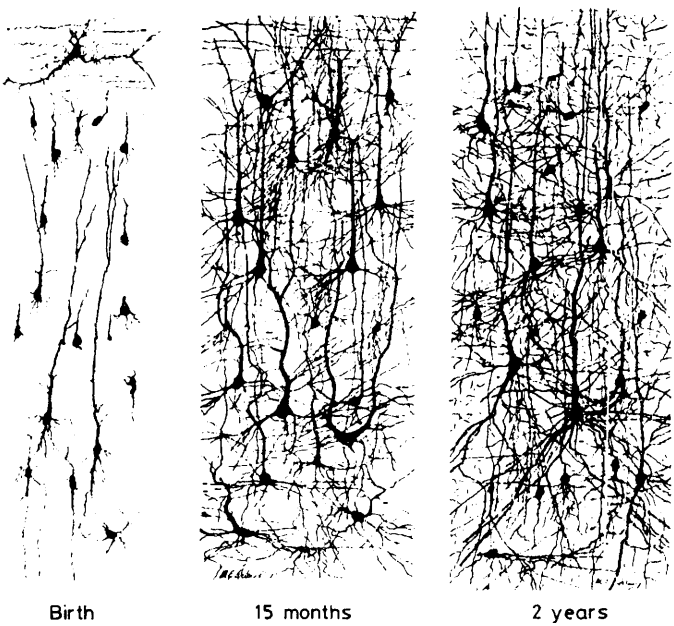


Figure 5 *Growth of connections between nerve cells in the human cerebral cortex during the first two years of life*

* Some neurons, *e.g.* the Purkinje cells in the cerebellum, have up to 10^5 interneuronal connections.

[55] (*a*) 'The Biological Basis of Behaviour', ed. N. Chalmers, R. Crawley, and S. P. R. Rose, Open University Press and Harper and Row, London, 1971; (*b*) S. P. R. Rose, *New Scientist*, 1978, (6 July), 31.

Growth of interneuronal connections is very rapid during the first few years, and is probably complete by about eighteen years of age. The early stages are depicted in Figure 5 which shows the progressive increase with age in the density of interneuronal connective tissue (dendrites) but not of the neurons themselves.[55b]

The mechanism of the process whereby this most complex of all states of matter becomes purposefully elaborated is one of the great unsolved mysteries of science, but it is believed to involve chemotaxis by neurotransmitter molecules such as dopamine. It may be that chemical signals which reach a neuron both from the extracellular environment and from adjacent cells interact with the neuron's internal genetically determined developmental programmes to modify and direct its overall pattern of development, including the elaboration of interneuronal connections. Although this may not be the whole story, neuronal development can certainly be permanently disturbed by chemical factors, including general maternal malnutrition before birth, and infant malnutrition,[22d] and more specifically by prenatal zinc deficiency, with irreversable effects on behaviour of the offspring.[56] I shall refer later to our own findings concerning the role of zinc, cadmium, and lead in foetal brain development.

C. Interaction of Social and Chemical/Nutritional Influences on Brain Development.—In general, the development of interneuronal connections depicted in Figure 5 appears to involve two distinct types of process conveniently, if inaccurately, termed 'hard' and 'soft' wiring. The blueprint, as it were, for the former appears to be programmed in some utterly mysterious way into the structure of the developing brain, or even the fertilized ovum, and the complex pattern of connections appears to elaborate itself independently of sensory inputs. In contrast, the 'soft' wiring is subject to modulation, if not control, by postnatal sensory inputs. For example, rats that were frequently handled and placed in a stimulating environment showed increased brain weight and interneuronal connections, and changes in brain chemistry, in comparison with rats kept on the same diet in a dull and unstimulating environment.[57] Thus physical brain development can be promoted both by social *i.e.* sensory, stimulus and by chemical stimulus, *e.g.* with protein or zinc. Denenberg has even claimed to be able to modify the personality, behaviour, and learning ability of experimental animals for good or ill by varying the social environment in which the neonate develops.[58] We may reasonably assume that these procedures modify the patterns of 'soft wiring' in the developing brain. Although some parents may take leave to doubt whether the personalities of many human children are quite as malleable as those of rats, there is good evidence for 'sensitive periods' of development during which children are best able to learn language and acquire various other abilities.[22d] It therefore appears that sensory stimuli can produce changes in personality, behaviour, *etc.* by inducing physical changes in the structure and chemistry of the developing brain. This conclusion

[56] C. L. Dvergsten, G. J. Fosmire, D. A. Ollerich, and H. A. Sandstead, *Brain Res.*, 1983, **271**, 217, and references therein.
[57] M. R. Rosenzweigh, E. L. Bennett, and M. C. Diamond, *Sci. Am.*, 1972, **226**, 22.
[58] V. H. Denenberg, 'Education of the Infant and Young Child', Academic Press, New York, 1970.

further emphasizes the intimacy of interacting 'social' and 'chemical' influences on behaviour, *etc.*

We return now to the neutronal processes by which behaviour is mediated, passing from the neural networks of Figure 5 to the typical neuron shown schematically in Figure 6. For obvious reasons, only small proportions of the *ca.* 10^4 dendrites and nerve endings are depicted. This specialized non-reproducing cell processes the sensory information from which behaviour, learning ability, *etc.* emerge as resultants. The dendrites receive this information from the *ca.* 10^4 contiguous neurons in the network, *via* neurotransmitter molecules and associated ionic changes, as described below. Once the neuron's negative electrical potential, initially *ca.* -70 mV, decreases to *ca.* -40 mV, it 'fires' becoming transiently positively charged to some $+20$—30 mV, and relays the sensory information essentially as a Na^+ current along the axon to its own nerve endings by a rather complicated relay mechanism. Not surprisingly, chemical and electrical influences can disturb these processes. Pb^{2+} for example acts as a Ca^{2+} antagonist, and thereby interferes with the neuron's utilization of the energy from ATP required for these complex processes.[30] It also inhibits dendrite growth, and can disturb biosynthesis of the fatty myelin sheath (a phospholipid–protein complex) shown in Figure 6 which serves something of the function of an electrical insulator around the axon. Dietary copper deficiency can also cause demyelination, probably owing to inadequate function of the copper-dependent terminal respiratory enzyme cytochrome oxidase critically required for phospholipid biosynthesis.[59] Furthermore, molybdenum and lead can induce or exacerbate copper deficiency, and thence demyelination, through the effects on copper uptake and utilization.[60] These are just a few of the ways in which interacting environmental chemical factors can influence neuronal development and function, and thence the processing of sensory information.

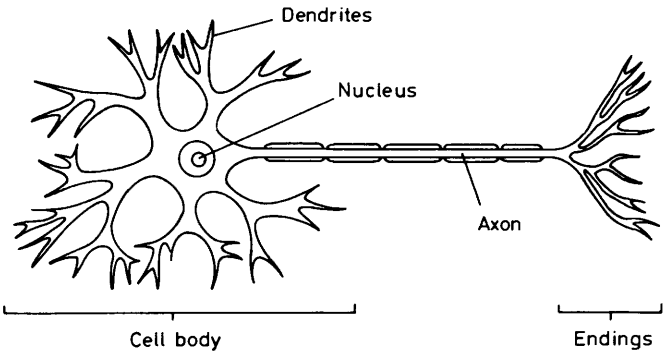
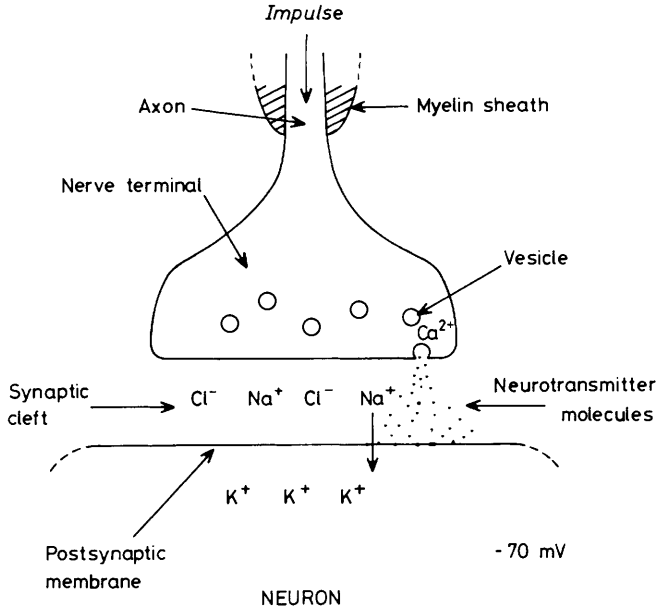


Figure 6 *Diagram of a typical neuron*

[59] B. F. Fell, C. F. Mills, and R. Boyne, *Res. Vet. Sci.*, 1965, **6**, 10; C. H. Gallagher and V. E. Reeve, *Aust. J. Exp. Biol. Med. Sci.*, 1971, **49**, 21.

[60] E. J. Underwood, 'Trace Elements in Human and Animal Nutrition', 4th Edn., Academic Press, London, 1977.

We now come to the *synapse*, that most important aqueous fluid-filled gap of *ca.* 200 Å between a nerve ending and the surface of its contiguous neuron: see Figure 7. With some justification, the synapse has been described as the primary site of decision making in the CNS. It functions as a sophisticated chemical switch for communication between neurons. A full description of the chemistry involved would go far beyond the scope of this article, but the following outline may serve to explain why behaviour, personality, *etc.* have a biochemical basis which is fundamental to the processing of information from social interactions, *etc.*



Excitation - Na^+ enters neuron, -ve potential falls

Inhibition - Cl^- enters neuron, or K^+ leaves, -ve potential rises

Figure 7

For most neurons, the arrival of the positive action potential at the nerve ending—the terminal bouton shown in Figure 7—causes the influx of extraneuronal Ca^{2+} ions which, possibly *via* calcium-stimulated phosphorylation of membrane proteins, causes release of neurotransmitter molecules from vesicles and cytoplasm into the synaptic cleft, across which they rapidly diffuse and bind onto specific sites on the postsynaptic membrane. (Certain steroids and prostaglandins may also play a part). Both Pb^{2+} and Cd^{2+} strongly inhibit this important influx of Ca^{2+} to presynaptic nerve terminals[61] and can thereby

[61] G. P. Cooper, J. B. Suszkiw, and R. S. Manalis, *Neurotoxicol.*, 1984, **5** (3), 247; G. P. Cooper, J. B. Suszkiw, R. S. Manalis, and G. Toth, *Brain Res.*, 1984, **323** (1), 31.

interfere with neurotransmitter release. Pb^{2+} has been shown to interfere with the release of several important neurotransmitters, including acetylcholine, dopamine, noradrenaline, and 4-aminobutanoic acid (GABA): the effects on GABA metabolism are further discussed below.

Several dozen neurotransmitters are now known or postulated, and some are shown in Figure 8; but these fall into two broad categories, *viz.* excitatory and inhibitory. (Some neurotransmitters, *e.g.* acetylcholine and glutamate, can be excitatory in one part of the nervous system and inhibitory in another, though both of these tend to show predominantly excitatory function.) Excitatory neurotransmitters bind onto postsynaptic membrane sites and thereby open channels through which Na^+ ions enter the adjacent neuron where their concentration is much lower. The effect of this influx of positive ions—an 'opening of the gates'—is to reduce the negative resting potential (*ca.* −70 mV) of the neuron. [The electrical imbalance largely arises from an imbalance in the concentrations of Na^+, K^+, Ca^{2+}, and Cl^- on opposite sides of the postsynaptic membrane which is maintained by energy from ATP (adenosine triphosphate) fission *via* ATP-ases: this latter process is one of a number significantly inhibited by Pb^{2+} at present-day levels in man.[62]] As previously mentioned, when the intraneuronal potential reaches *ca.* −40 mV, the neuron 'fires'. However, in order to prevent gross amplification of sensory information, this excitatory mechanism needs to be modulated by corresponding inhibitory processes involving the release of inhibitory neurotransmitters into the synaptic cleft, and their binding onto specific receptor sites on the postsynaptic membrane. Such binding opens membrane channels that permit the influx of Cl^- ions from the synapse and the continuing outflow of intraneuronal K^+ ions into the synapse down the corresponding concentration gradients, but they are relatively impermeable to the more highly hydrated Na^+ ions. Thereby, the neuron tends to become more negatively charged and is removed further from the firing potential.

Thus the vital question whether a given neuron fires, *i.e.* relays its information inputs onwards, depends on the change in its electrical charge arising as an integrated resultant of the excitatory and inhibitory chemical information it has received in the form of neurotransmitter molecules from its thousands of excitatory and inhibitory synaptic junctions. The fate of the neurotransmitters after stimulating the foregoing ion-transport processes also has major behavioural implications. Acetylcholine needs to be hydrolysed by cholinesterase, and anti-cholinesterases such as organophosphorus insecticides (now present in flour and bread) can certainly induce behavioural changes.[12] Dopamine on the other hand appears to be desorbed from the postsynaptic site: some is taken up again *via* the presynaptic membrane, and some diffuses out of the synaptic cleft to be degraded by amine oxidases. Anti-amine oxidase drugs are used in the treatment of depression, but can have adverse behavioural side-effects: see Figure 3, Note 1. Disorders of dopamine metabolism appear to be involved in the complex aetiology

[62] G. J. Siegel, S. K. Fogt, and M. J. Hurley, in 'Membrane Toxicity', ed. M. W. Miller and A. E. Shamoo, Plenum, 1977; G. C. Secchi, L. Alessio, and G. Cambiaghi, *Arch. Environ. Health*, 1973, **27**, 399.

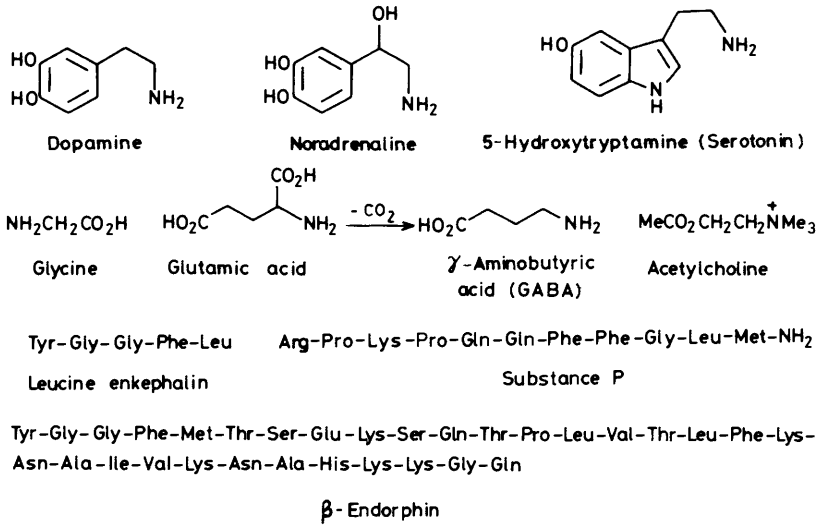


Figure 8 *Some neurotransmitters and related polypeptides*

of schizophrenia.[63a] Some types of schizophrenia appear to be associated with raised levels of copper in conjunction with low levels of zinc and/or manganese. Correction of these imbalances is reported to bring clinical improvement,[63b] though it is not yet known whether this interesting new treatment influences dopamine metabolism.

The 'social causation' theory of behavioural and social phenomena implicitly requires that these complex chemical cascades and networks involved in the regulation of behaviour and mentation should in some mysterious way be insulated from their chemical environment. It is clear that they are not. Nevertheless, the enormous chemical and physiological complexity of the neural networks involved in the determination and control of behaviour, personality, *etc.*, makes for complex dose–effect relationships, and for considerable variations in the behavioural response to a neurotoxin between one person and another. Most people are familiar with such variations in response to ethanol. One person may be rendered more excitable and aggressive by a few drinks, whereas another may become more relaxed and amiable. Some at least of the behavioural effects of nicotine stem from its action on acetylcholine metabolism. Aggressivity and tension are first decreased by cigarette smoking or nicotine alone, but subsequently increase after exposure ceases,[14a,64a] an effect possibly connected with increased release of acetylcholine from the cerebral cortex.[64b] 'Killer' rats have raised acetylcholine

[63](*a*) J. Traynor, *Chem. Brit.*, 1984, **20** (8), 798; (*b*) C. C. Pfeiffer and S. LaMola, *J. Orthomol. Psychiatry*, 1983, **12**, 215, and references therein.

[64](*a*) M. D. Schechter and M. J. Rand, *Psychpharmacologia*, 1974, **35**, 19; (*b*) A. K. Armitage, G. H. Hall, and C. M. Sellers, *Br. J. Pharmacol.*, 1969, **35**, 152.

levels in the diencephalon, and non-killers can be transformed into killers by administration of the anti-acetylcholine esterase pilocarpine; in contrast, atropine, which blocks acetylcholine uptake at 'muscarinic' sites on the postsynaptic membrane, transforms killers into non-killers: see reference 52, pp. 297 *et seq.* (It is interesting that similarities have been noted between the vagal neurotoxicity of pilocarpine and that of lead.[65]) The biosynthesis of acetylcholine appears partly determined by the intake of dietary choline,[66] and that of another neurotransmitter serotonin (5-hydroxytryptamine) by the intake of dietary tryptophan.[66,67] Therefore, behaviour is to some extent a function of these organic dietary components. Supplementary tryptophan is in fact used medically for its anti-depression activity.

Although it is unlikely that any single neurotransmitter uniquely controls any particular type of behaviour, it is particularly instructive to consider the effects of environmental influences on the neurotransmitters glutamate and GABA (4-aminobutanoic acid) since these are probably the two most important neurotransmitters in the cerebral cortex: glutamate is excitatory and GABA inhibitory. GABA is believed to play an important part in our response to stress and the relief of anxiety. Both ethanol[68] and benzodiazepine tranquillizers[69] appear to relieve the immediate effects of stress by modulating or stimulating GABA metabolism. In contrast, low levels of lead rapidly inhibit GABA metabolism,[70] a phenomenon that may well play a part in the lead-induced sensitization to various kinds of stress observed in man[71] and experimental animals.[70,72] It is therefore reasonable, if speculative, to envisage a role for lead pollution in the increased consumption of both alcohol and tranquillizers: and it is true that higher mean blood-lead levels are consistently found in groups of drinkers than non-drinkers.[73] In principle, drinking could be the cause and/or effect of the raised lead levels. The essential element zinc, which as previously noted is seriously deficient in many U.K. diets,[27,74,75] also comes into this picture for the following reasons. Lead is a zinc antagonist and *vice versa*, and ethanol promotes urinary excretion of zinc, and inhibits gastrointestinal absorption, thereby exacerbating the effects of dietary zinc deficiency. Lead strongly inhibits the zinc-dependent enzyme aminolaevulinate dehydratase involved in the biosynthesis of haem. The resulting

[65] A. Hamilton and H. L. Hardy, 'Industrial Toxicology', 3rd Edn., Publishing Sciences Group, Acton, Massachusetts, U.S.A., 1974, p. 96.
[66] R. J. Wurtman and J. Growdon in 'Food and Health—Science and Technology', ed. G. G. Birch and K. J. Parker, Applied Science, London, 1980, p. 501.
[67] J. D. Fernstrom and R. J. Wurtman, *Science*, 1971, **173**, 149.
[68] J. N. Nestoros, *Science*, 1980, **209**, 708.
[69] R. W. Olsen, *J. Neurochem.*, 1981, **37**, 1; 'Actions and Interactions of GABA and Benzodiazepines', ed. N. G. Bowery, Raven Press, New York, 1984.
[70] E. K. Silbergeld, L. P. Miller, S. Kennedy, and N. Eng, *Environ. Res.*, 1979, **19**, 371.
[71] American Academy of Pediatrics, *Pediatrics*, 1969, **44**, 291.
[72] J. P. Filkins and B. J. Buchanan, *Proc. Soc. Exp. Biol. Med.*, 1973, **142**, 471; S. R. Overmann, D. A. Fox, and D. E. Woolley, *Neurotoxicol.*, 1979, **1**, 125 and 149.
[73] A. G. Shaper, S. J. Pocock, M. Walker, C. J. Wale, B. Clayton, H. T. Delves, and L. Hinks, *Br. Med. J.*, 1982, **284**, 299; P. Grandjean, N. B. Olsen, and H. Hollnagel, *Int. Arch. Occup. Environ. Health*, 1981, **48**, 391.
[74] Ministry of Agriculture, Fisheries and Food, Food Surveillance Paper No. 14, H.M.S.O., London, 1984, p. 6.
[75] D. Bryce-Smith and R. I. D. Simpson, *Lancet*, 1984, ii, 350.

partial metabolic block leads to raised tissue levels of the intermediary metabolite δ-ALA (δ-aminolaevulinic acid). Although δ-ALA was once regarded merely as a metabolically inactive indicator of lead intoxication, it is in fact now known to be a neurotoxin in its own right which readily crosses the blood-brain barrier, interferes with transport of Na^+ across membranes (*cf.* Figure 7) and can induce hyperactivity[76a] and altered social behaviour[76c] in rodents. Some of the behavioural effects of δ-ALA (and hence of lead, and perhaps zinc deficiency) appear to result from its ability to act as a 'false neurotransmitter' which imperfectly mimics the structurally related GABA.[70,77]

Pyridoxal (vitamin B_6) is important in neurotransmitter chemistry by virtue of its role (possibly jointly with zinc), as a co-factor in the enzymatic decarboxylation of amino-acids to neurotransmitter amines. For example, selectively impaired decarboxylation of glutamate (excitatory) to GABA (inhibitory) (Figure 8) might be expected to lead to an excess of excitatory response to sensory stimuli. In practice, the opposite is found (in mice if not men), probably because other neurotransmitter systems are also affected, and hyperexcitability is associated with raised levels of pyridoxal phosphate, zinc, and copper in the brain.[78] Copper is a co-factor for hydroxylase enzymes involved in the biosynthesis of the neurotransmitters dopamine and noradrenaline, and for amine oxidases involved in the catabolism of neurotransmitters. Anti-amine oxidase drugs act as powerful antidepressants.

Calcium, magnesium, and manganese are also elements of great neurochemical importance: the last two are powerful CNS depressants, and all are ubiquitous in diet, but in varying amounts. Calcium plays numerous roles in neural function, including pre-synaptic neurotransmitter release, as already mentioned, energy utilization by neurons, and regulation of the balance between excitatory and inhibitory functions in the brain. The early symptoms of hypocalcaemia (low blood calcium) are identical with those of anxiety neurosis (a condition conventionally regarded as of psychosocial rather than biochemical origin), and artificially lowering the availability of calcium in the blood by injection of sodium lactate induces serious symptoms of anxiety neurosis, preventable by supplying extra calcium, in persons prone to that condition while leaving most normal persons unaffected.[79] The antagonism between Pb^{2+} and Ca^{2+} is one of the most notable features of lead toxicology, and appears to be involved in some, though not all, aspects of the neurobehavioural effects of lead.[76] In contrast, the powerful anti-psychosis activity of lithium appears to depend at least partly on the ability of this element to stimulate calcium metabolism and reduce the loss of calcium in the urine. Lithium is ubiquitous in human tissues, and is regarded by some workers as

[76] (*a*) F. B. McGillion, M. R. Moore, and A. Goldberg, *Scott. Med. J.*, 1973, **18**, 133; (*b*) A. Goldberg and F. B. McGillion, *Proc. Pharamacol. Soc.*, 1973, 178P; (*c*) M. G. Cutler, M. R. Moore, and F. G. Ewart, *Psychopharmacol.*, 1979, **61**, 131.

[77] (*a*) E. K. Silbergeld and J. M. Lamon, *J. Occup. Med.*, 1980, **22**, 680; (*b*) E. K. Silbergeld in 'Lead versus Health', ed. M. Rutter and R. R. Jones, Wiley, Chichester, 1983, p. 191, and references therein.

[78] S. H. Chung and M. Johnson, *Proc. R. Soc. London, Ser. B.*, 1984, **221**, 145.

[79] F. N. Pitts and J. M. McClure, *N. Engl. J. Med.*, 1967, **277**, 1329; see also Editorial, *Br. Med. J.*, 1968 (6 Apr.), p. 5.

a nutritionally essential element, though the doses used in psychiatry are much greater than those from any normal diet.

Lithium has in fact proved very successful in abating the violent propensities of criminals, and moreover without producing any undesirable side-effects on behaviour or intelligence;[80] whereas lead works in the opposite direction, as further discussed in the next Section. Such humane approaches to correcting the neural causes of antisocial propensities have yet to be generally adopted, possibly because they blur the sharp distinction which Society finds it convenient to draw between illness and wickedness.

Despite the great complexity of the neurochemical mechanisms involved in the regulation and control of behaviour *etc.*, many behavioural phenomena can be broadly understood in terms of the undue dominance of either excitatory or inhibitory neurotransmitter functions, and/or impaired regulation of balance between these in response to potentially stressful sensory inputs. Some of the relationships are listed in Figure 9. The behavioural effects of chemically induced neurological imbalances are no doubt modulated by genetically and socially determined aspects of an individual's personality, so considerable variations in individual responses are to be expected: as for example, the varying effects of ethanol previously mentioned. Even laboratory rats carefully bred for uniformity show marked individual differences in their behavioural responses to a neurotoxin such as lead under standardized conditions. I find this rather reassuring.

Figure 9 *Neurochemistry and behaviour*

Excitatory neurotransmitter functions dominant	⟶	Hyperactivity (hypoinhibition) Restlessness Poor impulse control Mania Euphoria Insomnia Epilepsy
Inhibitory neurotransmitter functions dominant	⟶	Hypoactivity (hyperinhibition) Lethargy Mental depression
Impaired homeostatic regulation of excitatory–inhibitory balance (negative feedback)	⟶	Anxiety neurosis Lowered threshold of stress Manic-depressive psychosis

D. Environmental Chemical Factors in Delinquency and Crime.—Conventionally, antisocial phenomena are still presumed to have social causation, even though attempts to abate these by social approaches (*e.g.* 'softer' prisons, 'harder' prisons,

[80] M. H. Sheard in 'Neurobiology of the Trace Elements', ed. I. E. Dreosti and R. M. Smith, Vol. 2, Humana Press, Clifton, New Jersey, U.S.A., p. 275.

'short sharp shocks') have proved almost totally unsuccessful.[81] The idea that an environmental neurotoxin such as lead might be a significant factor in promoting criminal behaviour was first mooted by Stöfen,[82] and subsequently discussed in detail by Waldron and myself.[83] Inspection of Figure 9 indicates that several of the chemically induced behavioural disorders, particularly those associated with deficits of inhibitory function, are likely to predispose towards inadequately controlled or overtly anti-social behaviour. This is confirmed in practice. Thus, follow-up studies of children originally diagnosed as hyperactive have shown, in comparison with controls, a higher drop-out and expulsion rate from school, a higher rate of involvement in motor vehicle accidents, a greater tendency to be involved in alcohol and drug abuse, and a greater risk of coming before the Courts.[84,85] During a (voluntary!) visit to a modern U.K. prison for young male adults convicted of serious crimes, I was informed by the prison psychiatrist that nearly all the inmates were hyperactive. Hyperactivity, or as I prefer it, hypoinhibition, is a neurochemical dysfunction which can result from various causes, including brain injury caused by a birth trauma, meningitis and other diseases involving the brain, food allergies, including idiosyncratic hypersensitivity to the food colorant tartrazine and the preservative benzoate,[85] pre-natal alcoholism in the mother,[86] and lead.[87] (In none of these cases can a damaged individual be held in the slightest degree responsible for the disorder of brain neurochemistry that may predispose him of her to commit antisocial acts). In those apparently fairly common cases where lead intoxication is a factor, David *et al.* have shown by an elegant double blind crossover study with placebo that hyperactivity can be effectively abated by penicillamine, a chelating agent which promotes urinary excretion of stored lead.[87] Discoveries such as this suggest that for many offenders, penicillamine may be a more appropriate option than prison, as we suggested eleven years ago.[83] But dietary control may be more acceptable.[6]

Ability to excrete lead in the urine varies considerably between individuals, and we proposed,[83] with supporting evidence,[88] that some prison inmates may comprise a subgroup at abnormal risk of accumulating lead owing to subnormal ability to excrete this toxin. Australian[89] and Canadian[90] workers have since reported markedly elevated lead burdens in delinquent and antisocial children, and violent criminals, respectively.

In a recent study, aggressive classroom behaviour in a group of 80 American schoolchildren was found to relate significantly to lead and cadmium levels in their

[81] Home Office studies, 1984, reported in *The Times*, 6th March, 1985.
[82] D. Stöfen, *Städtehygiene*, 1971, **22**, 171.
[83] D. Bryce-Smith and H. A. Waldron, *Ecologist*, 1974, **4**, 367.
[84] G. Weiss, L. Hechtman, and T. Perlman, *Ann. General Psychiatry*, 1979, **36**, 657.
[85] J. Egger, C. M. Carter, P. J. Graham, D. Gumley, and J. F. Soothill, *Lancet*, 1985, i, 540.
[86] R. de Obaldia, O. A. Parsons, and Y. Yohman, *Int. J. Neurosci.*, 1983, **20**, 173.
[87] O. J. David, S. Hoffman, and G. Grad, in *ref.* 77*b*, p. 297.
[88] J. R. Barnes, P. E. Smith, and C. M. Drummond, *Arch. Environ. Health*, 1972, **25**, 450.
[89] V. P. Garnys, R. Freeman, and L. E. Smythe, 'Lead Burden of Sydney Schoolchildren', University of New South Wales, Kensington, N.S.W., 1979, p. 289.
[90] R. O. Pihl, F. R. Ervin, S. M. Deikel, and W. Strain, *Can. J. Psychiatry*, 1982, **27** (6), 533.

hair.[91] Clearly these are pilot studies which need to be repeated under more elaborate protocols before the implications of the findings can be accepted without reserve. Nevertheless, the results are consistent with what we already know about the relationship between lead and mental dysfunction, even though lead is certainly not the only important factor involved. Apart from cadmium, and perhaps zinc, chromium seems a good candidate for further study, and reports are now starting to emerge from America of success in abating antisocial behaviour among prison inmates by careful dietary control.[92] Disordered carbohydrate metabolism, especially hypoglycaemia, appears to be particularly common among violent offenders in the U.S.A., and behavioural control is reported to improve when this is corrected.[92] Chromium in the form of the 'glucose tolerance factor' (GTF) plays a vital—if little recognized—role in carbohydrate metabolism, and thence energy utilization by cells; but through ignorance of its essential functions it is largely removed during refining of sugar and flour.* Chromium deficiency is therefore likely to be particularly serious for persons on those diets rich in refined carbohydrates that are commonly provided in prisons and other institutions, since it would tend to exacerbate any existing disorders of carbohydrate metabolism. Chromium supplementation (200 μg Cr^{3+} day^{-1}) has been reported to correct hypoglycaemia,[93] and therefore merits a trial in suitable prison populations.

Finally, I come to some recent studies in this field by my collaborators and myself.

E. Vanadium and Manic–Depressive Psychosis

Levels of the following seventeen elements of actual or potential biological significance have been measured in serum, whole blood, and hair of manic depressive patients and matched controls: Al, Ba, Br, Ca, Cl, Cu, I, Mg, Mn, Mo, Na, Pb, Rb, S, Se, Ti, and V. The most consistent and statistically significant differences were found for vanadium. In manic patients, hair-vanadium levels were significantly elevated, and correlated significantly with the 'manic severity score': they fell towards 'control' levels on recovery.[94,95] Depressed patients had raised vanadium levels in whole blood and serum which tended to fall with recovery.[95] In preliminary studies, needing confirmation, procedures designed to control vanadium metabolism proved of therapeutic value in mania and depression.[96]

Vanadium is now regarded as a nutritionally essential element, though like most other such elements it can be toxic at levels substantially in excess of normal dietary intakes. Its inhibitory action on the enzyme Na-K ATPase, reversible by

* I am grateful to Mr. D. A. Bryce-Smith for pointing out that such 'refining' may constitute an offence under the Food Act, 1984, Section I.

[91] M. Marlowe, J. Stellern, C. Moon, and J. Errara, *Aggressive Behav.*, 1985, **11**, 41.

[92] A. G. Schauss, *Int. Clin. Nutr. Rev.*, 1984, **4** (4), 172.

[93] R. Anderson, M. M. Polansky, N. A. Bryden, E. E. Roginski, W. Mertz, and W. Glinsmann, *Metabolism*, 1984, **32** (9), 894.

[94] G. J. Naylor, A. H. W. Smith, N. I. Ward, and D. Bryce-Smith, *Biol. Psychiatry*, 1984, **19** (5), 759.

[95] G. J. Naylor, A. H. W. Smith, N. I. Ward, and D. Bryce-Smith, *Psychol. Med.*, 1984, **14**, 767.

[96] G. J. Naylor and A. H. W. Smith, *IRCS Medical Science*, 1981, **8**, 446.

noradrenaline,[97] appears to play a part in regulating the transport of sodium ions across biological membranes, and it may also be involved in the oxidative catabolism of serotonin, dopamine, and other neurotransmitters.[98] Two independent groups have observed significantly low tissue vanadium levels in multiple sclerosis patients.[99,100] Grounds therefore exist for regarding vanadium as potentially a neurologically important element. For further information on the biological activity of vanadium, see references 60 and 95.

F. Zinc and *Anorexia Nervosa*.—This 'slimmers disease' now seriously affects about 10 000 patients in the U.K., mostly girls, and is conventionally viewed as of psychosocial or sexual origins—'all in the mind', 'defective body image', 'middle class values'. Even food is seen to have sexual symbolism in psychiatry.[101] But psychiatric treatment based on these theories is notoriously ineffective and the condition is sometimes fatal.[101] In contrast, we have been able to develop an effective treatment based on the recognition that although *anorexia nervosa* may involve contributions from certain social factors, the predominant factor is usually chemical—zinc deficiency.[75,102] We do not doubt that the initial reduction in food intake results mainly from social factors such as the pervasive association of thinness with sexual attractiveness. However, a point is liable to be reached at which starvation, as with other stresses, paradoxically causes increased loss of zinc in the urine, thereby exacerbating the effects of reduced intake. As the zinc status declines, impairment of the zinc-dependent senses of taste and smell can be expected to reduce further the desire for food.* Mental depression, a known symptom of zinc deficiency,[103] makes a bad situation worse. We reasoned that the vicious circle would be broken by providing extra zinc: the other inevitable dietary deficiencies would normally be automatically remedied as soon as the patients started eating normally and their mental depression abated. This new approach has proved gratifyingly successful in the hands of my medical collaborators, Drs. R. I. D. Simpson and D. Latto. *Anorexia nervosa* together with various other neurotic, compulsive, or depressive mental states, now appears to be easily curable by provision of 15—150 mg Zn day^{-1} (66—660 mg $ZnSO_4.7H_2O$) in the majority of cases where zinc deficiency is diagnosed as a factor by use of the 'taste test'.* Improvement is often apparent within days or sometimes hours even in patients where the illness has been of long standing.

Our published reports[75,102] have stimulated an extensive correspondence with

* In view of the unreliability of blood zinc as an index of an individual's zinc status,[103] we have developed a 'taste test' which appears to be a sensitive indicator of zinc deficiency, and is based on the taste reaction to 0.1% $ZnSO_4.7H_2O$. If the solution appears tasteless, a positive response to zinc supplementation can be expected.[102]

[97] E. E. Quist and L. E. Hokin, *Biochem. Biophys. Acta*, 1978, **213**, 741.
[98] G. M. Martin, E. P. Benditt, and N. Eriksen, *Nature*, 1960, **186**, 884.
[99] D. E. Ryan, J. Holzbecher, and D. C. Stuart, *Clin. Chem.*, 1978, **24**, 1996.
[100] N. I. Ward, D. Bryce-Smith, M. Minski, and W. B. Matthews, *Biol. Trace Element Res.*, 1985, **7**, 153.
[101] A. H. Crisp, *Br. Med. J.*, 1983, **287**, 855.
[102] D. Bryce-Smith and R. I. D. Simpson, *Lancet*, 1984, ii, 1162.
[103] P. J. Aggett and J. T. Harries, *Arch. Dis. Child.*, 1979, **54**, 909.

doctors, and their patients and patients' relatives in the U.K. and abroad, together with articles in the press and radio and television programmes. Although it has not as yet proved possible to organize a controlled clinical trial, up to the time of writing, 12 months after our first report in the *Lancet*,[75] only one case of *anorexia nervosa* that failed to respond to zinc has been reported to us. Moreover, Dinsmore *et al.* have recently reported that patients with *anorexia nervosa* have an abnormality of zinc metabolism consistent with malabsorption from the gut.[104] Such individuals would clearly be at heightened risk of developing a pathological state of zinc deficiency if they embark on a 'slimming' diet.

The example of *anorexia nervosa* nicely illustrates the interaction of social and chemical influences on behaviour discussed earlier, though the chemical influence—zinc deficiency—is evidently of dominant importance once a pathological state has developed. It is not surprising that previous psychiatric attempts to cure this illness have been so unsuccessful.[101]

The zinc deficiency in modern diets can probably be attributed to three modern agricultural practices: (1) the use of phosphate fertilizers which render zinc less readily taken up by growing plants;[105] (2) the failure to maintain the organic contents of many agricultural soils, which has a similar effect on zinc uptake;[105,106] and (3) the common failure to re-cycle zinc (and other nutritionally essential trace elements) to soils. Concerning (2), a Government survey has revealed that the organic content in much U.K. arable farmland has fallen to about 2—4%, in comparison with 10—20% for typical virgin grasslands.[107] Slowly renewing natural resources like soil (and oil for that matter) are being ruthlessly exploited for short-term economic profit, with little regard for longer term implications or adverse side effects, *e.g.* declining nutritional quality of food. *Anorexia nervosa* and other abnormal mental states would appear to be among the consequences.

G. Trace Elements and Pre-natal Development.—As previously emphasized, the foetal stage of brain development is very important, and factors which impair development of the foetal brain can and do have an impact on post-natal intelligence and behavioural characteristics; though much is dependent on the timing of such impairment and the degree of modulation by post-natal stimuli.[108] In a pilot study,[109] we found average five- to ten-fold elevations of cadmium and/or lead, and sometimes zinc deficiency, in the bones of stillborn infants, many of whom had serious malformations or maldevelopment of the CNS. These provocative findings led us to embark on a much more extensive investigation, now complete, of the possible roles of 37 biochemically active elements in human foetal

[104] W. W. Dinsmore, J. T. Allerdyce, D. McMaster, C. E. A. Adams, and A. H. G. Love, *Lancet*, 1985, i, 1042

[105] M. Sillanpää, 'Trace Elements in Soils and Agriculture', Food and Agriculture Organization of the United Nations, Rome, 1972, and references therein.

[106] 'Soil Erosion: Quiet Crisis in the World Economy', Worldwatch Institute, 1776 Massachusetts Ave., N.W., Washington D.C. 20036, U.S.A., 1984; see also *Chem. Eng. News*, 1984, (1 Oct.), p. 6.

[107] 'Modern Farming and the Soil', A.R.C./M.A.F.F., H.M.S.O., London, 1970, p. 38.

[108] J. Dobbing, *Am. J. Clin. Nutr.*, 1985, **41**, 477.

[109] D. Bryce-Smith, R. R. Deshpande, J. Hughes, and H. A. Waldron, *Lancet*, 1977, i, 1159.

development, using a cohort of 100 obstetrically normal births from Barnsley, Yorkshire. (This work has been carried out in collaboration with Drs. N. I. Ward and R. Watson: a full account is being prepared for publication.)

Although the levels of most of the 37 elements proved to be unrelated to foetal development, some remarkable and highly statistically significant dose-related relationships have been observed between the mean levels of cadmium, lead, and zinc in placenta, and both birthweight and head circumference. Since this latter is regarded as a measure of pre-natal brain development,[110] relates linearly to total brain DNA,[111] and in older infants (but not adults) shows associations with intelligence,[112,113] the findings are particularly relevant to the present theme, and are depicted in Figures 10—12. The relationship between birthweight and placental zinc is similar to that shown for head circumference in Figure 12. The positive associations with zinc, and the negative associations with its antagonist cadmium, suggest thresholds of effect, though there is no evidence for a threshold in the relationship between placental cadmium and birthweight (Figure 13). They are consistent with the findings in government surveys that the typical U.K. daily diet provides only about half of the 20 mg of zinc required by the pregnant woman:[27,74,75] vegetarian diets tend to provide even less zinc.[27] The negative associations with placental lead (Figure 10) extend throughout the whole of the studied population, and show a remarkably regular dose–effect relationship. Similar associations are found also for birthweight. (It is instructive to compare Figure 2 with Figure 10). Interestingly, American workers have recently reported negative correlations between lead levels in umbilical cord blood and various measures of postnatal mental development.[32,114] Of all environmental pollutants so far identified, the neurotoxin lead is evidently the most serious and widespread in its subtle and insidious impact on man. There now appears to be no observable threshold for its toxic effects on the development and function of the foetal and child brain. The adult brain is less sensitive to lead, though the elevated levels deemed acceptable in U.K. industrial workers are undoubtedly liable to produce adverse mental effects, *e.g.* increased tension, anger, and depression, and impaired memory.[115–117] But for adults there is no apparent threshold for the highly significant positive association between blood-lead and blood pressure.[118–120]

[110] R. S. Illingworth, 'The Normal Child', 8th Edn., Churchill Livingstone, London, 1983.
[111] M. Winick and P. Rosso, *J. Pediatr.*, 1969, **74**, 774.
[112] M. B. Stoch and P. M. Smythe, *Arch. Dis. Child.*, 1963, **38**, 546.
[113] K. B. Nelson and J. Deutschberger, *Dev. Med. Child. Neurol.*, 1970, **12**, 487.
[114] D. C. Bellinger, H. L. Needleman, A. Leviton, C. Waternaux, M. B. Rabinowitz, and M. L. Nichols, *Neurobehav. Toxicol. Teratol.*, 1984, **6** (5), 387.
[115] *Ref.* 27, pp. 74 *et seq.*
[116] E. L. Baker, R. G. Feldman, R. A. White, J. P. Harley, C. A. Niles, G. E. Dinse, and C. S. Berkey, *Br. J. Ind. Med.*, 1984, **41** (3), 352.
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[118] W. R. Harlan, J. R. Landis, R. L. Schmouder, N. G. Goldstein, and L. C. Harlan, *J. Am. Med. Assoc.*, 1985, **253**, 530.
[119] J. L. Pirkle, J. Schwarz, J. R. Landis, and W. A. Harlan, *Aus. J. Epidemiol.*, 1985, **121** (2), 246.
[120] D. G. Beevers, E. Erskine, M. Robertson, A. D. Beattie, B. C. Campbell, A. Goldberg, M. R. Moore, and V. M. Hawthorne, *Lancet*, 1976, ii, 1.

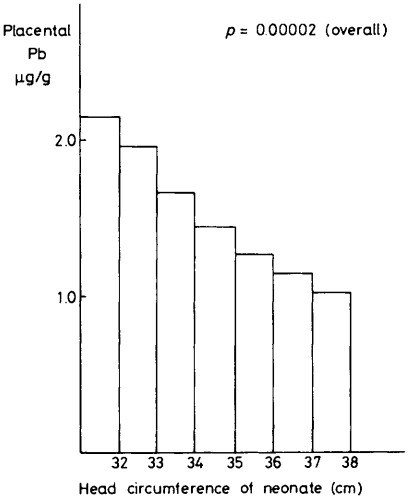

Figure 10 *Placental lead and head circumference*

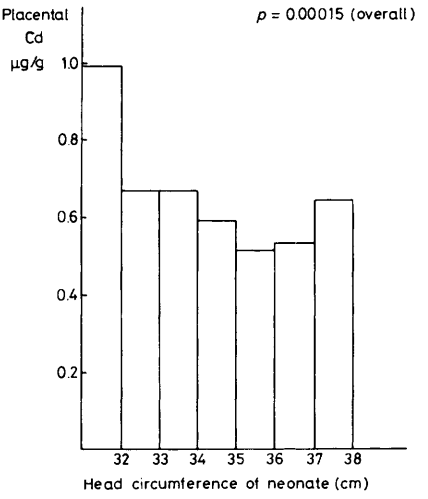

Figure 11 *Placental cadmium and head circumference*

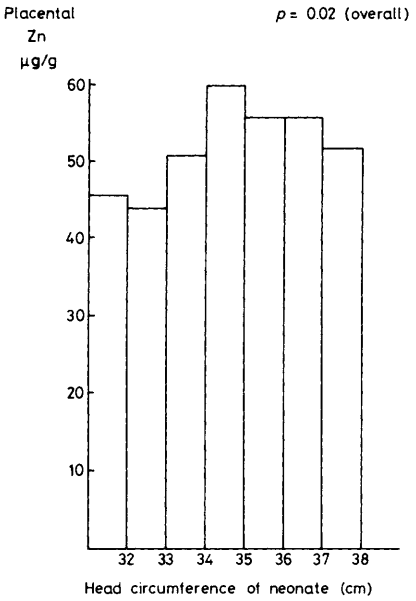

Figure 12 *Placental zinc and head circumference*

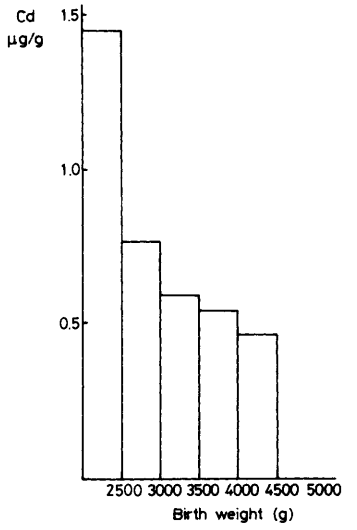

Figure 13 *Placental cadmium and birth weight*

Hypertension is one of the most important risk factors in death from cardiovascular disease, and death can, in a way, be regarded as the ultimate behavioural effect.

4 Conclusion

The main thesis can be simply stated. Changed brain chemistry can alter behaviour, and changed behaviour can alter brain chemistry: the interaction is two-way. It therefore follows that behaviour, cognition, social interactions, and other expressions of brain function are subject not only to the social environment but also to certain aspects of the chemical environment. The relevant chemical factors include (a) neurotoxic pollutants in general, of which lead is evidently now the most serious in its impact, (b) certain common nutrient deficiencies, particularly of zinc, and (c) neurotoxins of voluntary abuse, of which ethanol is still probably producing the most widespread social damage.

Environmental chemical influences on brain development and/or function tend to operate most strongly on the young and on the foetus; and some can even act on sperm before conception to produce behavioural effects on the eventual offspring. In comparison, direct social influences on behaviour *etc.* can only operate after birth.

Unfortunately, there is an influential and deeply entrenched body of belief in the fields of politics, sociology, and psychiatry that social phenomena, and the effects on individual behaviour *etc.* that give rise to these, result largely if not wholly from social factors. It is now evident that this neglect of the chemical dimension to the way we think and act may be responsible for much of the present failure fully to understand, treat, or prevent such varied behavioural phenomena as *anorexia nervosa*, hyperactivity, criminality, and educational underachievement. The environmental chemical approach is not merely an interesting hypothesis, but is in practice already providing effective new treatments which appear to go to the neurochemical roots of such normally intractable problems. Thus the beneficial changes in mood, mental attitudes, and personal relationships that normally occur rapidly when a sufferer from *anorexia nervosa* is supplied with small amounts of zinc sulphate are all the more striking because they can occur in the absence of any counselling or other conventional psychiatric treatment.

The prospect for further similar reforms in our attitudes towards the causation and treatment of behavioural and social problems is extremely promising, for example in the field of criminology where it is already well known that prisons are frequently used as dumping grounds for mental defectives and the mentally ill.[121] Progress will, however, require major reassessment of many cherished but over-simplistic social and political doctrines, abandonment of the present restrictive 'two cultures' approach to behavioural problems, and a degree of co-operation between workers in the physical, medical, and social sciences that has hitherto been conspicuously absent.

Acknowledgements. I would like to express my thanks for the invaluable help

[121] Anon., *Br. Med. J.*, 1985, **290**, 447.

received from a number of colleagues over the years, particularly Drs. R. I. D. Simpson, R. Stephens, and N. I. Ward. Dr. Ward was responsible for all the analytical work involved in the study of vanadium and manic depressive psychosis, and in the work on trace elements in relation to foetal development. I am also grateful for the financial support for our trace element work received from the Cooper Trust, Esso Petroleum, Foresight, the KIB Foundation, Sanity, The Shave Trust, the Trustees of the Greene Charitable Settlement, and Birthright (Royal College of Obstetricians and Gynaecologists).