the relationship between local cerebral glucose utilization and local cerebral blood flow in the rat brain. *J Cereb Blood Flow Metab* 1985;5:58–64.

25. Fabre LF, Farmer RW, Roach MK, Fritchie GE, McIsaac WM. Biochemical and metabolic aspects of alcoholism. *Ann NY Acad Sci* 1973; 215:346–355.

26. Erickson CK. Regional distribution of ethanol in rat brain. *Life Sci* 1976; 19:1439–1446.

27. Karwacka H. Ultrastructural and biochemical studies of the brain and

other organs in rats after chronic ethanol administration. *Exp Path* 1980; 18:118–126.

28. Harper C, Kril J, Daly J. Does a "moderate" alcohol intake damage the brain? *J Neurol Neurosurg Psychiat* 1988;51:909–913.

29. Mander AJ, Weppner GJ, Chick JD, Morton JJ, Best JJK. An NMR study of cerebral oedema and its biological correlates during withdrawal from alcohol. *Alc Alcoholism* 1988;23:97–102.

EDITORIAL

From the Cradle to the Grave: Alcohol and Its Effects Upon the Brain

Alcohol alters behavior, disturbs cognition, impairs consciousness and, at higher levels, causes death. These effects of alcohol, mediated via the central nervous system, can be produced by acute or short-term administration. Alcohol is also an addictive drug, and chronic abuse causes irreversible cellular damage to the major parenchymal organs, including the brain. We do not know why alcohol, or indeed any drug, is addictive. What significance mood alterations or reward mechanisms have in contributing to, or causing, addiction remains unclear. Consideration must also be given as to whether there is a genetic basis for preference for ethanol or other drugs of abuse. Similarly, is there a genetic basis for tolerance or nontolerance to ethanol and does this go hand in hand with individual or tissue vulnerability to ethanol?

Alcohol use is inextricably woven into the fabric of human life and by its very complexity remains a challenge that is still to be elucidated. We can be certain, however, that in its destructive capacity it presents both a pervasive and perverse challenge to humanity and has done so throughout our history. The manifest of destructive effects is well recorded in our literature and includes social upheaval, even cultural destruction. It has been assessed in socio-economic

and behavioral terms and evaluated as having immense cost to society. At the individual level, its effects are easily seen in the streets, not only in the impoverished sectors of our cities, but certainly amongst our wandering homeless. Less publicly evident are retardates rocking in the corners of developmental disability units, chronically impaired dements in our veterans homes and the memory impaired cognitively disordered caught in the revolving doors that represent our therapeutically bereft mental institutions and rehabilitation units.

Many options exist for experimental studies of the problems associated with the use and abuse of alcohol and the mechanisms by which it produces its effects. Radiotracer studies offer a means of examining the effects of ethanol on neuronal tissue at the molecular level both in vitro and in vivo. The goal of such studies is to reveal the molecular mechanisms which are involved. The assumption is that there will be an evident relationship between the induced functional depression of the nervous system and the behavioral and cognitive consequences, including addiction. A further goal is to achieve appropriate therapeutic interventions, pharmacological or otherwise, based upon a rational understanding of the underlying cellular and molecular mechanisms. Optimally, it appears that a combination of behavioral and biological approaches may be the most elegant, if methods can be devised

which are experimentally robust. Within the setting of experimental imaging paradigms, these approaches may be examined in a number of different ways to include, for example, subjective groups distinguished by preference of choice for the drug or induced subject mood effect (*1–3*). In a recent critical analysis regarding prenatal alcohol-induced brain damage, West et al. point out that . . . "researchers should choose well-defined dependent measures that are derived from models of brain function based on modern concepts of cognitive neuroscience." They further emphasize the need for the use of neuropsychological tests that serve as a basis for determining structure-function relationships (*4*).

How ethanol affects the brain is a complex problem to which at present we have only incomplete answers. In this issue of the *Journal*, Grünwald et al. report their findings on the acute and chronic effects of orally administered ethanol on regional brain glucose metabolism in rats using the quantitative autoradiographic 2-deoxyglucose (2DG) method (*5*). They demonstrate that acute and acute plus chronic administration of ethanol significantly depress metabolism in multiple brain regions. The most pronounced effects were found to occur in regions of the auditory system (*6,7*). However, chronic administration alone was not sufficient to produce a significant or conclusive effect. They relate their findings to ethanol activation of the inhibitory

GABAergic neurotransmitter system. They also refer to the possibility that the effects of alcohol on glucose metabolism may be mediated by a direct receptor effect of gamma-hydroxybutyrate (GHB) (8,9). GHB has been used successfully in the treatment of alcohol withdrawal symptoms and Haller et al. report reduction in glucose metabolism in auditory regions of cats as an effect of GHB (8). In using an oral administration of the drug, Grünwald et al. methodologically avoid the effects of acid-base disturbances which can depress cerebral metabolism. By employing the 2DG autoradiographic approach, which requires an equilibration period for metabolic measurement, acute effects of alcohol that may produce regional heterogeneity in blood flow are also eliminated. The reduced regional cerebral metabolism they observed was obtained with plasma alcohol levels on the order of 1.7–1.8 g/liter for the acute load and 2.5–2.6 g/liter for the acute plus chronic. In the chronic animal group, plasma values were low, approximating 0.10–0.14 g/liter. It is of interest that a progressive effect in reduction of regional glucose metabolism was not evident, even when plasma levels were increased approximately 50% between the acute and acute plus chronic level. Nor was a significant change in regional effect seen in the group with high plasma levels, with the exception of the temporal cortex (at the $p = <0.05$ level). Low metabolism was also seen in the temporal cortex in the chronically administered alcohol group alone, but not at a statistically significant level. Hippocampal metabolism, however, did fall significantly at the higher plasma levels. This finding is in contrast to that of Haller et al., in which GHB did not produce a major change in hippocampal glucose metabolism (8). Since cognitive disturbances in chronic alcoholics include intractable memory loss, these findings deserve consideration. They may also be related to other known effects of alcohol on the hippocampus, including effects at the NMDA

receptor which produces changes in calcium ion channel function (10). In short, it does not appear that simple analysis of varying drug plasma levels versus induced metabolic or blood flow changes will be a fruitful approach to determining mechanisms for the action of ethanol on the brain. That is not to say that animal studies cannot have inferential value per se in directing the design or planning of human experimental studies, but they are likely to be of more value when performed in association with behavioral correlates (4).

It is important to consider plasma alcohol levels in any attempt to relate these findings to human subjects and possible experimental approaches that may be achieved with positron emission tomography (PET). In these animal experiments, regional effects are seen at high plasma values. Equivalent levels in humans in the range of 170–260 mg/dl produce significant inebriation and are capable of inducing coma depending upon rate of administration and uptake, body habitus and other factors. Levels approaching these values have been studied in humans with PET but were used to evaluate blood flow changes (11). In other PET studies, de Wit et al. show that global reduction also occurs in cerebral glucose metabolism with lower plasma alcohol levels (1). However, in neither study were regional effects demonstrated to be comparable to those of the animal studies. Regional effects were found in a subsequent study with PET by Volkow et al., in which metabolism was reduced in the inferior parietal region but the subjects studied were chronic alcoholics (12).

Neither the animal studies of Grünwald et al. nor the previously mentioned preliminary human studies appear to suggest that lower plasma levels of ethanol given acutely necessarily act by selective regional effects on brain glucose metabolism. However, smaller regional metabolic effects, if they do occur at lower plasma ethanol levels, may be beyond the resolving capabilities of current PET systems. A question

then to be entertained is what is the magnitude of any regional effect induced by ethanol? The corollary question—"and can we detect it?"—is inherently involved with the problem of small signal amplitudes and their detection within imaging studies. We can perhaps gain part of the answer from the animal studies which show that, compared to controls, reduction of metabolism in the auditory cortex was on the order of 20%–25%. Higher levels of reduction in metabolism approaching 50% were seen in smaller regions and various mid-brain nuclei. The latter in humans are below the limits of current in vivo resolution and thus presents a problem of partial volume effect for quantitative studies. It appears that with PET approaches we face the "small signal" problem and consequently will be unlikely to directly measure regional metabolic changes quantitatively (13). This implies that if metabolic changes are to be pursued methods will be required that examine the problem from the perspective of signal averaging using challenge studies and change-distribution subtraction imaging. This approach has been elegantly developed for ^{15}O-water blood flow studies and applied successfully in multiple cognitive studies demonstrating neural system pathways in the brain (14,15). The feasibility of this approach for metabolic studies with PET using [18]F-2FDG, challenge tasks, image subtraction and change-distribution images with multi-modality integration has also been demonstrated (16).

In addition to metabolic measurements, current PET techniques that include new radioligands, new experimental approaches and image data analysis methods can provide alternatives to examine other mechanisms by which ethanol depresses neural function and induces cognitive change. In an extensive review, Deitrich et al. consider the molecular mechanisms that may be involved. These include the effects of alcohol on membrane fluidity, neuronal electrical activity and synaptic transmission, voltage or second messenger

gated ion channels, neurotransmitters and neuromodulators, protein phosphorylation and neuropeptides including opioids (17). This list alone indicates that alcohol is ubiquitous in its effects on the nervous system. Nonetheless, it does appear that ethanol has a specificity of action for neurons sensitive to its effects as well as a specificity based on genetic characteristics that render animals tolerant or nontolerant to ethanol (17).

Selective insights are clearly necessary if an erudite choice is to be made in regard to which mechanisms, which molecular pathways or which neuronal systems can be fruitfully studied with imaging methods. To this end and in regard to mechanisms of action and neuronal vulnerability to the effects of ethanol, consideration must be given to the fetal alcohol syndrome (FAS) and its companion, fetal alcohol effects (FAE). Recently described in Science as the unseen epidemic and a current leading cause of mental retardation, this syndrome was defined less than 25 yr ago and its name first coined in 1973 (18–21). The syndrome results from maternal alcohol consumption during pregnancy and the consequent prenatal exposure to alcohol. It is characterized by facial dysmorphogenesis, ocular abnormalities and central nervous system (CNS) effects that include microcephaly and retardation. Delayed development, hyperactivity, fine and gross motor incoordinations and associated behavioral problems also occur (22). Characterization of the syndrome continues as focused research efforts are directed at the multiple issues that are components of the problem, including alcohol teratogenesis and neurobiological and neurobehavioral sequelae (23,24). Alcohol intake during pregnancy— the amounts, the frequency, the timing—sufficient to produce the syndrome still remains to be clarified and gives rise to the consideration by West et al. that perhaps no amount of alcohol during pregnancy can be considered safe (4).

Recent work from in vivo animal studies by Clarren et al., however, reveals a possible underlying neurochemical mechanism to the effects of ethanol involving the dopaminergic system (25). They demonstrate, using gravid macaques, that changes occur in striatal dopamine concentration and dopamine receptor density as a result of fetal alcohol exposure. They were able to obtain an effect from a once weekly exposure to ethanol, thus producing maternal plasma ethanol levels at and above 140 mg/dl. The intermittent alcohol consumption pattern corresponds to that occurring most frequently in American women, and the intoxicating plasma level is achievable from four to six standard drinks in an average sized person (26). Apart from ocular malformations and ultrastructure changes in the caudate nuclei, neurochemical changes are evident without gross morphological or neurobiological changes and structural brain imaging studies appear normal (25). In many animal and in vitro studies, the concentrations of alcohol used to induce an effect are very high. Alcohol levels often cannot be related to in vivo plasma levels or consumption patterns in human subjects; indeed, many effects were derived at levels that would be lethal. This does not imply that such studies are of no value but does underscore the elegance of the design and the merit of the findings by Clarren et al. The changes they observed in the striatal dopaminergic system were not, however, straightforward, and although in animals exposed throughout pregnancy there was an increase in both dopamine concentration and receptor density, there was also a decrease in dopamine concentrations in a cohort of animals given increasing ethanol levels started after the fifth week of gestation. In parallel studies, Clarren et al. show that exposure to ethanol early in pregnancy produces more profound cognitive dysfunction than that occurring later in pregnancy, including much greater alcohol exposure levels (27). Thus, we have an animal model which appears closely analogous to the human FAS and FAE syndrome with evidence to suggest that neurochemical and neurocognitive changes may be seen without significant morphological changes. An implication is that human infants cannot be considered unaffected if exposed to alcohol even in the absence of evident structural brain changes and morphological effects (4).

Interest in the dopaminergic system as a potential target or pathway for the effects of alcohol is not new. Experiments in rats suggest that alcohol increases neuronal activity in the ventral tegmental area (VTA) and substantia nigra or potentiates the action of dopamine, the primary transmitter in projections of VTA to the mesolimbic and mesocortical areas (28). The effects are hypothesized as being due to ethanol suppression of GABAergic neurons that tonically inhibit firing of dopamine containing cells (17). A behavioral link is suggested inasmuch as ethanol activation of the mesolimbic and/or mesocortical dopamine systems may relate to endogenous reward mechanisms. Preference for alcohol and hence activation of dopaminergic systems may possibly be seen in persons at risk for alcoholism (17). From their neurochemical analyses, Clarren et al. were unable to find changes in dopamine concentrations outside the striatum, nor changes in epinephrine, norepinephrine or serotonin concentrations. Other studies, however, have shown changes in all of these neurotransmitters, and changes measured from ligand binding have been found in the GABA receptor channel system at the benzodiazepine receptors and in the serotonin receptor system (17). From an imaging perspective, the dopaminergic system has particular attraction since extensive prior work has provided both pre- and postsynaptic neurotransmitters with improved D1 and D2 receptor ligands suitable for use with PET (29,30). This allows for carefully planned studies, to include neurocognitive and behavioral parameters, in a variety of experimental paradigms. Preliminary work in this direction has been initiated

(Wegelius U, *personal communication*). In regard to ethanol and its effects on other neuronal systems, approaches using benzodiazepines and opioids are currently available that allow for imaging studies of the interactions of ethanol on neurotransmitters/neuromodulators and the neuropeptides (*31,32*). There is a great deal of evidence from both behavioral and neurochemical studies which indicates that alcohol enhances chloride-ion conductance through the $GABA_A$ channel and that this mechanism is involved in alcohol intoxication (*33–37*). It has been shown that benzodiazepine inverse agonists will diminish alcohol-induced ataxia, anesthesia and punished responding (*17*). The $GABA_A$ chloride channel consists of three subunits termed α, β and γ to which GABA, barbiturates and benzodiazepines respectively bind. Antagonists to benzodiazepines block the enhancing effects of GABA but do not reduce basal conductance of the chloride ion (*38*). Recent work with DNA cloning and sequencing studies indicates that the $GABA_A$ chloride channel has multiple protein subunits, not merely three as previously considered. This work, in addition to electrophysiology studies in the hippocampus, helps explain some of the conflicting evidence in regard to ethanol and the $GABA_A$ chloride channel. The consideration is that the receptor is heterogeneous in its structure and is also expressed as regional differences in receptor action in the CNS. Preliminary studies by Litton et al. using the benzodiazepine antagonist Ro 15-1788 and PET lend support to this consideration (*39*). In a controlled study of young drug-free alcoholics, they demonstrated a reduction in B max in the cerebellum and frontal cortex and no change in K_D in comparison to controls. This regional reduction in benzodiazepine receptor concentration in young alcoholics is worthy of reproduction and further consideration of its implications in regard to the effects of alcohol. An interesting possibility also exists for imaging studies directed at the effects of ethanol on protein phosphorylation and synaptic transmission involving long-term potentiation (LTP).

Protein phosphorylation occurs by activation of protein kinases, some of which are cAMP-dependent. Neurotransmitters, including dopamine, can initiate this process by action at their cell surface receptors and associated G-proteins. Binding of the adenylate cyclase enzyme with the coupling G-protein in turn activates cAMP. In vitro studies of ethanol on striatal tissue have shown activation of adenylate cyclase and increased dopamine stimulated enzyme concentrations (*40*). Ethanol also appears to disrupt inhibition of adenylate cyclase activity by adenosine derivatives (*41*). Unfortunately, cAMP levels are reduced when ethanol is given in vivo and the effects on adenylate cyclase thus appear paradoxical (*17*). Where and how ethanol affects protein phosphorylation (by changes in membrane fluidity, at the receptor or G-protein or at subsequent steps) remains uncertain. Radiolabeled forskalin, which binds to high affinity sites of adenylate cyclase in the Gs protein coupling step is a possible probe for imaging studies of the second messenger system (*42*).

Ethanol-induced memory impairment appears to be a result of its effects upon hippocampal neurons (*43*). Neuronal systems in the hippocampus are known to be involved in long-term storage of explicit memories and behavioral learning and also undergo prolonged enhancement of synaptic efficacy (LTP) following short bursts of high frequency stimulation. Mediated by the excitatory transmitter L-glutamate, LTP is induced following activation of the NMDA receptor with consequent calcium ion influx into the postsynaptic cell and activation of protein kinases. In turn, the protein kinase release is believed to activate retrograde synaptic messengers and enhance transmitter release by action on the presynaptic neuron terminals. New insight into the neurobiological process and behavioral correlates of this system appears likely with recently developed mutant mice deficient in nonreceptor tryosine kinase, in which impaired growth of hippocampal neurons, LTP blunting and deficiencies in spatial learning have been shown to occur (*44*). Where ethanol acts to disrupt the process remains uncertain. Recent reports by Farr et al. indicate that prenatal alcohol exposure, with peak maternal blood alcohol levels below 59 mg/dl, diminishes glutamate binding and alters long-term potentiation in the hippocampus of rats (*45*). Inasmuch as ethanol is an antagonist to the NMDA receptor, other antagonists, such as MK-801 and its analogs, and phencyclidine and its derivatives, which have been labeled for imaging studies, may prove useful in elucidating this aspect of the mechanism of ethanol effects. Initial studies with these agents, however, were not successful principally because of the high lipophilicity associated with marked nonspecific binding (*46*). The approach has not been abandoned and continuing consideration is being given to new analogs, challenge approaches and new image analysis and modeling methods (*47,48*). Approaches using cognitive activation such as conditioned eye blink paradigms and other selective forms of memory and learning challenges, may prove useful in radioligand studies and still offer an opportunity for ethanol effects to be measured using blood flow or metabolic imaging studies.

Blood flow and metabolic measurements using PET can play a significant role in studies on the mechanisms of ethanol effects. Behavior, mood and cognitive functions may be used as experimental variables in various designs of ethanol intake. Relevant cognitive studies, already explored using PET, include attention and vigilance, speech and language, learning and memory, and various subcategories such as facial recognition (*49–54*). Executive control functioning tasks, such as the Wisconsin Card Sorting Test and its variations, and studies of motor con-

trol can also be included. At the molecular level, receptor and neurotransmitter mechanisms can be probed with current imaging techniques aimed at GABAergic mechanisms, the dopaminergic system and potentially the glutamate-NMDA system. The direction such studies may take can be guided by genetic and mutant animal models and complemented by cloning and sequencing studies to identify normal structural variations or mutational changes in receptors. The latter may prove of value in defining regional and functional receptor heterogeneity, with the consideration that this may account for differing regional effects of ethanol, including tissue vulnerability in regions such as the hippocampus, cerebellum and frontal cortex. Neurotransmitter reuptake mechanisms may also prove relevant in studies of ethanol effects, and recent sequencing studies of the glutamate transporter protein are of particular interest (55–57). As with other neurotransmitter transporter proteins, differing amino acid sequences have been found, indicating there are multiple forms of the glutamate transporter. Diminished glutamate binding in the hippocampus from relatively low doses of ethanol, as noted by Farr et al., may be a consequence of transporter protein differences (46). A final consideration is that hippocampal neuronal damage may ensue from the effects of glutamate as an excitatory neurotransmitter.

It is clear that ethanol affects multiple neuronal systems and induces various physiological and neurochemical changes. The complexity of its ubiquitous effects also affords opportunity for carefully planned and selected imaging studies. Many choices now exist for such directed efforts using quantitative radiotracer techniques with autoradiography and PET. At issue are the important general questions as to whether we have sufficiently refined techniques and methods to obtain measurements of difference with adequate quantitative accuracy, the practicality of the methods for human studies and, fi-

nally, can we understand our findings in terms appropriately related to current concepts regarding the neurobiological, neurochemical and cognitive relationships of the system or mechanism under study. Single-system probes and data interpretation, however, must be approached cautiously in light of abundant data demonstrating the diffuse and varying effects of ethanol on the CNS. Dose-effect relationships indicate a "biphasic" action to ethanol whereby low doses are stimulating and high doses depressive. The relationship of this effect to tissue and neurochemical system vulnerability remains unclear. The findings of Clarren et al. of inverse striatal dopamine concentrations are possibly one such example (25). Similarly, in regard to the GABAergic system, an activating response to ethanol by this inhibitory system is hypothesized for diminished glucose metabolism and a lessening of the inhibitory response by GABA neurons proposed to account for dopamine increase in the VTA-striatal pathways. Change in a single parameter such as the Bmax for receptor concentration must be viewed cautiously before implications of its functional significance are reliable. This and similar concerns are emphasized by June et al. and by Dewey et al. in their considerations of functional linking of the various receptor-transmitter systems in differing syndromes (58,59). These concerns serve to emphasize the need for hypothesis-driven studies derived from a priori data and models that can serve to relate molecular mechanisms and neurocognitive function (4). Clearly, there are many choices and differing directions in which we can proceed with relevant imaging studies. Potentially, the most fruitful direction for imaging studies on ethanol effects may be in studies of adolescent and adult survivors of FAS/FAE, where extensive ongoing work is developing links between neuronal damage, developmental, behavioral and cognitive impairment and neurochemical disturbances. The intimacy of the relationship between behavior, cognition and

molecular mechanisms of neuronal function is a perspective worth preserving (60). Rapid advances are being made in these aspects of neural science and will prove advantageous in imaging studies of ethanol and its effects upon the brain.

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REFERENCES

1. de Wit H, Metz J, Wagner N, Cooper M. Behavioral and subjective effects of ethanol: relationship to cerebral metabolism using PET. Alcohol Clin Exp Res 1990;14:482–489.
2. de Wit H, Metz J, Wagner N, Cooper M. Effects of diazepam on cerebral metabolism and mood in normal volunteers. Neuropsychopharmacology 1991;5:33–41.
3. de Wit H, Metz J, Cooper M. Studying psychoactive drugs with positron emission tomography: relationships between mood and metabolic rate. Neurobiological Approaches to Brain-Behavior Interation: Natl Inst Drug Abuse Res Monogr Ser 1992;124:117–134.
4. West JR, Goodlett CR, Brandt JP. New approaches to research on the long-term consequences of prenatal exposure to alcohol. Alcohol Clin Exp Res 1990;14:684–689.
5. Grünwald F, Schröck H, Biersack H-J, Kuschinsky W. Changes in local cerebral glucose utilization in the awake rat during acute and chronic administration of ethanol. J Nucl Med 1993;34:793–798.
6. Church MW, Holloway JA. Effects of prenatal ethanol exposure on the postnatal development of the brainstem auditory evoked potential in the rat. Alcohol Clin Exp Res 1984;8:258–265.
7. Church MW, Gerkin KP. Hearing disorders in children with fetal alcohol syndrome: findings from case reports. Pediatrics 1988;82:147–154.
8. Haller C, Mende M, Schuier F, Schuh R, Schröck H, Kuschinsky W. Effect of gamma-hydroxybutyrate on local and global glucose metabolism in the anesthetized cat brain. J Cereb Blood Flow Metab 1990;10:493–498.
9. Kuschinsky W, Suda S, Sokoloff L. Influence of γ-hydroxybutyrate on the relationship between local cerebral glucose utilization and local cerebral blood flow in the rat brain. J Cereb Blood Flow Metab 1985;5:58–64.
10. Jahr CR. High probability opening of NMDA receptor channels by L-glutamate. Science 1992;255:470–472.
11. Volkow ND, Mullani N, Gould L, et al. Effects of acute alcohol intoxication on cerebral blood flow measured with PET. Psychiatry Res 1988;24:201–209.
12. Volkow ND, Hitzemann RH, Wolf AP, Fowler JS, Dewey SL, Wang GJ. Decreased metabolic activity in the brain of chronic alcoholics [Abstract]. J Cereb Blood Flow Metab 1991;11(suppl 2):5809.
13. Rottenberg DA. General introduction: pro-

ceedings of the PET data analysis workshop. *J Cereb Blood Flow Metab* 1991;11:A1–A2.

14. Fox PT, Mintun MA, Reiman EM, Raichle ME. Enhanced detection of focal brain responses using intersubject averaging and change-distribution analysis of subtracted PET images. *J Cereb Blood Flow Metab* 1988; 8:642–653.

15. Fox PT, Perlmutter JS, Raichle ME. A stereotactic method of anatomical localization for positron emission tomography. *J Comput Assist Tomogr* 1985;9:141–153.

16. Metz JT, Chen C-T, Jiang M, Chou J-S, Cooper M. Detection of physiological (PET) signals in individual subjects [Abstract]. *Soc Neurosci Abstr* 1992;18:865.

17. Deitrich RA, Dunwiddle TV, Harris RA, Erwin VG. Mechanism of action of ethanol: initial central nervous system actions. *Pharmacol Rev* 1989;41:489–537.

18. Holden C. Random samples. *Science* 1992; 258:739.

19. Lemoine P, Harousseau H, Borteyru JP, Menuet JC. Les enfants de partents alcooliques. Anomalies observees. A propos de 127 cas. *Ourst Med* 1968;21:476–492.

20. Jones KL, Smith DW. Recognition of the fetal alcohol syndrome in early infancy. *Lancet* 1973;2:999–1001.

21. Jones KL, Smith DW, Ulleland CN, Streissguth AP. Pattern of malformation in offspring of chronic alcoholic mothers. *Lancet* 1973;1: 1267–1271.

22. Conry J. Neuropsychological deficits in fetal alcohol syndrome and fetal alcohol effects. *Alcohol Clin Exp Res* 1990;14:650–655.

23. Streissguth AP. Prenatal alcohol-induced brain damage and long-term postnatal consequences: introduction to the symposium. *Alcohol Clin Exp Res* 1990;14:648–649.

24. Schenker S, Becker HC, Randall CL, Phillips DK, Baskin GS, Henderson GI. Fetal alcohol syndrome: current status of pathogenesis. *Alcohol Clin Exp Res* 1990;14:635–647.

25. Clarren SK, Astley SJ, Bowden DM, et al. Neuroanatomic and neurochemical abnormalities in non-human primate infants exposed to weekly doses of ethanol during gestation. *Alcohol Clin Exp Res* 1990;14:674–683.

26. Wilsnack SC, Klassen AD, Wilsnack RW. Drinking and reproductive dysfunction among women in a 1981 national survey. *Alcohol Clin Exp Res* 1984;8:451–458.

27. Clarren SK, Astley SJ, Bowden DM. Physical anomalies and development delays in non-human primate infants exposed to weekly doses of ethanol during gestation. *Teratology* 1988; 37:561–570.

28. Gesa GL, Muntoni F, Collu M, Vargiu L, Mereu G. Low dose of ethanol activate dopaminergic neurons in the ventral tegmental area. *Brain Res* 1985;348:201–203.

29. Mukherjee J, Luh KE, Yasillo N, et al. Dopamine D-2 receptors imaged by PET in cebus apella using [F-18]benzamide neuroleptic. *Eur J Pharmacol* 1990;175:363–364.

30. Mukherjee J, Yang Z-Y, Perry BD, Cooper M. High affinity and selective [F-18]fluorinated

derivatives of SCH 38548 as potential PET radiotracers for dopamine D-1 receptors. [Abstract] *J Nucl Med* 1992;33:829.

31. Carson RE, Channing MA, Blasberg RG, et al. Comparison of bolus and infusion methods for receptor quantitation: application to [^{18}F]cyclofoxy and positron emission tomography. *J Cereb Blood Flow Metab* 1993;13:24–42.

32. Frost JJ, Mayberg HS, Sadzot B, et al. Comparison of [^{11}C]diprenorphine and [^{11}C]carfentanil binding to opiate receptors in humans by positron emission tomography. *J Cereb Blood Flow Metab* 1990;10:484–492.

33. Hunt WA. The effect of ethanol on GABAergic transmission. *Neurosci Biobehav Rev* 1983;7:87–95.

34. Kulonen E. Ethanol and GABA. *Med Biol* 1983;61:147–167.

35. Aguayo LG. Ethanol potentiates the GABA$_A$-activated Cl current in mouse hippocampal and cortical neurons. *Eur J Pharmacol* 1990; 187:127–130.

36. Suzdak PD, Schwartz RD, Skolnick P, Paul SM. Ethanol stimulates γ-aminobutyric acid receptor-mediated chloride transport in rat brain synaptoneurosomes. *Proc Natl Acad Sci* 1986;83:4071–4075.

37. Suzdak PD, Glowa JR, Crawley JN, Schwartz RD, Skolnick P, Paul SM. A selective imidazobenzodiazepine antagonist of ethanol in the rat. *Science* 1986;234:1243–1247.

38. Kandel ER, Schwartz JH. Directly gated transmission at central synapses. In: Kandel ER, Schwarts JH, Jessell TM, eds. *Principles of neural science*, 3rd edition. New York: Elsevier Science Publishers; 1991:153–172.

39. Litton JE, Farde L, Neiman J, Halldin C, Sedvall G. PET of benzodiazapine receptors in alcoholics—equilibrium quantification [Abstract]. *J Cereb Blood Flow Metab* 1991; 2(suppl 2):S617.

40. Rabin RA, Molinoff PB. Activation of adenylate cyclase by ethanol in mouse striatal tissue. *J Pharmacol Exp Ther* 1981;216:129–134.

41. Bauche F, Bourdeaux-Jaubert AM, Giudicelli Y, Hordmann R. Ethanol alters the adenosine receptor-Ni-medicated adenylate cyclase inhibitory responses in rat brain cortex in vitro. *FEBS Lett* 1987;219:296–300.

42. Worley PF, Baraban JM, DeSouza ED, Snyder SH. Mapping second messenger systems in the brain: differential localizations of adenylate cyclase and protein kinase C. *Proc Natl Acad Sci USA* 1986;83:4053–4057.

43. Swartzwelder HS, Farr KL, Wilson WA, Savage DD. Prenatal exposure to ethanol decreases physiological plasticity in the hippocampus of the adult rat. *Alcohol* 1988;5:121–124.

44. Grant SGN, O'Dell TJ, Karl KA, Stein PL, Soriano P, Kandel ER. Impaired long-term potentiation, spatial learning, and hippocampal development in fyn mutant mice. *Science* 1992;258:1903–1910.

45. Farr KL, Montano CY, Paxton LL, Savage DD. Prenatal ethanol exposure decreases hippocampal ^{3}H-glutamate binding in 45-day-old rats. *Alcohol* 1988;5:125–133.

46. Mukherjee J, Murphy SN, Hartwig W, Miller RJ, Cooper MD. N-(3-F-18 Fluoropropyl) MK-801: a PET tracer for in vivo studies of the N-methyl-D-apartate receptors. *J Nucl Med* 1988;29:932.

47. Treffert JD, Yap JT, Cooper MD, Chen C-T. Model-based quantitation using knowledge-based factor analysis [Abstract]. *J Nucl Med* 1992;33:947.

48. Miletich RS, Ferrarese C, Kieservetter D, et al. In vitro excitatory amino acid neurotransmission assessed by [F-18]flourothienylcydohexylpiperidine and PET. *J Nucl Med* 1991; 32:1008.

49. Posner MI, Petersen SE, Fox PT, Raichle ME. Localization of cognitive operations in the human brain. *Science* 1988;240:1627–1631.

50. Zatorre RJ, Evans AC, Meyer E, Gjedde A. Lateralization of phonetic and pitch discrimination in speech processing. *Science* 1992;256: 846–849.

51. Grady C, Haxby J, Horwitz B, Schapiro M, Herscovitch P, Papoport S. Activation of regional cerebral blood flow in extrastriate cortex during a face matching task in patients with dementia of the Alzheimer type [Abstract]. *Soc Neurosci Abstr* 1990;16:149.

52. Petersen SE, Fox PT, Posner MI, Mintun M, Raichle ME. Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature* 1988;331:585–589.

53. Metz JT, Rose RP, Debbold LI, Luchins DL. Effect of memory task and ACTH on cerebral metabolism [Abstract]. *J Cereb Blood Flow Metab* 1989;9(suppl 1):S377.

54. Metz JT, Yasillo NJ, Cooper MD. Relationship between cognitive functioning and cerebral metabolism [Abstract]. *J Cereb Blood Flow Metab* 1987;7(suppl 1):S305.

55. Kanai Y, Hediger M. Primary structure and functional characterization of a high-affinity glutamate transporter [Abstract]. *Nature* 1992;360:467.

56. Pines G, Danbolt NC, Bjoras M, et al. Cloning and expression of a rat brain L-glutamate transporter [Abstract]. *Nature* 1992;360:464.

57. Storck T, Schutle S, Hofmann K, Stoffel WH. Structure, expression, and functional analysis of a Na$^+$-dependent glutamate/aspartate transporter from rat brain [Abstract]. *Proc Natl Acad Sci USA* 1992;89:10-955.

58. June HL, Lummis GH, Colker RE, Moore TO, Lewis MJ. RO15-4513 attenuates the consumption of ethanol in deprived rats. *Alcohol Clin Exp Res* 1991;15:406–411.

59. Dewey SL, Smith GS, Logan J, et al. GABAergic inhibition of endogenous dopamine release measured in vivo with ^{11}C-Raclopride and positron emission tomography. *J Neurosci* 1992;12:3773–3780.

60. Kandel ER. Cellular mechanisms of learning and the biological basis of individuality. In: Kandel ER, Schwarts JH, Jessell TM, eds. *Principles of neural science*, 3rd edition. New York: Elsevier Science Publishers; 1991: 1009–1031.