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SUPPLEMENT

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CORRESPONDENCE

We may shorten letters to the editor unless the authors specifically state that we may not. This is so that we can offer our readers as wide a selection of letters as possible. We receive so many letters each week that we have to omit some of them. Letters must be typed with double spacing between lines and must be signed personally by all their authors, who should include their degrees. Letters critical of a paper may be sent to the authors of the paper so that their reply may appear in the same issue.

Correspondents should present their references in the Vancouver style (see examples in these columns). In particular, the names and initials of all authors must be given unless there are more than six, when only the first three should be given, followed by et al; and the first and last page numbers of articles and chapters should be included.

Benzodiazepines on trial

SIR,—We support the view of Dr P J Tyrer (14 April, p 1101) that benzodiazepines, which are relatively safe and efficacious drugs, should be "prescribed more carefully and with better awareness of their dangers." These concerns were the basis for the recent World Health Organisation recommendation that benzodiazepines be subject to international control by the 76 signatories to the 1971 Convention on Psychotropic Substances.

Among the activities of the WHO on drug dependence are evaluation of the evidence on the dependence liability of substances and formulation of recommendations to the United Nations Commission on Narcotic Drugs for their control.[1] At its February 1984 meeting over two thirds of the 40 members of the commission endorsed the recommendation that the 33 benzodiazepine derivatives marketed as of February 1983 be placed under schedule IV of the Psychotropic Convention.[2] In addition to requiring a prescription, when the decision takes effect licenses will be required nationally for their manufacture, trade, and distribution. This least restrictive control will serve primarily to alert the health professions, governments, and the public about the abuse potential of these agents. The measures will have the greatest impact in countries currently lacking adequate national drug control mechanisms.

Among the 14 drugs with abuse potential previously added to schedule IV were selected barbiturate and non-barbiturate sedative hypnotics (for example, phenobarbital, meprobamate), anorectics (for example, phendimetrazine), and psychostimulants (for example, pipradrol).

The recommendation to control diazepam was based partly on clinical evidence showing physical dependence and partly on clinical reports and epidemiological studies that show it is being abused on a scale warranting international control. The results of experimental studies suggest that it possesses low to moderate psychological dependence potential relative to the short acting barbiturates, psychomotor stimulants, and opiates (WHO, unpublished document MNH/83.28).[3]

Individual evaluation of the other 32 benzodiazepines led to the conclusion that their abuse liability had been actually shown or could be predicted because of their similarity to diazepam in chemical structure, receptor binding characteristics, and pharmacological action. The other drugs to be subject to international control are: alprazolam, bromazepam, camazepam, chlordiazepoxide, clobazam, clonazepam, clorazepate, clotiazepam, cloxazolam, delorazepam, estazolam, ethyl loflazapate, fludiazepam, flunitrazepam, halazepam, haloxazolam, ketazolam, loprazolam, lormetazepam, medazepam, nimetazepam, nitrazepam, nordazepam, oxazepam, oxazolam, pinazepam, prazepam, temazepam, tetrazepam, and triazolam.

Over the years differencies in abuse potential have been recognised among barbiturates and non-barbiturate sedative hypnotics. While differences may also exist among benzodiazepines, insufficient evidence has been adduced in experimental or clinical published reports permitting their differentiation on the basis of absolute or even relative dissimilarities in abuse potential. It may be that when such evidence is evinced some benzodiazepine derivatives will be descheduled while others may be rescheduled subject to more rigorous international control.

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[1] Rexed B, Edmondson K, Khan I, Samson RJ. *Guidelines for the control of narcotic and psychotropic substances in the context of the international treaties.* Geneva: WHO, 1984.
[2] Anonymous. UN Commission on Narcotic Drugs. *Lancet* 1984;i:637.
[3] WHO Review Group. Use and abuse of benzodiazepines. *Bull WHO* 1983;61:551-62.

SIR,—Dr Heather Ashton (p 1135) and Dr P J Tyrer suggest that the symptoms of benzodiazepine withdrawal constitute a syndrome qualitatively different from other withdrawal syndromes, particularly because of the unusual frequency of perceptual disturbances.

Both γ-aminobutyric acid and benzodiazepine receptors are widely distributed throughout the central nervous system, and the general γ-aminobutyric acid facilitatory properties of benzodiazepines as sedatives, muscle relaxants, and anticonvulsants are to be distinguished from their more specific anxiolytic effects. These are probably mediated by depression of activity in septum and hippocampus by ascending noradrenergic and serotinergic pathways and the ascending dopaminergic mesolimbic pathway acting via prefrontal and cingulate cortices.[1] Rebound activity in this latter pathway may well be responsible for the perceptual disturbances that seem to make benzodiazepine withdrawal different; Dr Ashton's observation that these disturbances responded to haloperidol would support this.

Alterations in septohippocampal function are receiving renewed attention in recent research into the pathogenesis of the functional psychoses, and changes predominantly in this area have been shown on depth electroencephalography,[2] computed tomography,[3] and at necropsy (paper presented by R Brown and others at the biannual workshop on schizophrenia in Davos, Switzerland, 1984). Lesions in septum and hippocampus