Clonazepam: effective treatment for restless legs syndrome in uraemia

SIR,—We read with interest the report by Dr D J Read and others (3 October, p 885) concerning the therapeutic efficacy of clonazepam in uraemic patients suffering from the restless legs syndrome.

We have recently completed a survey of restless legs syndrome in 54 surgical outpatients. Assessment involved the administration of a semi-structured questionnaire, designed to elicit the subjective symptoms of the condition, as described by Ekbom.[1] In addition, a brief neurological examination and an assessment of abnormal involuntary movements were carried out. Eight (15%) of these patients fulfilled the criteria for the restless legs syndrome—that is, unpleasant sensations in the legs associated with inability to keep the legs still. This experience was invariably worse when they were sitting or lying down in the evening. A further seven (13%) patients complained of non-specific restlessness; in most cases this appeared to be related to anxiety. The onset of symptoms was not related to surgery in any of the restless patients. None of the patients seen was taking drugs which can cause akathisia and none was known to be suffering from any physical condition, including renal disease, identified as being associated with Ekbom's syndrome.

Thus, applying relatively stringent diagnostic criteria, we found a prevalence rate of 15% for the idiopathic restless legs syndrome. This finding challenges the statement of Dr Read and his colleagues, based on their estimate of a 15-20% occurrence, that uraemia is the most common cause of the restless legs syndrome. The possibility arises that the exacerbation of the syndrome observed with uraemic patients receiving dialysis may be partly accounted for by increased complaints and distress in patients with the idiopathic condition when required to lie relatively still for long periods. The authors note that clonazepam is also beneficial in the treatment of uraemic myoclonus. As myoclonus is a well-described, associated phenomenon in the restless legs syndrome,[2,3] it would have been of interest to know whether any of the patients in their study had also exhibited myoclonus.

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**We sent this letter to the authors, who reply below.—ED, *BMJ*.

SIR,—We know of no accurate figures for the prevalence of Ekbom's syndrome in the general population but is it generally regarded as being a rare condition even in busy neurological clinics. We were very surprised that in a small sample of a relatively selected surgical outpatient population the incidence of this syndrome was found to be as high as 15%. This may, of course, be because symptoms were deliberately sought rather than spontaneously volunteered. In this connection it would be helpful to know how brief the "brief neurological examination" was and what active steps (for example, measurement of serum iron and folate levels) were taken to establish that none of these patients was in fact suffering from any condition known to be associated with Ekbom's syndrome.

Since September 1978 all new patients attending our medical outpatient department have filled in a detailed symptom questionnaire which includes questions on both restlessness and pain in the legs. Of the 452 people who filled in questionnaires, fewer than 20 complained of restlessness, which on detailed questioning turned out to be very non-specific and not characteristic of Ekbom's syndrome; these symptoms may have been related to anxiety. These findings are in keeping with the generally held view that Ekbom's syndrome is a rarity. We should also like to point out that in all our renal patients the symptoms of restless legs were complained of spontaneously and were always of sufficient severity to disrupt normal life. Two of our patients found it necessary to sleep apart from their spouses because of the sleeplessness induced in the partner. The syndrome was more troublesome at night and did not occur only when patients resumed dialysis. Predialysis patients constituted five of our fifteen cases. It would therefore be untrue to say that this syndrome appeared only in those "required to lie relatively still for long periods." Lastly, there was no evidence of myoclonus in any of our patients.

On the basis of our experience we are quite unable to agree with Drs Braude and Barnes that their small survey in any way constitutes a challenge to the assertion that uraemia is the commonest cause of Ekbom's syndrome.

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Alcohol in the Third World

SIR,—Dr Richard Smith in his article on alcohol in the Third World (16 January, p 182) gives little information about Africa. From my experience in a general hospital in Zululand, South Africa, I have no doubt that excessive drinking has assumed epidemic proportions in the indigenous population.

An analysis of 1500 consecutive admissions to the hospital during six months in 1979 showed that 17% of patients were admitted as a result of deliberately inflicted injury. This was the most common single reason for admission, commoner than such "traditional" Third World problems as diarrhoea, malnutrition, or pneumonia. The majority of these patients were injured on Friday and Saturday nights and in most cases either they or their assailants exhibited clinical evidence of drunkenness.

Subsequently the Synod of the Anglican Church in Zululand considered the problem to be so serious that it passed a resolution calling on the homeland government to take urgent preventive action. More recently I wrote to six other hospitals in the area in an attempt to place an alcoholic member of staff in an environment away from the temptations of drinking friends, but they all replied that alcoholism in their own locality was too serious to allow them to help.

Comments I have had from doctors working in other countries in southern Africa, together with my own observations, suggest that despite any measures which may have been taken by governments alcohol abuse is already producing widespread damage to whole communities in the subcontinent.

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ABC of Alcohol

SIR,—We would like to add to the list of clinical manifestations of alcoholism given by Dr A Paton and others (12 December, p 1594) the thrombopathic haemorrhagic syndrome that is sometimes seen in heavy drinkers. Haemorrhagic manifestations of the alcoholic are traditionally thought to be secondary to liver cirrhosis alone. Alcohol has been reported, however, as a cause of thrombocytopenia and platelet dysfunction, presumably through a direct toxic effect on the bone marrow.[1]

We have studied the platelet count, Ivy bleeding time, and aggregation in response to adenine diphosphate (ADP), epinephrine, and collagen of 65 heavy drinkers in order to assess the frequency, importance, and clinical manifestations of thrombocytopenia and platelet dysfunction in alcoholism. The Ivy bleeding time and platelet count were within normal limits in most cases while platelet aggregation in response to at least one of the agents tested was impaired in about 50% of cases. Studies performed two weeks after alcohol withdrawal showed that the mean Ivy bleeding time had significantly shortened, the mean platelet count had increased (rebound thrombocytosis has been reported in some cases),[2] and the results of the platelet aggregation tests had become normal, an unusual hyperaggregability having been detected in one patient.

Significant bleeding manifestations were observed in only four patients, who presented on admission prominent ecchymoses and petechiae as well as mucosal bleeding (epistaxis and gingivorrhagias). Two of them had compensated liver cirrhosis. A high Ivy bleeding time, moderate-to-severe thrombocytopenia, and severe platelet aggregation impairment in the cases where the platelet count allowed us to study it were the prominent laboratory features in these cases—the previous administration of antiaggregating and thrombocytopenia-inducing drugs having been excluded. Results of blood clotting tests and serum folic acid were within normal ranges in all of them. Two weeks after alcohol withdrawal, the clinical signs of bleeding had completely resolved and the Ivy bleeding time, the platelet count, and the platelet aggregation tests were normal.

Our study provides evidence that severe bleeding manifestations due to quantitative and qualitative platelet defects may be a rare but well-defined clinical symptom of alcoholism and that qualitative defects without apparent clinical significance are a common finding in heaving-drinking alcoholics. These qualitative defects may account, at least in part, for the reported protection given by alcohol against coronary heart disease.[3]

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[1] Cowan DH. *Semin Hematol* 1980;**17**:137-47.
[2] Haselager EM, Vreeken J. *Lancet* 1977;i:774-5.
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SIR,—The authors of "ABC of Alcohol: Nature of the problem" (14 November, p 1318) are to be congratulated on publicising the enormity of this problem, which is currently

so prevalent in our society and regrettably in our own profession.

As a recovering alcoholic, with only just over one year's sobriety, I feel that I am in a position to stress the great help I have received from Alcoholics Anonymous. Only by regular attendances and by following their programme have I been able to control this disease up to today. Anyone who feels that they may have a drink problem are welcomed at their local meetings, and may come and go as they please, and surname anonymity is a top priority. The nearest meeting for your patient can be had from the Central Office in London by phoning 01-352 9779.

Doctors and dentists with a drink/drug problem may also find help and encouragement by attending the monthly meetings of the British Doctors' and Dentists' Group. This is an independent group that has regular meetings in Northern Ireland, Glasgow, Durham, Manchester, Bristol, Petersfield (Hants), and London. Many recovering doctors and dentists attend these meetings as well as Alcoholics Anonymous meetings. The Doctors' Group may be contacted through the Medical Council on Alcoholism, telephone 01-235 4182. All inquiries will be dealt with in the strictest confidence.

A doctor member of Alcoholics Anonymous

Assessment of iron stores in inflammation by assay of serum ferritin concentrations

SIR,—Dr D R Blake and others studied serum ferritin concentrations in inflammatory synovitis (31 October, p 1147). They did not exactly demonstrate a correlation between ferritinaemia and iron stores, since no direct measurement was performed in their patients. Rather they pointed out that a serum ferritin concentration below 55 μg/l indicates iron deficiency complicating chronic inflammation. From a practical point of view, it is very useful to have this upper limit defined, as the classical value of transferrin saturation below 0·16[1] is not very helpful for detecting iron deficiency in chronic disorders. These findings have been verified in another kind of inflammatory disease—namely, chronic pulmonary tuberculosis.

We have studied 28 adult patients (24 women and four men). Our findings were reported to the 18th congress of the International Society of Haematology, Montreal, in August 1980. Iron stores were evaluated directly, marrow haemosiderin being graded from 0 to 6+ (low, 1-2; normal, 3-4; increased, 5-6)[2] and the percentage of marrow sideroblasts being determined. At the same time serum ferritin concentration was determined by a commercially available radioimmunoassay (FerK-Kit, CIS, France), and transferrin saturation was measured by a standard method (BD-Merieux, France). A positive correlation was observed between the ferritin concentration and haemosiderin score (log ferritin value v haemosiderin score: $r=0{\cdot}5108$, $p<0{\cdot}01$), but not between the transferrin saturation and haemosiderin score ($r=0{\cdot}0540$).

The ferritin concentration was below 55 μg/l (4-44) in a group of five women, with an average haemosiderin score below 1 (0, 0, 1, 1, 2) and no marrow sideroblasts. The ferritin concentration exceeded 55 μg/l in the 23 others, with a mean haemosiderin score value of 3·5 (low, normal, and increased in 4, 12 and 7 cases respectively), no marrow sideroblasts in eight cases, and 1-14% in 15. The transferrin saturation values were below 0·16 in 19 patients, whose mean haemosiderin score was 3·0 (low, normal, and increased in eight, six, and five cases respectively).

Thus, of the indirect methods for evaluating iron stores, determining the serum ferritin concentration is better correlated with a direct method than is determination of the transferrin saturation in patients suffering from chronic diseases (arthritis, tuberculosis, regional enteritis,[3] or even sickle-cell anaemia[4]) complicated by iron deficiency; and the latter condition can be safely inferred from a serum ferritin concentration below 55 μg/l.

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[1] Bainton DF, Finch CA. *Am J Med* 1964;**37**:62-70.
[2] Baumgartner-Staubli R, Back EA. *Acta Haematol* 1977;**57**:24-31.
[3] Thomson ABR, Brust R, Ali AM, Mant MJ, Valberg LS. *Am J Dig Dis* 1978;**23**:705-9.
[4] Vichinsky E, Kleman K, Embury S, Lubin B. *Blood* 1981;**58**:563-8.

Fake!

SIR,—"Fake," the fascinating article by Dr T J Hamblin (19-26 December, p 1671) prompts me to recall a particularly audacious example of scientific faking of half a century ago, in which I was very indirectly involved.

In 1930 the *Lancet* published an article of eight full pages entitled "The aetiology of disseminated sclerosis."[1] The author, Kathleen Chevassut, MSc, claimed to have isolated a specific pathogen from the cerebrospinal fluid of 176 of 189 patients with multiple sclerosis but never from 269 patients with other organic nervous diseases, almost burying this startling discovery beneath a mass of technical details. For this work she had been assisted by grants from the Medical Research Council (MRC), the University of London, and the John Burford Carlill Endowment. Sir James Purves-Stewart, physician to Westminster Hospital, who had requested her to undertake this research, had made her a personal gift of a "special microscope and other apparatus," and had provided the clinical material. According to Miss Chevassut, her organism bore a "striking resemblance to the organism which is regarded as the causative agent of bovine pleuro-pneumonia."

Chevassut's article was immediately followed by a five-page report by Purves-Stewart called "A specific vaccine treatment in disseminated sclerosis."[2] He had requested Chevassut to prepare from her cultures of the organism—which they had decided to name *Spherula insularis*—autogenous vaccines, which were administered intravenously to 128 patients, with "suggestive" results.

Attempts by the MRC to make an independent appraisal of Chevassut's claims were thwarted by her evasiveness, but early in 1931 the Halley Stewart Trust decided to endow an institute at Hampstead to enable her to pursue her work under the best conditions.[3] This consisted of nursing staff and a laboratory assistant and accommodation for 12 inpatients, Chevassut also receiving a personal grant. The philanthropist Sir Halley Stewart persuaded one of his sons—Dr B Halley Stewart, who had retired—to accept the position of medical superintendent of the institute, but he left after a few weeks because "Miss Chevassut resented my presence there."

Over four months later Dr Halley Stewart returned to the institute in order to establish "a system of controls of all the lumbar punctures." According to him, Chevassut's strategems to meet this new challenge included replacing culture tubes by "dummy tubes," turning the incubator up to 50°C, and making new slides of her *Spherula insularis* from "four or five culture tubes which she carried about with her in the pocket of her white coat." In the meantime, S R Douglas, FRS, of the MRC, reported that four "positives" from Chevassut showed "a pure culture of the virus of bovine pleuropneumonia."

By then Chevassut was totally discredited, and Purves-Stewart publicly "dissociated" himself from her—but not from *Spherula insularis*. He continued to find the organism not only in the cerebrospinal fluid of multiple sclerosis patients but also in that of patients with other organic nervous diseases, and in pus-containing fluids from the pleura, the peritoneum, and syphilitic chancres. Far from being discouraged by the apparent non-specificity of "*Spherula*," he prepared from the cerebrospinal fluid of 101 multiple sclerosis patients "autogenous vaccines," the administration of which allegedly produced arrest or clinical improvement in most of them.

In 1933 I became a house physician to the Metropolitan Hospital, Kingsland Road, London, and found that Chevassut was continuing her operations there, clad in a white coat and brewing her "autogenous vaccines" under the patronage of the neurologist C Worster-Drought, FRCP, who was also physician to the West End Hospital for Nervous Diseases. His private patients came from many parts of the country to be admitted to the Metropolitan Hospital for a few days for lumbar puncture, culture of the "pathogen," and administration of the "vaccine." On many occasions I had the distasteful duty of participating in this exploitation of the sick by performing the lumbar punctures on them.

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[3] Stewart BH. *Br Med J* 1932;ii:326-7.

SIR,—Dr T J Hamblin's enlightening article (19-26 December, p 1671) on the dark corners of science speaks of Burt as, firstly, fabricating his evidence and, secondly, fixing his facts. The evidence would seem to be that his earlier data were reliable, but their numerical interpretation became "fixed" beyond the likely vagaries of chance despite further, but poorly documented, data.

As with Mendel and, in a similar context, Newton, there is no reason to doubt the magnitude of the numerical value, which seems consistent with the mechanism and with other studies. It is hardly Burt who should be blamed for the widespread confusion between heritability and ineducability.

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Gonadotrophin and the human secondary sex ratio

SIR,—I have suggested[1 2] that the sex ratio (proportion of boys) of infants born after the induction of ovulation is low. Dr Ina Cholst and others (7 November p 1264) report the births of 79 boys and 73 girls after the induction of ovulation. They correctly write: "... our data do not support a recent report of an alteration in the sex ratio in infants conceived after the induction of ovulation." It seems nevertheless fair to add that their data do not powerfully impugn the hypothesis either: the sex ratio of their sample is not significantly different from that of the sex ratio of the 257 boys and 333 girls in the study already referred to.

The accompanying table gives the sexes of the infants in further samples which have be-