with this syndrome can be easily recognized in large numbers of long-term hospital populations." R. Degkwitz hammered home the same point at the same symposium,[4] "During the last 15 years drugs have been given to a large portion of psychiatric patients with little thought of what the risks are."

Today we may smile at Dr. Parkinson's guesses and shudder at the barbarous treatment inflicted in his day. Unhappily, our knowledge of the aetiology and pathology of the major psychotic diseases remains largely conjectural. But the treatment we mete out to the sufferers may actually prove to be more damaging than taking blood from the upper part of the neck or applying vesicatories to it.

[1] Parkinson, J., *An Essay on the Shaking Palsy*, reproduced in *Archives of Neurology and Psychiatry*, 1922, 7, 681.
[2] *The American Handbook of Psychiatry*, 2, ed. S. Arieti. New York, Basic Books Inc., 1959.
[3] Celesia, G. G., and Wanamaker, W. M., *Diseases of the Nervous System*, 1972, 33, 577.
[4] *Psychotropic Drugs and Dysfunctions of the Basal Ganglia: A Multidisciplinary Workshop*. Proceedings of a Workshop in Bethesda, Maryland 31 October—2 November 1968, ed. G. E. Crane and R. Gardner, jun. Maryland, National Institute of Mental Health, Chevy Chase, 1969.

Radioactivity and Lymphocytic Chromosomes

The technique of culturing blood lymphocytes in vitro so as to induce them to go into cell division is of help in the study of diseases in which cell-mediated immune reactions may play a part.[1] The frequency of chromosomal abnormalities in such cultures has been proposed as a biological means of measuring the dose of radiation a person has received.[2] The frequency is increased after whole-body exposure to atomic bomb radiation or accidentally, and after localized exposure such as luminizers who work with radium receive or such as patients acquire from radiotherapy.[2]

A. C. Stevenson and colleagues[3] have recorded the frequency of some chromosome abnormalities in blood lymphocytes of 70 patients treated by intra-articular injections of radioactive gold or yttrium in particulate form. Blood samples were obtained 1 day to 8 years later. The frequency of affected cells was almost always increased above the control level of 1/3,000 for the general population. In five patients the increase was dramatic; 12-29% of the cultured and surviving lymphocytes showed abnormalities when blood samples were taken 5-12 months after the injections. The authors suggest that such high levels could be attained only if a large proportion of the blood lymphocytes, say one-fifth, received a radiation dose of about 100-200 rads. Earlier[4] they had proposed that injected material can leak out of the synovial cavity and that most of the escaping radioactive particles would be trapped in the regional lymph nodes. Radioactivity due to leakage has now been shown to be localized as expected (though no anatomical details are given) in 15 of 20 patients given injections into the knee joint—in all 10 receiving Au-198 and in 5 of 10 receiving Y-90.

The degree of leakage varied greatly between different individuals, in agreement with the highly variable frequency of abnormal lymphocytes, and on the whole was less for yttrium than for gold. Repeat measurements suggested that, once trapped, the particles did not move on. There was a striking correlation between frequency of chromosome abnormalities and the estimated total radiation dose in the iliac lymph nodes. The hypothesis proposed to account for the chromosome changes in blood lymphocytes is that radioactive particles retained in the lymph nodes irradiate lymphocytes as they pass through the nodes in their normal circulation out of the blood into the tissues and back again via the lymphatic vessels.

Intra-articular injections of radioactive material can benefit some patients. Can any harm result from the local irradiation of the joint, the leakage of radioactivity, and its retention in regional lymph nodes or from the associated chromosomal abnormalities in blood lymphocytes? Induced malignant disease would be the main hazard, and the degree of risk depends on the radiosensitivity of the particular tissues involved and on the magnitude of the radiation dose. An overall estimate is given in numerical terms[3] on the assumption that the injected radioactive material irradiates the whole body uniformly. But this is open to question. Even if the injection had all been intravenous, irradiation would not have been uniform because the material was particulate and would have been taken up by the phagocytic cells of the reticuloendothelial system in liver, spleen, bone marrow, and lymph nodes. Intravenous administration of Thorotrast, for instance, is followed decades later by a relatively high frequency of the normally rare haemangioendothelioma of the liver[5 6] and an appreciable frequency of induced leukaemia.[6] But after intra-articular injection very little Au-198 was detected in the liver by external counting. An uptake in the liver of 1% of the amount injected would give an effective radiation dose less than 1/1,000 that in the typical Thorotrast case. The risk of malignant disease from 10 mCi injected into a joint can then be calculated by using the commonly accepted but not necessarily valid[7] linear hypothesis and will be small, perhaps of the order of 1 in 100,000 in the next 30 years.

The risk in the locally irradiated tissues must also be considered. The dose to the synovial tissues after a typical intra-articular treatment is in the therapeutic range of 2,000-3,000 rads, and the fixed cells of the regional lymph nodes will receive 6,000-9,000 rads if there is a 10% local leak.[3]

Therapeutic doses may well be less risky than expected on a linear hypothesis[7] but will always carry some risk depending on the sensitivity of the tissue to induction of malignant disease by radiation, which can be variable.[8] Lymph node tissue as a whole seems to be several times less sensitive than the whole bone marrow, and the risk after irradiation of regional lymph nodes will be several times smaller still in proportion to the fraction of the whole lymphoid system which is irradiated. Synovial tumours have been attributed to radiotherapy very rarely, if ever, and muscle and skeletal tissues are generally along the less radiosensitive tissues. Numerical estimates of cancer risk for irradiation of such relatively insensitive tissues cannot be provided simply because so few have been seen in irradiated people in contrast to leukaemia and cancers of bone, breast, lung, and thyroid.[9] The expected very low risk following intra-articular irradiation would appear to be minimized by using Y-90 rather than Au-198, because the particles are larger and the leaks are smaller.

[1] Pathological Society Meeting, Cambridge, January 1973.
[2] United Nations Scientific Committee on the Effects of Atomic Radiation. General Assembly Official Records, 24th session. Supplement 13 A/7613. New York, United Nations, 1969.
[3] Stevenson, A. C., *et al.*, *Annals of the Rheumatic Diseases*, 1973, 32, 112.
[4] Stevenson, A. C., Bedford, J., Hill, A. G. S., and Hill, H. F. H., *Lancet*, 1971, 1, 837.
[5] Faber, M., in *Proceedings of the 1st International Congress of Radiation Protection*, ed. W. S. Snyder *et al.*, Part 2, p. 1521. Oxford, Pergamon Press, 1968.

[6] da Silva Horta, J., Abbatt, J. D., da Matta, L. C., and Tavares, H. M., *Zeitschrift für Krebsforschung*, 1972, 77, 202.
[7] Mole, R. H., *British Medical Bulletin*, 1973, 29, 78.
[8] International Commission on Radiological Protection, *Radiosensitivity and Spatial Distribution of Dose*. Oxford, Pergamon Press, 1969.
[9] United Nations Scientific Committee on Effects of Atomic Radiation, *Ionizing Radiation: Levels and Effects*, 2. New York, United Nations, 1972.

Enuresis Again

Enuresis is an ever present problem for the children's parents, for it causes them an immense amount of unpleasant work, and it seems to be unending—continuing week after week, month after month, and year after year. To many children it is more than just unpleasant at night. They are apt to be scolded in the morning and given sermons in the evening. Both courses are singularly irrational, for the child can hardly be blamed for what he does in his sleep. If he wets by day as well, he is apt to be ostracized by his siblings and given offensive nicknames at school because of the smell. It is calculated that about half a million bedwetters are attending schools in England and Wales. About 10% of all children are still wetting at least occasionally when they start school. Numerous articles on the subject continue to appear, and in spite of the evidence to the contrary[1] there are still doctors who regard enuresis as nothing more than a psychological problem.

A recent article[2] is of particular interest because it aimed at providing a descriptive analysis of an unselected sample of bedwetters and comparing the effect of imipramine, the electric buzzer (pad and bell), and a placebo. Through the school medical service at Newcastle upon Tyne I. Kolvin and colleagues, members of the department of psychiatry in the university, surveyed 2,472 children in 15 schools and studied 94 bedwetters in detail, submitting them to a range of tests, and then dividing them at random into three groups for treatment. Their mean age was 9 years 4 months; there was a slight preponderance of boys. The mean age of walking without support was a little late (15·9 months), but as a milestone it is not a good measure of development. Among the wetters there was no unusual incidence of ambidexterity, coercive toilet training, or personality deficits, but there was a rather high incidence of parental divorce or separation, a lower social class, a larger family size, and rather more behaviour problems. In over 60% there was a family history of bed wetting. And 78% were of the primary type, never having been dry.

Imipramine was rapidly effective and significantly better than a placebo, but relapse on discontinuing it was frequent. The electric buzzer gave a slower response, but was highly significantly more effective than the placebo, and the relapse rate was low—in fact lower than that of the imipramine group.

The authors discussed the various theories about enuresis, including those of S. H. Lovibond.[3] He has suggested that enuresis is due to faulty learning or conditioning, or difficulty in conditioning, or a breakdown of acquired habit as a result of psychological stress. Kolvin and colleagues did not consider that the causes were mainly psychological, though they agree that psychological factors resulting from scolding and other unpleasantness were often superimposed on other causes, particularly maturational delay, exaggerated by errors of training. Since some children of comparable intelligence are later than others in all other aspects of development—smiling, chewing, sitting, walking, talking, reading, and other skills—it would be indeed surprising if some were not also late in controlling the bladder. One obvious explanation would be delay in maturation of the relevant part of the nervous system. It is difficult to disagree with F. J. W. Miller's comment[4] that "the social correlations were such that it is reasonable to think that most enuresis occurs in a child with a slow pattern of maturation when that child is in a family where he does not receive sufficient care to acquire proper conditioning. We doubt if the continuous type of enuresis is caused by major psychologic difficulties at the outset, though we acknowledge that psychologic difficulties can occur as an overlay."

In the treatment of this condition imipramine is often an effective drug, like the other tricyclic antidepressants. It is not helpful to change from one to another (for example, to amitriptyline or nortriptyline) if imipramine fails. The possibility of side effects should be borne in mind. R. S. Illingworth[5] listed some 33 known side effects. The makers of imipramine recommend a dose of 25 mg at night for children from 5 to 12 years but a dose of 50 mg at night for an average child of 5 to 7 or 8 may be needed, and 75 mg for an older or bigger child, though the physician should be reluctant to exceed the dose recommended by the makers. It is wise to discontinue the drug as soon as possible—but then relapse is common.

Taken as a gross overdose (the child having helped himself to a bottle of his own or his mother's tablets), imipramine is highly dangerous. J. M. Parkin and M. S. Fraser[6] found that between 1962 and 1969 31 children had died of imipramine poisoning; their age was 9 months to 5 years. The symptoms are mainly convulsions and those of severe myocardial damage. Severe symptoms are usual when the dose exceeds 20mg/kg body weight. There is no specific antidote, treatment being mainly supportive and symptomatic, preferably in an intensive care unit.

The electric buzzer is a highly effective method of treatment provided that (1) it awakens the child; (2) the child has to get out of bed to stop the buzzer; (3) the child has the buzzer long enough—rarely less than three months. But it is not free from risks.[7 8] If the pad is carelessly used in a disarranged bed, ulceration of the skin can occur. And unless a reliable make is used and properly connected up there could theoretically be a danger of electric shocks.

It is not fair to tell a mother that "he will grow out of it" and do nothing more to help her with a distressing problem. Nor is it enough merely to prescribe a tricyclic antidepressant and forget its possible risks, or to supply a buzzer and not try to ensure that it is used properly. In any case the doctor should try to stop parental scoldings, reprimands, and other causes of superadded psychological problems.

[1] Hallgren, B., *Acta Psychiatrica et Neurologica Scandinavica*, 1957, 32, Supplement 114.
[2] Kolvin, I., *et al.*, *Developmental Medicine and Child Neurology*, 1972, 14, 715.
[3] Lovibond, S. H., *Conditioning and Enuresis*. Oxford, Pergamon, 1964.
[4] Miller, F. J. W., *New England Journal of Medicine*, 1966, 275, 683.
[5] Illingworth, R. S., *Treatment of the Child at Home: A Guide for Family Doctors*. Oxford, Blackwell, 1972.
[6] Parkin, J. M., and Fraser, M. S., *Developmental Medicine and Child Neurology*, 1972, 14, 727.
[7] Neal. B. W., and Coote, M. A., *Archives of Disease in Childhood*, 1969, 44, 651.
[8] Borrie, P., and Fenton, J. C. B., *British Medical Journal*, 1966, 2, 151.