applying there, it could be bridged by the appointment of a hospital resettlement officer. Attempts to initiate this arrangement at other hospitals, from, as it were, the Health Service end, have not been successful.

However, and this is the point of my letter, the Employment Services Agency has recently taken the initiative by appointing hospital employment resettlement advisers at several hospitals throughout the country. There are now sixteen such officers in post. The appointments have not been going on for long enough for them to be assessed objectively. This experiment is acknowledged in passing by Drs D A Brewerton and P J R Nichols (15 October, p 1006), who then go on to suggest that a group of "vocational counsellors" employed by the hitherto laggardly Health Service should be created. Now is surely not the time to confuse the issue. The ESA's initiative should be encouraged. It would now be churlish to do otherwise—and more years would be wasted before anything useful happened.

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Anxieties and fears about plutonium and other radionuclides

SIR,—Dr J D Watts (10 December, p 1544) raises several different questions in his comments on my article (17 September, p 743) and subsequent correspondence (12 November, p 1288). The article was specifically about plutonium in the context of the Windscale inquiry and would have had to be much longer to deal with fission products as well. I do not recall anyone outside a military context more concerned with fission products than with plutonium, but perhaps Dr Watts's phrase "much more toxic radioactive waste products" was intended to refer to the α -emitting nuclides other than plutonium-239 which are found in irradiated nuclear fuel. If so, I do not think that omitting specific mention of them was an important defect since broadly they damage tissues in a similar way to plutonium.

Lung cancer from inhalation of plutonium (or other α -emitting nuclides) is a problem to be considered not merely in occupations involving plutonium but also as an environmental hazard for the general public. Much has been made of the latter and, although Dr Watts seems to think it relatively unimportant, it has been a major, if not the major, concern of many professionals¹ and environmentalists and of the media.

Hereditary damage follows radiation exposure of the gonads but not radiation exposure of any other tissues. Thus in comparison with cancer induction hereditary damage is not an important consequence of exposure to plutonium isotopes or to such fission products as strontium-90 or the radioactive iodines. These radioactive materials are not selectively concentrated in the gonads and irradiation of the gonads from uptake in other tissues or from external exposure is small or minimal.

Twenty years ago a great deal of public attention was attracted to the hypothesis that a relatively small increase in the human mutation rate—say, a doubling of it—might be enough to threaten the survival of the human species because of the increased hereditary damage that would follow. The hypothesis is especially linked with H J Muller, the distinguished geneticist whose discoveries included the first demonstration that ionising

radiation causes mutations, and has been the basis of much anxiety and fear. Even at the time, however, many geneticists had serious reservations about the correctness of Mullerian predictions and these have not been confirmed experimentally. Repeated observations on drosophila and laboratory mammals using radiation exposures at a level sufficient to increase the natural mutation rate by a number of times have failed to show the predicted deterioration in the numbers or "fitness" of an irradiated population.²⁻⁴ This was so even when the irradiation was continued for 30+ successive generations.^{3,4} It should also be recalled that no definite excess of hereditary damage has been found in the children of Japanese bomb survivors in spite of intensive search,⁵ an observation which indicates that the human species is not markedly more sensitive to radiation mutagenesis than laboratory mammals.

In the past 20 years information about and understanding of human genetics has greatly increased, especially in regard to the mechanisms maintaining the population frequencies of genetically handicapped individuals.^{3,4,6,7} Increasingly selection has come to be regarded as more important and new mutation less so with the result that the predicted effect of increasing the mutation rate is also smaller than used to be thought. One consequence is to be seen in the newly revised recommendations of the International Commission on Radiological Protection.⁸ Here hereditary damage has ceased to be regarded as the overwhelmingly important effect of irradiation of human populations even when the whole body is uniformly irradiated and the radiation dose in the gonads is as high as in any other tissue. With uniform irradiation, as by caesium-137 or carbon-14, the frequency of induced cancer is considered to be larger than the frequency of induced hereditary damage. With most radionuclides of common concern irradiation of the body is non-uniform, the radiation dose in the gonads is smaller or much smaller than the dose in other tissues, and induced hereditary damage therefore even less important as compared with induced cancer.

If the more pessimistic of two hypotheses is taken as the basis for prediction of harmful effects it will be found to happen sometimes, as fuller understanding develops, that the less pessimistic hypothesis turns out to be the more scientifically acceptable. In the past 20 years there have been two examples of this in the radiation field, in relation to carcinogenesis by strontium-90⁹ and again in relation to hereditary damage, with the difference that in the latter case there is as yet no explanation why predictions based on genetic theory are not borne out experimentally.^{3,4}

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¹ Medical Research Council, *The Toxicity of Plutonium*. London, HMSO, 1975.

² Green, E L, *Annual Review of Genetics*, 1968, 2, 87.

³ Newcombe, H B, in *Human Genetics: Proceedings of the Fourth International Congress of Human Genetics 1971*, ed J de Grouchy, F J G Ebling, and I W Henderson, p 45. Amsterdam, Excerpta Medica, 1972.

⁴ Newcombe, H B, in *Radiation Research, Biomedical, Chemical and Physical Perspectives: Proceedings of the Fifth International Congress of Radiation Research*, ed O F Nygaard, H I Adler, and W K Sinclair, p 937. New York, Academic Press, 1975.

⁵ UNSCEAR, *Sources and Effects of Ionizing Radiation*, Annex H, Genetic Effects of Radiation. New York, United Nations, 1977.

⁶ Ash, P, Vennart, J, and Carter, C O, *Lancet*, 1977, 1, 849.

⁷ Ash, P, Vennart, J, and Carter, C O, *Journal of Medical Genetics*, 1977, 14, 305.

⁸ International Commission on Radiological Protection, *Recommendations*. Oxford, Pergamon, 1977.

^{*} Medical Research Council, *Criteria for Controlling Radiation Doses to the Public after Accidental Escape of Radioactive Material*. London, HMSO, 1975.

Salbutamol: lack of evidence of tumour induction in man

SIR,—Recent statements in *Scrip* and the national press concerning the Food and Drug Administration's action on salbutamol (albuterol in the USA) in the United States of America require comment, particularly as they may engender unnecessary anxiety about the use of salbutamol-containing preparations in the United Kingdom and elsewhere. The purpose of this letter is to summarise the results which give rise to the statements and to place them in perspective.

In 1971 Nelson and Kelly,¹ of Mead Johnson Inc, reported that prolonged oral administration of soterenol, a potent β -adrenoceptor stimulant which they were developing as a bronchodilator, resulted in the formation of mesovarian leiomyomas in Sprague-Dawley rats. Clinical work with this compound was discontinued and the patients involved have been regularly examined for possible tumours, with negative results. The Mead Johnson workers subsequently found that mesuprine hydrochloride, an analogue of soterenol, also caused mesovarian leiomyomas in Charles River CD (Sprague-Dawley-derived) rats.² Because induction of these leiomyomas might be a general property of β -stimulants they did further tests using both Charles River CD and Long Evans rats and used salbutamol sulphate as a control substance; soterenol was the other compound tested. The preliminary results of these experiments, including the formation of mesovarian leiomyomas in rats treated with either salbutamol or soterenol and an indication that yet another Mead Johnson β -stimulant had also induced these leiomyomas, were reported in May of this year to the Schering Corporation, which is Glaxo Group's licensee for salbutamol products in the USA, and to Allen and Hanburys Research Ltd. Mead Johnson's complete report on salbutamol and soterenol was received by us in October.

We also learnt during May that mesovarian leiomyomas were found during a comprehensive long-term Schering study in which Charles River CD rats were treated with salbutamol sulphate, the highest dose level being 50 mg/kg, the maximum tolerated dose. All the 10 expert histopathologists who have examined the rat leiomyomas agree that the tumours are benign with no sign of malignancy.

Salbutamol was not oncogenic in the mouse in either of two 18-month studies carried out at Allen and Hanburys Research Ltd and at Schering, using daily oral doses up to 2000 times the human oral daily intake of the drug. Salbutamol was not mutagenic when tested at concentrations up to 1 000 000 times its effective concentration on β_2 -adrenoceptors in in-vitro tests involving four different micro-organisms with and without metabolic activation with liver microsomes.

We informed the Committee on Safety of Medicines of Mead Johnson's and Schering's preliminary results on 3 June and sent them a special report which dealt with all the long-term toxicological tests carried out with salbutamol sulphate in August. On 4 October we were advised by the committee that "no licensing action with regard to salbutamol sulphate is proposed at the present time."

In early November a second special report was sent to all national drug authorities concerned with salbutamol in order to take account of the data in the complete Mead Johnson report on salbutamol and soterenol. The main conclusions of this report were that the only tumours specifically associated with the long-term administration of salbutamol sulphate were mesovarian leiomyomas in certain strains of rats, that this effect was probably mediated by β -adrenoceptors, that salbutamol sulphate was not carcinogenic in the mouse or the rat, and that there was no good reason for supposing that therapeutic use of salbutamol preparations would

cause mesovarian leiomyomas or any other kind of tumour in human beings.

During November the Pulmonary, Allergy and Clinical Immunology Advisory Committee of the US Food and Drug Administration considered the special report on salbutamol and other evidence at an open meeting in Washington and recommended, in essence, that the status quo concerning β -stimulant bronchodilators in the USA should be maintained and that, in order to clarify the toxicological position, long-term studies should be carried out in higher species, and especially in monkeys, on the β -stimulants currently marketed in the USA as well as those at the development stage. The effect of this recommendation on salbutamol in that country is that clinical trials will remain suspended until the new toxicity test requirements have been met.

A diffuse, largely inexpert, discussion of possible drug-induced lesions in the rat other than mesovarian leiomyomas also took place at the November meeting. As a result, we sent an addendum to the special report to the advisory committee and to all national drug authorities in order to present the opinions of the experts who were intimately involved with the long-term Schering rat studies, opinions which were not adequately presented at the open meeting. These opinions make clear the nature and significance of the other lesions found in the rats and accord with their conclusion that no tumours other than mesovarian leiomyomas occurred with toxicologically significant frequency.

Mesovarian leiomyomas are extremely rare in human beings and any substantial increase in their incidence which resulted from the use of adrenergic drugs would be obvious because the ovaries are regularly examined during common gynaecological operations. There is no evidence to suggest that the systemic use of adrenergic drugs, which started with ephedrine about 50 years ago in western countries, has had any effect on the incidence of smooth-muscle tumours in women. No such lesions have been reported in association with treatment with oriprenaline, which has been used for more than 15 years, or with salbutamol or terbutaline, which have been extensively used for nearly 10 years. This is, of course, the expected result because human beings are never regularly exposed to the intensity of β -adrenergic challenge to which all the treated rats were exposed in the oncogenic studies. The cardiovascular effects and muscle tremor which would accompany the use of such high doses of β -stimulants in man would be intolerable.

Having considered all the evidence, we have offered the following advice to Glaxo Group companies:

(1) There is no evidence that the therapeutic use of salbutamol-containing preparations, by inhalation or by mouth, for nearly 10 years has resulted in an increase in tumours of any kind or in any other serious drug-induced side effect in patients.

(2) There is no good reason for supposing that the therapeutic use of salbutamol will cause mesovarian leiomyomas or any other kind of tumour in human beings because rats, the only known sensitive species, are known to respond aberrantly in other ways to β -stimulants and because, given the pharmacological nature of β -stimulant drugs, human beings have never been and never will be subjected to prolonged intense systemic β -stimulation.

(3) There is no evidence that salbutamol is carcinogenic in any species and much evidence that it is most unlikely to be so.

(4) Salbutamol, the first highly selective β_2 -adrenergic bronchodilator, is a valuable drug in the management of bronchial asthma; there is no rational basis for discontinuing its use.

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¹ Nelson, L W, and Kelly, W A, *Veterinary Pathology*, 1971, 8, 452.

² Nelson, L W, Kelly, W A, and Werkel, J H, *Toxicology and Applied Pharmacology*, 1972, 23, 731.

Schistosomiasis in China

SIR,—I thought your leading article on schistosomiasis in China (19 November, p 1304) very timely, but it contains several misconceptions.

Reduction in the incidence of schistosomiasis in China is a clear manifestation of the ideology underlying the Chinese health delivery system. An attack on snails was initiated only after prolonged discussion between medical experts and the equally important peasant experts. The parasitologists defined the life cycle and vulnerability of the fluke and this was their contribution. The peasants, with their intimate knowledge of irrigation, could suggest how the enormous practical problems of digging in the snails might be overcome. It is because of this combined approach involving many groups of people that mass mobilisation was possible.

Your reference to "a striking disregard for or nonchalance about" these labour demands reflects the general misconception prevalent in the West that these mass campaigns, so successful in China, are imposed on people. What the Chinese have shown is that when ordinary people are given responsibility for their own health they respond with a commitment and positive attitude that does make light of the problems which confront them, and it is this essential ingredient which you have failed to take note of in your article.

I think the fact that the Chinese are the only nation in the world to reduce schistosomiasis radically in their country testifies to the effective manner in which mass health campaigns can advance a nation's health. Your article does not sufficiently stress that point either.

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Life with spina bifida

SIR,—As a parent of a child who had spina bifida I was most interested in the article by Professor R B Zachary (3 December, p 1460) concerning "Life with spina bifida" and his discussion of the controversy around attitudes in management: "Should they be allowed to die?"

It seems extremely sad that the proposal that those children who would naturally die at an early age should be allowed to do so rather than have to suffer the trauma of such a series of operations as is described in Professor Zachary's first section should be misinterpreted by those managing the care of those children in hospital. It is indeed horrifying that doctors should deliberately administer drugs to hasten the death of a child. Yet it is not altogether surprising. With the development of drugs which will prolong life unnaturally (keeping going worn-out bodies) and of those which will hasten death, suppressing vital energy, the medical profession faces the increasing dilemma of "playing God." Surely the only answer to this dilemma is to turn to God himself, who alone has the right to give and take away life.

I feel that part of this whole problem is the widespread acceptance of the premise that "their parents should not have the burden of looking after them." When the burden of responsibility is shifted from the parents to the hospital a strain is imposed on the already overstretched financial and staffing resources which leads to the exploration of every avenue for the relief of that strain, be it ethical or not. The result is effectively euthanasia—an effective if unethical means of reducing the problem.

The parent has the natural God-given advantage of maternal or paternal love. By God's grace and with the help of the medical profession the parents can give to a child afflicted with spina bifida the best possible care at home. I believe that many more parents than those who do so at present would opt to do this if the true facts of the case were laid before them. Unfortunately many parents stand in awe of hospital doctors and accept their advice as law and do not take the opportunity to make their own decision. Perhaps too many doctors underestimate the decision-making ability and potential for loving response to great demands that lies in parents.

My husband and I were thankful that when our son was born with spina bifida (I suppose he would have fallen into Professor Zachary's category 3, grade 3, or perhaps category 2) we were immediately given as full a picture as possible of the prognosis as far as it could be determined and the alternative courses of management. We opted to allow our child to live and die as naturally as possible, submitting him to no surgical trauma other than that which would relieve his discomfort. Although no one suggested that we should take him home, it seemed strange to us that the assumption apparently was that he should stay in hospital and we took him home as quickly as possible, six days after my caesarean section. So far as we were concerned he was simply our baby and our management of him was exactly as it would have been for any other baby, apart from the minor additional task of changing his dressing. He did not seem to suffer pain or sleeplessness that would have warranted the use of any sedative. For a time he was a bright-eyed, responsive baby that would have rejoiced any mother's heart. I recognise that some parents have to face increasing problems as the child grows older. Our child lived only 11 weeks, but I had at my disposal all God's resources to cope with those 11 weeks and believe they would have still been available whatever problems I would have faced had he lived longer. Our son thrived for the first few weeks. He was a great delight to us and when he died in the way and at the time that God appointed we had the satisfaction of knowing that we had done everything we could for him. I know that not all parents have the relationship with God that we enjoy. I know that not all general practitioners are prepared to give the unfailing help, support, and encouragement that our GP gave us. Yet I believe that many more parents are able to care for and enjoy their children with spina bifida, even when very severely affected, than at present do so. We need to rethink our welfare-state attitudes and doctors must encourage parents in assuming their responsibilities instead of taking over the rights and responsibilities of both parents and God.

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