lacks the necessary degree of external support. Consequently, the only course of action open to the D.H.S.S. is to withdraw the report and to inform interested bodies accordingly.—I am, etc.,

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SIR,—Dr. I. K. Scott (8 September, p. 541) praises the report of the D.H.S.S. on promotion of research in deafness.[1] It is, in many ways, a very informative report, specially to those who are not familiar with the various problems of research in the subject. But similar general descriptions can already be found in numerous publications, symposia, or reports of working parties.

So far as the solution of major problems of sensorineural hearing loss is concerned stagnation has set in during the past few years. An important stage in research has been almost completed. Variables were studied in isolation, by individual research workers, or small groups in isolated research units. No further progress can be made until the various fragments of information could be brought together from a very large field of knowledge and studied how they influence each other and how they are linked. A new way of thinking and a new approach is called for. I suggested a few years ago that a new type of research centre should be created with adequate facilities where research workers from a wide field could work together. This idea was incorporated in an Act of Parliament,[2] and the Department of Health and Social Security was given the task to carry out a detailed analysis of the major problems and conditions for research. A report was called for which would enable the M.R.C. to consider whether a new research centre should be created. The Rawson report is criticized principally because it did not fulfil the task given to the D.H.S.S. by the Act of Parliament. It is difficult to imagine how a single person not familiar with this type of research could prepare such an analysis requiring an insight to complex problems of hearing loss and fundamental problems of research. This was the task for a small working party.

Dr. Scott mentioned as a great merit of Dr. Rawson's report that it drew attention to certain problems of adult deafness. This, of course, has been done even more forcefully and in greater detail many times in the past. Dr. Rawson quotes extensively from the report of a working party on the elderly deaf (of which I happened to be the chairman), which was submitted to the Department of Health and Social Security a couple of years ago. It was pointed out what the deficiencies were concerning the care of the adult and elderly deaf. What happened to this report goodness knows.

It is clear that an entirely new approach is required in order to solve the urgent problems of sensorineural hearing loss. The conclusion of Dr. Rawsons' report, and subsequently of the Medical Research Council, is that we should carry on more or less in the same manner as we did for years. It is suggested that present facilities should be increased, perhaps a few more grants should be given, a few more small isolated research centres should be created, some kind of committee to "coordinate" research should be formed, and so on.

This shows a fundamental misunderstanding of what the real problem of research into major problems of deafness is.—I am, etc.,

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1 Department of Health and Social Security, *Deafness: Report of a Departmental Enquiry into the Promotion of Research. London*, H.M.S.O., 1973.
2 Chronically Sick and Disabled Persons Act, 1970, Chapter 44.

Neurotoxicity of Intrathecal Chemotherapy for Leukaemia

SIR,—Though intensive intrathecal chemotherapy for the prophylaxis and/or treatment of acute leukaemia of the central nervous system has greatly contributed to increased survival, serious neurological damage is being reported not infrequently after both methotrexate and cytarabine (cytosine arabinoside). Six cases of severe neurotoxicity, ranging from seizures to paraplegia, have been assembled by Saiki *et al.*[1] and another two have been reported by Kay *et al.*[2] All were in young patients with acute lymphoblastic leukaemia and the chief offending drug was methotrexate. We wish to report briefly the case of an adult with acute myelogenous leukaemia in which the nervous damage was caused by intrathecal cytarabine.

A 50-year-old physician was diagnosed as having acute myelogenous leukaemia in September 1971. He was treated with various combinations of vincristine, daunorubicin, cytarabine, and 6-thioguanine and went into complete remission, fully resuming his medical activity, until January 1973, when he developed hand tremors and somnolence. On 9 February he was admitted to hospital because of severe retronuchal headache and drowsiness. Though the bone marrow and blood were normal, the cerebrospinal fluid contained 400 blast cells/mm^3, and 10 mg each of methotrexate and cytarabine were given intrathecally. The methotrexate was dissolved in 5 ml of saline and the cytarabine in 5 ml of distilled water containing 45 mg of benzylic alcohol (the diluent supplied by the manufacturers). Three days later the cerebrospinal fluid was clear of blasts, while signs and symptoms disappeared within 24 hours. He was treated with the same combination, first twice weekly, then weekly, and later every two weeks.

On 10 March the patient was given 50 mg of cytarabine intrathecally. After a few hours he developed a non-productive cough and hoarseness. After three days he was swallowing with difficulty and after five days he had complete dysphagia and aphonia. Later he developed diplopia and left accessory nerve paralysis, so that the clinical deficit included the sixth, ninth, tenth, and eleventh cranial nerves. The patient was treated conservatively, and complete recovery of all pareses occurred in about three weeks except for persistence of moderate diplopia, which cleared up in two months.

Two theories have been proposed for the mechanism of antimetabolite neurotoxicity, which is still unclear. The possibility of damage by the antimetabolites to the nerve roots within the subarachnoid space[1] is supported by its reversal with folinic acid.[2] However, the demonstration of neurotoxicity in two preservatives, methhydroxybenzoate and benzyl alcohol,[3-5] has made them also highly suspect.[1] Perhaps a better prophylaxis of antimetabolite neurotoxicity will be achieved by avoiding both higher doses and dilution with preservative-containing diluents.—We are, etc.,

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1 Saiki, J. H., Thompson, S., Smith, F., and Atkinson, R., *Cancer*, 1972, **29**, 370.
2 Kay, H. E. M., *et al.*, *Lancet*, 1971, **2**, 542.
3 Nathan, P. W., and Sears, T. A., *Nature*, 1961, **192**, 668.
4 Duncan, D., and Jarvis, W. H., *Anaesthesiology*, 1943, **4**, 465.
5 Schauf, C., and Agin, D., *Nature*, 1969, **221**, 768.

Active Management of Labour

SIR,—The recent letter from Professor M. K. O'Driscoll and Mr. J. M. Stronge (15 September, p. 590) calls for comment on more than one point.

They state that "when the results of epidural anaesthesia in labour are evaluated *the total welfare of mother and child must be considered. . . .*" (my italics). They follow this by quoting the number of perinatal deaths in first-born infants due to intracranial haemorrhage as being 17—15 of whom were delivered by forceps—between 1963 and 1970 in their hospital. Without any mention of what part, if any, epidural analgesia played in these particular cases, they proceed to the generalization that epidurals create a high incidence of forceps (though Doughty[1] gives a figure of 26% under close supervision), the implication being that there is a connexion between the particular as quoted and the subsequent generalization. This is a complete non sequitur.

The authors then leave a deafening silence over the "total welfare of the mother," which they have stipulated as a mandatory consideration. Admittedly, selective quotation is a somewhat sterile exercise. Nonetheless, in this instance it is justifiable to point out that in the *Report on Confidential Enquiries into Maternal Deaths in England and Wales, 1967-1969*,[2] to quote the exact wording, "there were no deaths due to local infiltration, pudendal blocks, epidural or caudal analgesia, despite the more frequent use of these methods of pain relief in labour and for operative deliveries." Is not this fact relevant when considering the "total welfare of the mother?"

Finally, it has been stated and reiterated that pain in labour is an emotive subject. But the effect on the mother actually experiencing it is severe, and the degree of severity depends not solely, as is implied by Professor O'Driscoll, upon the *duration* of the stimulus; it depends equally upon the *intensity* of each succeeding stimulus. With full respect to the authors, diminution or modification of but one of these factors cannot put the problem in a "new setting." Admittedly, pain may well be a subjective phenomen, and in labour it may well have an emotive background as well as an emotive effect. But if the woman feels—and the key word is "feels"—severe pain, she receives some degree of psychological impact, the impingement of which is not fortuitously delayed for a latent period of 12 hours.

The history of the recognition of the value of epidural nerve block both to mother and to fetus is one of a long and an uphill

struggle; what has been so hardly won is not to be lightly discarded.—I am, etc.,

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1 Doughty, A., *British Journal of Anaesthesia*, 1969, 41, 1058.
2 Department of Health and Social Security, *Report on Confidential Enquiries into Maternal Deaths in England and Wales, 1967-1969*, p. 71. London, H.M.S.O., 1972.

SIR,—May I comment on Professor M. K. O'Driscoll and Dr. J. M. Stronge's remarks (15 September, p. 590) regarding active management of labour?

While the responsibility for mother and child in labour rests with the obstetrician, the mother should surely have some say in the matter of pain relief. Safety must take precedence above all else so far as the obstetrician is concerned, but I believe many mothers would be prepared to accept any small risk involved in order to have a tolerable labour. I have been told by women on several occasions in the past that the pain they had to endure during labour was, in their opinion, equivalent to the pain of a surgical operation. If this could possibly be true, one must then ask who would prefer to be operated on without anaesthesia simply because the anaesthetic carried a small risk?

I am also certain that if men were the child-bearers of the world, an epidural service on demand would have been initiated many years ago.—I am, etc.,

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SIR,—Professor Kieran O'Driscoll and his colleagues (21 July, p. 135) and Dr. J. S. Crawford (25 August, p. 453) are entirely correct in underlining the importance of reducing pain and delay in labour. My experience is that it is unacceptable pain which for many women mars what should otherwise be an enjoyable event.

While it is clear that obstetric pain is a complex phenomenon, I belive that the commonest cause of severe pain and delay in labour is to be found in impaired mobility of the sacroiliac joints, which gives rise during uterine contraction to pain of sacroiliac distribution. Pain of this kind is best treated by lifting the patient by one knee so that she comes to lie on her side, facing away from her attendant and with her opposite hip swinging just clear of the bed. The patient is allowed to lie on her back between pains and the procedure is repeated—usually at the patient's request—with the onset of each subsequent uterine contraction.

I have used this method without mishap for the past 25 years.[1] It will be apparent that in this position considerable traction is being applied to both sacroiliac joints and that it is likely that the mobility of these joints and the size of the pelvic cavity are then maximal. The relief of pain is quite dramatic and so is the rapidity of labour from then on, the patient being able to bear down uninhibited by pain.—I am, etc.,

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1 Eastwood, N. B., *Journal of the College of General Practitioners*, 1958, 1, 304.

Abnormal Mixed Leucocyte Reaction in Bone Marrow Aplasia

SIR,—We wish to report the observation of an abnormal mixed leucocyte reaction (M.L.R.) in a case of bone marrow aplasia. The patient's lymphocytes responded normally to allogeneic leucocytes but failed to stimulate allogeneic lymphocytes. The M.L.R. study of the patient and his family was performed in view of a possible bone marrow transplantation from an HL-A-identical sibling.

The patient (referred by Dr. Mannoni (Henri Mondor Creteil Hospital)) was a 20-year-old man with an idiopathic bone marrow aplasia which had the following features: (*a*) a lymphopenia (about 500 lymphocytes per ml) which had already been present three months before the onset of the disease. (*b*) a hypogammaglobulinaemia with IgG 600 mg/ml, IgM 40 mg/ml, and normal IgA level (65 mg/ml). Furthermore, since the age of 5 he had had numerous pulmonary infections but without documented bronchiectasis. Death occurred three months after the onset of the aplasia, which was not influenced by two months of androgen therapy. At the time of the M.L.R. study the patient had not recently received any steroids or transfusions.

The M.L.R. technique used was the one described by Hartzmann *et al.*[1] with slight modifications[2]. Lymphocytes were purified by a Ficoll-Hypaque gradient. 1×10^5 responding cells were cultivated with 4×10^5 mitomycin-treated (25μg/ml) stimulating cells in a total volume of 0·2 ml for 120 hours in Falcon microplates. RPMI 1640 supplemented with 20% heat-inactivated (56°C, 30 min.) pooled human plasma was used throughout the experiments. In the same conditions, 1×10^5 lymphocytes were exposed to phytohemagglutinin (PHA) in a final concentration of 1:100 for 72 hours. Blastic transformation was measured by ^{3}H-thymidine incorporation during a 16-hour period.

The results, which are summarized in tables I and II, were reproducible on two occasions with different allogeneic controls.

TABLE I—*PHA Transformation (counts/min)*

Source of Lymphocytes	Without PHA	With PHA
Patient	216	5,263
Patient's brother ..	304	65,724
Control subject ..	483	78,800

The patient's cells clearly showed: (1) a markedly decreased response to PHA stimulation, (2) a normal response to allogeneic leucocytes, and (3) an inability to stimulate allogeneic lymphocytes (related or unrelated). There was therefore a dissociation between the responding and stimulating ability of the patient's cells in the M.L.R. test and also a dissociation between their ability to respond to PHA and to allogeneic cells.

Whereas we cannot eliminate a possible increase in sensitivity of the patient's cells to mitomycin C treatment or a non-specific cytotoxic effect of these lymphocytes for allogeneic cells, these explanations seem unlikely. Furthermore, the interaction of an inhibitory factor present in the patient's serum can be ruled out since the lymphocytes were extensively washed before setting up the culture in a medium supplemented with pooled human plasma. The lack of response to PHA associated with an intact response to allogeneic cells has been described in many cases with combined immune deficiency disease by Dupont *et al.*[3] However, such a dissociation between the stimulating and the responding ability has not been reported to our knowledge.

These observations raise some questions. (1) What is the frequency of such dissociation in immune deficiency states? The number of systematic studies of the M.L.R. reported in these states is small, especially with regard to the stimulating capacity of the patient's lymphocytes. (2) What is the nature of the dissociation? The hypothesis of a heterogeneic lymphocyte population in which one type of cells responds to PHA and another to allogeneic leucocytes has been already proposed by Meuwissen *et al.*[4] This hypothesis has received some experimental support, especially from the observations of Colley *et al.*[5] who were able to separate different populations of T lymphocytes, one of which responds to PHA and the other to allogeneic cells. Zeylemaker *et al.*[6] have made a similar observation in man. Carr *et al.*[7] also have reported some relevant data showing that fetal lymphocytes acquire the ability to respond to allogeneic cells and to PHA at different stages of development.

Our data could support the hypothesis suggested by Meuwissen *et al.* but one must then consider the existence of a third population responsible for the stimulating activity.

Another explanation, however, can be proposed—that is, that only one population is involved and in some patients with combined immune deficiency disease specific receptors for PHA or for M.L.R. stimulation are lacking. The inability of combined immune deficiency cells to produce a soluble mediator which may be necessary to stimulate allogeneic lymphocytes can also be postulated to explain our case report.

Finally, whatever the nature of the phenomenon, it could be secondary either to

TABLE II—*Mixed Lymphocyte Culture between Patient (P), Mother (B), Brothers (C and D), and Control Subjects (T_1 and T_2)*

Responding Cells	Stimulating (Mitomycin-treated) Cells: P		B		C		D		T_1	
	c.p.m.	I	c.p.m.	I	c.p.m.	I	c.p.m.	I	c.pm	I
P	216		N.D.		315	1.5	N.D.		19,944	92
B	397	0.5	872		24,236	28	28,621	33	50,084	57
C	304	0.4	53,370	75	706		67,711	96	46,697	66
D	369	1.1	21,072	64	31,605	96	328		N.D.	
T_1	483	1.5	21,556	70	19,435	63	5,597	18	308	
T_2	635	1	N.D.		101,626	101	N.D.		N.D.	

HL—A genotypes are: B=HL—A10, W14/HL—A3, 5; P and C=HL—A2, W27/HL—A10, W14; D=HL—A2, 12/HL—A3, 5. Counts per minute (c.p.m.) are means of triplicate cultures. I=index, N.D.=not done.