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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Institute of Laryngology and Otology,
London W.C.1

Sirs,—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, especially 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.

If we consider the situation 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 specified for 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 for 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 multiple 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 examination of the major problems and conditions for research. A report was called for which would enable the M.R.C. to consider whether the new research centre should be created. The Rawson report is criticized principally because it did not fulfill 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 field 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 some two years ago. It was pointed out what the deficiencies were concerning the care of the old and elderly deaf. What happened to this report good news.

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. Rawson's 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 the whole problem of research into major problems of deafness is.—I am, etc.,

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Institute of Laryngology and Otology,
London W.C.1

Neurotoxicity of Intrathecal Chemotherapy for Leukaemia

Sirs,—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 ascribed by Stajich et al. and another two have been reported by Kay et al.3 All were in young patients with acute lymphoblastic leukaemia and the chief offending drug was methotrexate. We wish to report briefly the case of a 62-year-old woman 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, and cytarabine. He was discharged in 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 retroocular headache and drowsiness. Though the bone marrow and blood were normal, the cerebrospinal fluid contained 400 blast cells/mm3, and 10 mg of methotrexate and cytarabine were given intracerebrospinalally. Three days later the cerebrospinal fluid was clear of blast cells, 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 diaphoresis 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 antimitabolite neurotoxicity, which is still unclear. The possibility of damage by the antimitabolites to the nerve roots within the subarachnoid space1 is supported by its reversal with folic acid.2 However, the demonstration of neurotoxicity in two preservatives, methyldihydroxybenzote and benzyl alcohol,3 has made them also highly suspect.1 Perhaps a better prophylaxis of antimitabolite neurotoxicity will be achieved by avoiding both higher doses and dilution with preservative-containing diluents.—We are, etc.,

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University of Genoa.


Active Management of Labour

Sirs,—The recent letter from Professor M. K. O'Driscoll and Mr. J. M. Stroke (15 September, p. 590) calls for comment on more 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 of local infant mortality, in-hospital mortality, or 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

1 Professor O'Driscoll gives a figure of 26%, which is well below the figure quoted in the Labour report. As Professor O'Driscoll1 says, the figures are, etc.,...
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 25-year-old man with an idiopathic bone marrow aplasia which had the following features: (a) a lymphopenia (about 100 lymphocytes per mm³) 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 Hartmann et al. with slight modifications. Lymphocytes were purified by a Ficoll-Hypaque gradient. $1 \times 10^8$ responding cells were cultured with $4 \times 10^7$ 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, $1 \times 10^5$ lymphocytes were exposed to phytohemagglutinin (PHA) in a final concentration of 1:100 for 72 hours. Blastic activity was measured by 3H-thymidine incorporation during a 16-hour period.

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

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<td>304</td>
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<tr>
<td>Control subject</td>
<td>483</td>
<td>78,800</td>
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The patient’s cells showed clearly: (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.

The possibility 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 PHA, serum, and with PHA added after incubation. The interaction of this inhibitory factor with PHA associated with an intact response to allogeneic cells has been described in many cases with combined immune deficiency disease. It has been suggested by D’Ympn et al. that a dissociation between the stimulating and the responding ability has not been reported to our knowledge.

These observations raise some questions. (1) Does the existence of such a 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 heterogenous lymphocyte population in which one type of cells responds to PHA and another to allogeneic leucocytes has been already proposed by Meuwissen et al. This hypothesis has received some experimental support, especially from the observations of Colley et al. 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. have made a similar observation in man. Carr et al. also have reported some relevant data showing that fetal lymphocytes are able 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 such 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

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