Guidelines should be based on systematic reviews of the evidence

EDITOR.—After surveying 39 intensive care units D R Jeevaratnam and D K Menon conclude that many use treatments that are “at odds with an emerging consensus about the management of patients with severe head injury.”¹ Use of steroids despite “increasing evidence of their lack of efficacy” is given as an example of this. The authors call for clinical guidelines.

Although guidelines may reduce variations in practice, we believe that a more important obstacle to the effective management of head injury is the lack of reference to large scale randomised evidence on the effectiveness of treatment.² This evidence could be obtained by conducting systematic reviews of all relevant previous trials and, when necessary, by conducting large scale randomised trials. Like Jeevaratnam and Menon, we will use steroids as our example.

Worldwide, head injury is a major cause of premature death. For a problem as important as this even a moderate reduction in mortality from an intervention as simple and inexpensive as steroids could save thousands of lives.² In support of their statement that steroids are ineffective Jeevaratnam and Menon cite three randomised trials.³⁻⁵ Table 1 shows the effect of steroids on six month mortality in these trials. The pooled result has a wide confidence interval, and it is impossible to exclude a moderate intervention effect. Much larger trials would be required to detect a moderate effect of steroids on mortality.

Table 1—Result of pooling data from trials showing effect of steroids on six month mortality

Trial	Steroid	Placebo	Odds ratio (95% confidence interval)
Gianotta <i>et al</i>	34/72	7/16	0.86 (0.30 to 2.45)
Cooper <i>et al</i>	26/49	13/27	1.14 (0.38 to 3.37)
Saul <i>et al</i>	8/50	9/50	1.21 (0.47 to 3.08)
Trials pooled	68/171	29/93	1.07 (0.59 to 1.92)

Another reason why the possibility that steroids may prove useful should not be dismissed is that Jeevaratnam and Menon cite only a fraction of the evidence available. We are conducting a systematic review of steroids in head injury and have so far identified 15 randomised trials. Inclusion of all the randomised evidence in a systematic review minimises random error and avoids systematic error, which can arise when a biased selection of trials is reviewed. Guidelines are needed for the management of severe head injury, but these should be based on a systematic review of all the relevant randomised trials⁶ and not on an emerging consensus ignoring the evidence. If systematic reviews fail to provide clear answers then the answers should be sought in large randomised trials.

IAN ROBERTS
Senior lecturer in epidemiology

Institute of Child Health,
University of London,
London WC1N 1EH

PHIL ALDERSON
Senior registrar in public health medicine

UK Cochrane Centre,
Oxford OX2 7LG

KATHY ROWAN
Director

Intensive Care National Audit and Research Centre,
London WC1H 9HR

1 Jeevaratnam DR, Menon DK. Survey of intensive care of severely head injured patients in the United Kingdom. *BMJ* 1996;312:944-7. (13 April.)

2 Peto R, Collins R, Gray R. Large-scale randomized evidence: large simple trials and overviews of trials. *J Clin Epidemiol* 1995;48:23-40.

- Gianotta SL, Weiss MH, Apuzzo MLJ, Martin E. High dose glucocorticoids in the management of severe head injury. *Neurosurgery* 1984;15:497-501.
- Cooper PR, Moody S, Clark WK, Kirkpatrick J, Maravilla K, Gould AL, *et al*. Dexamethasone and severe head injury: a prospective double blind study. *J Neurosurg* 1979;51:507-16.
- Saul TG, Ducker TB, Salzman M, Carro E. Steroids in severe head injury: a prospective randomized clinical trial. *J Neurosurg* 1981;54:596-600.
- Chalmers I, Haynes B. Reporting, updating and correcting systematic reviews of the effects of health care. *BMJ* 1994;309:862-5.

Author's reply

EDITOR.—The primary purpose of our audit was to document clinical practice in this aspect of intensive care, and we believe that our results provide strong evidence for the variability in practice among centres. These findings are echoed in the data provided by M D D Bell.

We were careful to discuss the deficiencies of a telephone based audit and are interested in the data provided by J D Palmer and colleagues. Since our paper was accepted for publication, however, we have undertaken (at the suggestion of one of the reviewers of the paper) a documentary survey that covered the issues addressed in our original telephone survey. The survey was sent to senior medical staff in the neurosurgical units that were targeted in the telephone survey, and, as might be expected, resulted in a lower response rate.¹ Except for data on the use of corticosteroids, the findings from the two surveys were similar, in support of the general accuracy of data in our paper.

We agree with Graham Teasdale and colleagues that the report by the task force of the American Association of Neurological Surgeons and Joint Section in Neurotrauma and Critical Care is an important advance in the management of patients with acute head injuries,² and we believe that its findings support the case for guidelines based on the available evidence. While we were unaware of the activities of the working party of the Society of British Neurological Surgeons, its agreement that there is a need for synthesis of such activities and the production of national guidelines is welcome, and we strongly support the case for national research.

The report by the task force provides a clear level I recommendation against the use of corticosteroids in acute head injury, one of the few areas in which it thought that the evidence was sufficient for it to make such a firm recommendation. We look forward with interest to the results of the meta-analysis being undertaken by Ian Roberts and colleagues. Clearly, practice may change on the basis of new evidence or a new analysis of available evidence, and we agree that there is a case to be made for both reducing variations in practice and analysing the efficacy of treatments. The purpose of our paper, however, was to highlight the first of these two issues.

D K MENON
Honorary consultant

Neurosciences Critical Care Unit,
Addenbrooke's Hospital,
Cambridge CB2 2QQ

1 Matta BF, Menon DK. Audit of intensive care of acute head injury in the United Kingdom. *Crit Care Med* (in press).

2 Task Force of the American Association of Neurological Surgeons and Joint Section in Neurotrauma and Critical Care. *Guidelines for the management of severe head injury*. Brain Trauma Foundation, 1995.

Assay used in serum screening for Down's syndrome may depend on ethnic make up of population

EDITOR.—The purpose of our report on serum screening for Down's syndrome was to “highlight the need for outcome data on [such screening] to

be collected by ethnic group.”¹ We argued that only when this is done can problems specific to different ethnic groups (such as important differences in the incidence of Down's syndrome pregnancies and in the medians of biochemical markers, etc) be identified and addressed. We are pleased to have achieved this objective, as three laboratories with data on large numbers of ethnic minorities have now reported their results,²⁻⁴ which are interesting.

Clare Ford and colleagues use intact human chorionic gonadotrophin (as we did), and their results are similar to ours,² with a higher false positive rate in Indian Asians, indicating that the median value of intact human chorionic gonadotrophin is higher in that group. P J Holloway and S Bulusu³ and Kevin Spencer's laboratories⁴ use free β human chorionic gonadotrophin, and their results suggest that when this assay is used the false positive rate is lower in South Asian and Indian Asians and higher in Afro-Caribbeans. These reports therefore support our recommendation that “medians for the biochemical markers and risk estimates should be derived from within the population.” It also seems that certain assays may be better in certain populations.

There is much dispute among laboratories over the best assay or combination of assays for screening maternal serum, and Connor, in an editorial on biochemical screening for Down's syndrome, made a plea that commercial considerations should not interfere with the publication of data.⁵ We hope that, despite the pressure of the internal market and competition among laboratories for providing screening services, the laboratories will continue to publish data that will help determine which assay is best for each population.

L GILBERT
Consultant obstetrician and gynaecologist

Doncaster Royal Infirmary,
Doncaster DN2 5LT

JON NICHOLL
Director

Medical Care Research Unit,
University of Sheffield,
Sheffield S10 2RX

ANTHONY MANDER
Consultant obstetrician and gynaecologist

Royal Oldham Hospital,
Oldham OL1 2JH

- Gilbert L, Nicholl J, Alex S, Smethurst I, Mander A, Andrews A, *et al*. Ethnic differences in the outcome of serum screening for Down's syndrome. *BMJ* 1996;312:94-5. (13 January.)
- Ford C, Moore A, Bartlett WA, Jones AF. Ethnic differences in outcome of serum screening for Down's syndrome. *BMJ* 1996;312:1040. (20 April.)
- Holloway PJ, Bulusu S. Ethnic differences in outcome of serum screening for Down's syndrome. *BMJ* 1996;312:1041. (20 April.)
- Spencer K. Ethnic differences in outcome of serum screening for Down's syndrome. *BMJ* 1996;312:1041. (20 April.)
- Connor M. Biochemical screening for Down's syndrome. *BMJ* 1993;306:1705.

Why interferon beta 1b was licensed is a mystery

EDITOR.—Patients with multiple sclerosis are interested in whether they can still go to work, get out of bed to go to the lavatory, or stand on one leg to put the other one through their pants—that is to say, they are interested in disability. Interferon beta 1b has been shown to reduce the rate of relapse in relapsing multiple sclerosis by one third¹ and to diminish the accretion of disease as shown by magnetic resonance imaging.² Unfortunately, neither of these two variables has any convincing or direct relation to disability. I have patients who have several relapses a year, or who seem on magnetic resonance imaging to have no brains left, who lead full and active lives; I have patients who are seriously disabled after one or two relapses; I have patients with severe disability whose scans apparently show trivial disease.

Interferon beta 1b has to be self administered subcutaneously every other day. Patients run the risk of feeling that they have chronic flu³ or of becoming depressed,³ and 38% of them will have neutralised the drug by the development of antibodies after three years.³

Interferon beta 1b has no significant effect on the development of disability in multiple sclerosis.³ Quite why it has been licensed is a mystery to many of us. Why is Schering allowed to advertise it in the *BMJ*?

PETER HARVEY
Consultant neurologist

Royal Free Hospital,
London NW3 2QG

- 1 IFNB Multiple Sclerosis Study Group. Interferon-beta 1b is effective in relapsing-remitting multiple sclerosis. Clinical results of a multicentre, randomised, double-blind placebo-controlled trial. *Neurology* 1993;43:655-61.
- 2 Patey DW, Li DKB, UBC MS/MRI Study Group, IFNB Multiple Sclerosis Study Group. Interferon-beta 1b is effective in relapsing-remitting multiple sclerosis. MRI analysis results of a multicentre, randomised, double-blind, placebo-controlled trial. *Neurology* 1993;43:662-7.
- 3 IFNB Multiple Sclerosis Study Group and UBC MS/MRI Analysis Group. Interferon-beta 1b and the treatment of multiple sclerosis: final outcome of a randomised controlled trial. *Neurology* 1995;45:1277-85.

Non-Hodgkin's lymphoma and solar ultraviolet radiation

Data are inconsistent

EDITOR,—Graham Benthall confirms known geographical patterns when he reports a positive association between the incidence of non-Hodgkin's lymphoma and ambient solar ultraviolet radiation in England and Wales.^{1 2} His results conflict with those from the United States, where a negative association was reported,³ further fuelling the debate over whether exposure to solar ultraviolet radiation increases the risk of non-Hodgkin's lymphoma. If there is a positive association then those people working in outdoor occupations might be expected to be at increased risk of this malignancy.

We examined the risk of non-Hodgkin's lymphoma among people judged to spend most of their working day outdoors, using one of the largest population based cancer registration datasets in the world. The data and methodology have been fully described elsewhere.⁴ Briefly, occupational information was available on 252 663 men and 119 227 women registered as having cancer in England between 1981 and 1987. Ten job groups were defined as outdoor occupations (see table 1); they accounted for a total of 17 636 registrations in men and 960 in women. Proportional registration ratios were used to estimate the relative risk of specific cancers in outdoor workers compared with workers in all occupations combined, with adjustment for age (five year age groups), social class (six classes), and cancer registry of origin (13 registries). All registrations for which the occupation was adequately described formed the standard for comparison.

Table 1 shows the risks for all cancer sites in outdoor workers by sex. In men there was a significant 19% excess of non-melanocytic skin cancer, suggesting high exposure to solar ultraviolet radiation⁵ but no excess of non-Hodgkin's lymphoma. In women the reverse was found, with a significant 56% excess of non-Hodgkin's lymphoma but no excess of non-melanocytic skin cancers. It is notable that 25 of the 27 women diagnosed as having non-Hodgkin's lymphoma were farmers and that similar observations among agricultural employees have been attributed by others to exposure to pesticides.⁶

We also examined the relation between the occupation specific risks for non-melanocytic skin cancers and non-Hodgkin's lymphoma

Table 1—Adjusted proportional registration ratios (95% confidence intervals) for outdoor workers* aged 20-74, England, 1981-7

Cancer (ICD code, 9th revision)	Men		Women	
	No Observed	Adjusted proportional registration ratio	No Observed	Adjusted proportional registration ratio
Oral cavity (141, 143-145)	130	96 (81 to 115)	6	160 (59 to 349)
Salivary (142)	22	91 (57 to 138)	0	—
Pharynx (146-148)	79	78 (62 to 98)	2	70 (9 to 255)
Oesophagus (150)	452	103 (94 to 113)	14	111 (61 to 187)
Stomach (151)	1180	96 (91 to 102)	26	89 (59 to 131)
Small intestine (152)	37	124 (88 to 172)	2	161 (20 to 584)
Colon (153)	927	95 (90 to 102)	49	103 (77 to 137)
Rectum (154)	848	103 (97 to 111)	31	117 (80 to 167)
Liver (155)	116	99 (82 to 119)	1	29 (1 to 167)
Gall bladder (156)	66	74 (58 to 95)	8	152 (66 to 300)
Pancreas (157)	591	104 (96 to 113)	21	101 (63 to 155)
Retroperitoneum (158.0)	10	78 (38 to 145)	0	—
Peritoneum (158.8-158.9)	10	80 (38 to 147)	1	234 (6 to 1307)
Nose and nasal sinuses (160)	40	111 (80 to 152)	1	70 (2 to 394)
Larynx (161)	233	95 (84 to 109)	0	—
Lung (162)	5354	98 (95 to 101)	115	101 (84 to 122)
Pleura (163)	67	69 (54 to 89)	1	61 (2 to 342)
Thymus and mediastinum (164)	22	138 (87 to 209)	2	309 (38 to 1117)
Bone (170)	32	103 (71 to 146)	2	123 (15 to 448)
Soft tissue (171)	65	93 (72 to 119)	7	207 (84 to 428)
Melanoma (172)	125	94 (79 to 113)	9	67 (31 to 128)
Non-melanocytic skin (173)	1564	119 (114 to 126)	49	88 (65 to 117)
Female breast (174)	NA	—	190	96 (84 to 112)
Male breast (175)	28	98 (65 to 142)	NA	—
Uterus (179, 181, 182)	NA	—	30	99 (67 to 143)
Cervix (180)	NA	—	37	88 (63 to 123)
In situ cervix (233.1)	NA	—	105	93 (76 to 113)
Ovary (183)	NA	—	44	99 (72 to 133)
Prostate (185)	1126	108 (102 to 115)	NA	—
Testis (186)	190	100 (86 to 115)	NA	—
Other male genital organs (187)	57	110 (84 to 144)	NA	—
Bladder (188, 189.1-189.9)	925	89 (84 to 95)	15	84 (48 to 140)
Kidney (except pelvis) (189.0)	268	88 (79 to 100)	8	98 (43 to 195)
Eye (190)	19	82 (49 to 128)	1	85 (2 to 479)
Brain and meninges (191, 192, 225, 237.5-9, 239.6)	489	104 (95 to 114)	24	113 (73 to 169)
Malignant brain (191)	373	107 (97 to 119)	11	87 (44 to 156)
Thyroid (193)	39	97 (69 to 133)	8	131 (57 to 259)
Suprarenal and other endocrine organs (194)	8	59 (26 to 118)	0	—
Ill defined and secondary (195-199)	894	94 (89 to 101)	50	112 (84 to 149)
Non-Hodgkin's lymphoma (200, 202)	401	95 (86 to 105)	27	156 (103 to 228)
Hodgkin's disease (201)	120	88 (73 to 105)	3	63 (13 to 187)
Myeloma (203)	211	112 (98 to 128)	3	42 (9 to 126)
Leukaemia (204-208)	395	105 (96 to 117)	12	85 (44 to 149)

ICD = International Classification of Diseases. NA = Not applicable.

*Outdoor workers were defined by using the Southampton occupational classification and included the following job groups (number of registrations given in parentheses): farmers (men, 8245; women, 838); foresters (men, 194; women, 6); fishing and related workers (men, 292; women, 3); scaffolders (men, 298; women, 4); bricklayers and tilers (men, 2957; women, 0); roofers and glaziers (men, 556; women, 16); builders etc (men, 3760; women, 79); rail track workers (men, 358; women, 2); road construction workers and paviours (men, 662; women, 9); mains and service layers (men, 314; women, 3).

because it is well known that exposure to solar ultraviolet radiation increases the risk of skin cancer.⁵ No linear association was observed, for either men (correlation coefficient 0.07) or women (correlation coefficient -0.02).

The aetiology of non-Hodgkin's lymphoma is poorly understood, and many factors are likely to be important. Given the inconsistencies in the data presented here and elsewhere, more detailed research is clearly required before a causal role is ascribed to solar ultraviolet radiation.

ROBERT NEWTON
Medical Research Council training fellow
EVE ROMAN
Staff scientist
NICOLA FEAR
Doctoral student

Imperial Cancer Research Fund,
Cancer Epidemiology Unit,
Radcliffe Infirmary,
Oxford OX2 6HE

LUCY CARPENTER
Statistical epidemiologist

Department of Public Health and Primary Care,
Radcliffe Infirmary

- 1 Benthall G. Association between incidence of non-Hodgkin's lymphoma and solar ultraviolet radiation in England and Wales. *BMJ* 1996;312:1128-31. (4 May.)
- 2 Swerdlow A, dos Santos Silva I. *Atlas of cancer incidence in England and Wales 1968-85*. Oxford: Oxford University Press, 1993.
- 3 Hartge P, DeVessa SS, Graumen D, Fears TR, Fraumeni JF. Non-Hodgkin's lymphoma and sunlight. *JNCI* 1996;88:298-300.
- 4 Roman E, Carpenter LM. Cancer incidence in England 1981-87. In: Registrar General. *Occupational health. Decennial supplement for England and Wales 1995*. London: HMSO, 1996:77-102.
- 5 World Health Organisation. Solar and ultraviolet radiation. *IARC Monogr Eval Carcinog Risks Hum* 1992;No 55.
- 6 Linet MS, McLaughlin JK, Walker HS, Chow WH, Weiner JA, Stone BJ, et al. Occupation and hematopoietic and lymphoproliferative malignancies among women: a linked registry study. *J Occup Med* 1994;36:1187-98.

Basal cell carcinoma may be linked to haematological malignancy

EDITOR,—Graham Benthall shows that the incidence of non-Hodgkin's lymphoma is positively associated with exposure to solar ultraviolet radiation,¹ giving insights into the previous