

aware that the spontaneous but variable incidence of birth defects unassociated with drug intake is between 2% and 7%.

How can the uncertainties be resolved? One answer is to do a cohort study, in which women are identified whether or not they have been exposed to Debendox. The hope is that the women in the non-exposed group prove to be as nearly identical as possible with those in the exposed group. Many women need to be studied, often many thousands. Conventionally the results are expressed as a relative risk—that is, the incidence rate in the exposed group relative to the incidence rate in the non-exposed group. The standard error of the relative risk may also be determined, as may the 95% or 99% confidence limits.

Almost all the cohort studies performed have shown no increase in the relative risk of Debendox causing fetal malformations.¹⁻¹¹ Some of the trials have been criticised for lack of relevant controls, but in general they stand up well to criticism. Possibly some of the controls might have been exposed to Debendox inadvertently since it was available over the counter in Britain (and this caused problems for the defence in the first court action), but in fact it seems that very few women obtained Debendox in this way.¹² An assessment of these studies combined gave a relative risk of 0.89 with 95% confidence limits of 0.76 and 1.04.¹³ Thus the data exclude a high grade teratogenic risk, but at conventional levels of probability ($p \leq 0.05$) they do not exclude the drug being a low grade teratogen with a risk above background of 4-5%. This is just the level of risk that the Debendox action groups are claiming.¹⁴

The second approach is the case-control investigation, in which women are identified whose infants have the defects under study (usually cleft lip, cleft palate, limb reduction deformities, and cardiovascular abnormalities) and a control group of women is chosen whose children do not have these defects. Often the control women considerably outnumber the test group. Information about prior exposure to Debendox is sought, and the odds ratio with its standard error can be determined. This type of study is sometimes considered more powerful than a cohort study, but it has problems, too, such as over the counter sales of the drug and recall bias. Clearly mothers whose infants are deformed will remember more accurately the drugs they took in pregnancy than those with normal children, particularly if the birth in question was several years earlier. Several case-control studies have been performed and in general they have found no association between Debendox and fetal abnormalities.¹⁵⁻¹⁸ A weak association was found, however, between congenital heart defects¹⁹ and oral clefts²⁰ and Debendox. Elbourne and her colleagues have attempted to overcome some of the problems of the case-control studies²¹ and have repeated Golding's work.²⁰ In studies in Cardiff and Aberdeen they found no evidence of an association between oral clefts and an exposure to Debendox.

What can we conclude from this saga? To leave the legal discussions aside, a meaningful public debate will not be possible on such topics as this until the public is better informed about biological matters. Debendox may be a low grade teratogen, but the case will almost certainly be impossible to prove either way in a scientific sense. Indeed, the identification of any low grade teratogen will always be very difficult. For both cohort and case-control studies many thousands of women need to be studied, with their controls carefully chosen. Even so, such studies will always be at the mercy of the well chosen anecdotal report.

What the public should be told is that we can never prove a drug to be 100% safe in man. Drug treatment should always

be limited to those patients in whom its potential benefits outweigh the risks, and for nausea of pregnancy the equation will often be negative, since non-drug measures are often effective.¹

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- 1 Anonymous. Debendox is not thalidomide [Editorial]. *Lancet* 1984;ii:205-6.
- 2 Langman MJS. Debendox in pregnancy. Many last words. In: Dukes MNG, ed. *Side effects of drugs annual*. No 6. Amsterdam: Excerpta Medica, 1982:316-7.
- 3 Bunde CA, Bowles DM. A technique for controlled survey of case records. *Current Therapeutic Research* 1963;5:245-8.
- 4 General Practitioner Research Group. Drugs in pregnancy survey. *Practitioner* 1963;191:775-80.
- 5 Milkovich L, Van den Berg B. An evaluation of the teratogenicity of certain antiemetic drugs. *Am J Obstet Gynecol* 1976;125:244-8.
- 6 Newman NM, Correy JF, Dudgeon GI. A survey of congenital abnormalities and drugs in a private practice. *Aust NZ J Obstet Gynaecol* 1977;17:156-9.
- 7 Smithells RW, Sheppard S. Teratogenicity testing in humans: a method demonstrating safety of Bendectin. *Teratology* 1978;17:31-5.
- 8 Fleming DM, Knox JDE, Crombie DL. Debendox in early pregnancy and fetal malformation. *Br Med J* 1981;283:99-101.
- 9 Jick H, Holmes LB, Hunter JR, Madsen S, Stergachis A. First trimester drug use and congenital disorders. *JAMA* 1981;246:343-6.
- 10 Harron DWG, Griffiths K, Shanks RG. Debendox and congenital malformations in Northern Ireland. *Br Med J* 1980;281:1379-81.
- 11 Gibson GT, Colley DP, McMichael AJ, Hartshorne JM. Congenital anomalies in relation to the use of doxylamine/dicyclomine and other antenatal factors. *Med J Aust* 1981;i:410-4.
- 12 Korcock M. The Bendectin debate. *Can Med Assoc J* 1989;123:922-8.
- 13 MacMahon B. More on Bendectin. *JAMA* 1981;246:371-2.
- 14 Hall JB. Debendox in pregnancy. *Lancet* 1981;ii:154-5.
- 15 Nelson MN, Forfar JO. Associations between drugs administered during pregnancy and congenital abnormalities of the fetus. *Br Med J* 1971;ii:523-7.
- 16 Greenberg G, Inman WHW, Weatherall JAC, Aldelstein AM, Haskey JC. Maternal drug histories and congenital abnormalities. *Br Med J* 1977;ii:853-6.
- 17 Cordero JF, Oakley GP, Greenberg F, James LM. Is Bendectin a teratogen? *JAMA* 1981;245:2307-10.
- 18 Mitchell AA, Rosenberg L, Shapiro S, Slone D. Birth defects in relation to use of Bendectin in pregnancy. *JAMA* 1981;245:2311-4.
- 19 Rothman KJ, Fyler DC, Goldblatt A, Kreidberg MB. Exogenous hormones and other drug exposures of children with congenital heart disease. *Am J Epidemiol* 1979;109:433-9.
- 20 Golding J, Vivian S, Baldwin JA. Maternal anti-nauseants and clefts of lip and palate. *Hum Toxicol* 1983;2:63-73.
- 21 Elbourne D, Mutch L, Dauncey M, Campbell H, Samphier M. Debendox revisited. *Br J Obstet Gynaecol* (in press).

Families who care

Relatives of patients with stroke and head injury are said to express anger and guilt and to tend to denial of their relative's illness—reactions which are familiar to doctors who treat these disorders.^{1 2} In both cases the illness has a behavioural as well as a physical component. Which is the more important in terms of the burden on relatives? What differentiates a normal coping strategy from a maladaptive one?

Emotional regression in patients with cerebral dysfunction may lead to their spouses feeling trapped and isolated and not having their own dependency needs met.³ The ability of the relatives to cope may be critical for patients' welfare. Isaacs argued that the strain on relatives of patients with dementia was often the trigger for admission.⁴ In a review of the psychological consequences of childhood leukaemia McGuire found that 20-30% of parents required psychiatric treatment (mainly for depression or anxiety), that 25% of mothers described chronic sexual difficulties, and that 20% of parents had serious marital disharmony.⁵ But are these figures atypical of adjustment in the community at large?

Among techniques used to rate the burden on relatives has been asking them to rate their own level of distress. One quarter of spouses of victims of myocardial infarction recorded moderate to high stress two months after the episode.⁶ Almost two thirds of the relatives of victims of

closed head injury recorded similar distress throughout the following year.⁷

The concept of "stress" is, however, difficult to define, and self ratings lack objectivity. An alternative approach is to use standardised rating scales and so to make comparisons with the normal population. The ubiquitous general health questionnaire⁸ has often been used to rate the severity of psychological distress in relatives and to measure psychiatric "caseness"—that is, the likelihood of being sufficiently disturbed to merit the term "case."⁹ The wives of victims of myocardial infarction scored higher on the general health questionnaire during the patients' first admission with an infarction than did the patients themselves—though the effect of sedation on the victims' anxiety was not taken into account.¹⁰ Similarly, Kinsella and Duffy found high scores on the general health questionnaire in the spouses of victims of stroke, particularly when patients were aphasic.¹¹ A third of the relatives of the total population of schizophrenics who had used the services of a district hospital psychiatric unit in the study year scored at "case" level on the general health questionnaire 28.¹² High scores were recorded in parents of children with cystic fibrosis or leukaemia who overestimated the severity of their children's symptoms.¹³

The general health questionnaire may define "cases," but cases of what? The nature of the psychological distress in relatives seems likely to be a minor disorder of mood. Depression was found in the relatives of patients with stroke,¹¹ while a prospective study of victims of severe closed head injury and their relatives found that 39%, 20%, and 23%¹⁴ scored above the threshold on the Wakefield depression inventory at one month, six months, and 12 months after the trauma respectively.¹⁵ Higher levels of depression were recorded in the wives of Israeli military men with head injury than in the wives of paraplegics or of staff members, but the numbers studied were small.¹⁶

Another study found that women relatives of men patients with severe closed head injury had a higher incidence of anxiety states,¹⁷ as defined by the Leeds scales,¹⁸ than did relatives of patients with minor head injury three months after the trauma. Over a third of the relatives of the severely injured group continued to score at case level on these rating instruments throughout the year after injury as well as having high scores on the subscale relating to anxiety.¹⁹ Minor mood disorder is common, with an incidence of 18% in the community,²⁰ but the results for these relatives of patients with head injury were almost double this and—perhaps of greater importance—the disturbance remained at least for one year. These results were validated by concurrent administration of a standardised interview as a secondary psychiatric screen.²¹

These burdens on relatives may be viewed in social as well as psychological terms. Social and leisure activity, marital, and indeed global social adjustment scores (social adjustment scale²²) were rated poorer in the relatives of victims of aphasic stroke.¹¹ Evidence of social maladjustment (social adjustment scale—self report²³) in relatives of patients with head injury began to emerge six months after the injury, particularly in roles related to the home, and the maladjustment was still present one year after injury.¹⁹ Thomsen²⁴ and Panting and Merry²⁵ suggested that wives of victims of head injury fared worse than mothers, but Oddy and Humphrey reported the opposite trend.²⁶ Two recent studies in Glasgow found little evidence to support either a qualitative or quantitative difference in the psychiatric or social burden of wives or mothers of men with head injuries.^{17 19}

The stresses on the relatives of victims of head injury

seem to be associated more with their behavioural and cognitive changes than with the physical sequelae of the injury.^{14 24 25 27 28} It is, furthermore, the relative's perception of the burden imposed by the patient which appears to be important.^{7 16 19} This perception may not be related closely to the outcome, since the relatives of people with head injury often complain of inadequate or poorly understood information from doctors.²⁵

What conclusions may we draw? Clearly illness may be associated with a measurable social and psychiatric burden in relatives (compared with control populations). This burden may persist beyond the acute episode and is likely to be related to behavioural as well as physical factors in the illness. As NHS resources decline more families may have to cope with the sick at home, particularly the elderly,²⁹ and doctors will be required to support them. Community resources which should provide back up are inadequately developed, particularly for patients with mental illness and mental handicap.³⁰ Careful prospective controlled studies with defined populations of patients and relatives, such as that of Leff and coworkers, are required to evaluate therapeutic interventions with relatives.³¹ Meanwhile, doctors need to be aware of the normal patterns of adjustments of relatives as well as of patients when ill health strikes.

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- 1 D'Affliti JG, Weitz GW. Rehabilitating the stroke patient through patient-family groups. *Int J Group Psychother* 1974;24:323-32.
- 2 Romano MD. Family response to traumatic head injury. *Scand J Rehabil Med* 1974;6:1-4.
- 3 Lezak MD. Living with the characterologically altered brain injured patient. *Clinical Psychiatry* 1978;39:592-8.
- 4 Isaacs B. Geriatric patients: do their families care? *Br Med J* 1971;iv:282-6.
- 5 McGuire GP. Psychological consequences of childhood leukaemia. *J R Soc Med* 1980;73:217-8.
- 6 Mayou R, Williamson B, Foster A. Outcome two months after myocardial infarction. *J Psychosom Res* 1978;22:439-45.
- 7 Brooks DN, McKinlay WW. Personality and behavioural changes after severe blunt head injury—a relative's view. *J Neurol Neurosurg Psychiatry* 1983;46:336-44.
- 8 Goldberg D. *Manual of the general health questionnaire*. Windsor, Berkshire: NFER Publishing Company, 1978.
- 9 Goldberg D. The concept of a psychiatric case in general practice. *Soc Psychiatry* 1982;17:61-5.
- 10 Kay EL. Psychological aspects of cardiac rehabilitation. *Hospital Update* 1982 Feb:161-70.
- 11 Kinsella GJ, Duffy F. Psychosocial readjustment in the spouses of aphasic patients. *Scand J Rehabil Med* 1979;11:129-32.
- 12 Gibbons JS, Horn SH, Powell JM, Gibbons JL. Schizophrenic patients and their families. A survey in a psychiatric service based on a district general hospital unit. *Br J Psychiatry* 1984;144:70-7.
- 13 Frydman MI. Perception of illness severity and psychiatric symptoms in parents of chronically ill children. *J Psychosom Res* 1980;24:361-9.
- 14 Oddy M, Humphrey M, Uttley D. Stresses upon the relatives of head injured patients. *Br J Psychiatry* 1978;133:507-13.
- 15 Snaith RP, Ahmed SN, Metha S, Hamilton M. Assessment of severity of primary depressive illness. *Psychol Med* 1971;1:143-9.
- 16 Rosenbaum M, Najenson T. Changes in life patterns and symptoms of low mood as reported by wives of severely brain injured soldiers. *J Consult Clin Psychol* 1976;44:881-5.
- 17 Livingston MG, Brooks DN, Bond MR. Three months after severe head injury: psychiatric and social impact on relatives. *J Neurol Neurosurg Psychiatry* (in press).
- 18 Snaith RP, Bridge GW, Hamilton M. The Leeds scales for the self-assessment of anxiety and depression. *Br J Psychiatry* 1976;128:156-65.
- 19 Livingston MG, Brooks DN, Bond MR. Patient outcome in the year following severe head injury and relatives' psychiatric and social functioning. *J Neurol Neurosurg Psychiatry* (in press).
- 20 Goldberg D, Kay C, Thomson L. Psychiatric morbidity in general practice and the community. *Psychol Med* 1976;6:565-9.
- 21 Wing JR, Cooper JE, Sartorius N. *The measurement and classification of psychiatric symptoms*. Cambridge: Cambridge University Press, 1974.
- 22 Weissman MM, Paykel ES. *The depressed woman*. Chicago: University of Chicago Press, 1974.
- 23 Weissman MM, Bothwell S. Assessment of social adjustment by patient's self-report. *Arch Gen Psychiatry* 1976;33:1111-5.
- 24 Thomsen IV. The patient with severe head injury and his family. *Scand J Rehabil Med* 1974;6:180-3.
- 25 Panting A, Merry PH. The long term rehabilitation of severe head injuries with particular reference to the need for social and medical support for the patient's family. *Rehabilitation (Stuttg)* 1972;38:33-7.
- 26 Oddy M, Humphrey M. Social recovery during the year following severe head injury. *J Neurol Neurosurg Psychiatry* 1980;43:798-802.
- 27 Oddy M, Humphrey M, Uttley D. Subjective impairment and social recovery after closed head injury. *J Neurol Neurosurg Psychiatry* 1978;41:611-6.
- 28 McKinlay WW, Brooks DN, Bond MR, Martinage DP, Marshall MM. The short term outcome of severe blunt head injury as reported by relatives of the injured person. *J Neurol Neurosurg Psychiatry* 1981;44:527-33.
- 29 Gilleard CJ, Belford H, Gilleard E, Whittick JE, Gledhill K. Emotional distress amongst the supporters of the elderly mentally infirm. *Br J Psychiatry* 1984;145:172-7.
- 30 Anonymous. Community care [Editorial]. *Br Med J* 1985;290:806.
- 31 Leff J, Kuipers L, Berkowitz R, Eberlein-Vries R, Sturgeon D. A controlled trial of social intervention in the families of schizophrenic patients. *Br J Psychiatry* 1982;141:121-34.