She said that the GMC "successfully kept the whole question of self regulation off the agenda." Although the absolute number of lay members was increased their proportion had decreased. "It could be argued," she wrote, "that the act, rather than being a radical reform, was a revision, a revision which made it possible for a medical elite, as little changed as possible, to remain in power and for professional self-regulation to continue unchallenged." For Stacey the reforms of 1978 reunited the profession—which has so often threatened to split into factions of academics, royal colleges, and general practitioners—but did little for the public interest.

Stacey thinks—with others—that self regulation looks anachronistic at the end of the twentieth century. "A task," she said, "which now faces the profession, and commentators upon it, is to think through what might be viable alternatives, more appropriate for modern health care practice. . . ."

Conclusion

Originally it was primarily doctors who wanted a General Medical Council—in order to keep out the quacks. The difficulties in forming the council resulted from conflicts among the factions of the profession, and because of these conflicts the first council had few effective powers. It had to fight the royal colleges to gain power over undergraduate education, which remained inadequate long after the council was formed. Now the council is struggling to exert its influence over postgraduate and continuing education; still it is being

resisted. Since the beginning of the council general practitioners have had to struggle to be represented, and although elected members are now in the majority, many think that they are excluded from real power.

The public interest, meanwhile, does not seem to have been the first concern of the council, although most members will insist that such is the council's first concern. In the early days priority was given to bringing together the various factions and little attention was paid to education and still less to discipline. Until very recently the council seemed to be more concerned with doctors bringing the profession into disrepute than with them failing in their clinical performance. The emphasis is beginning to change, but the question is whether the council can change fast enough to fend off demands for a body dominated by lay people or directly answerable to government.

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Lesson of the Week

Valproate and spina bifida

Pippa Oakeshott, Gillian M Hunt

Pregnant women taking valproate should be counselled about the risk of spina bifida and offered ultrasonography and amniocentesis

In 1983 it was shown that when a pregnant woman takes the antiepileptic drug sodium valproate (Epilim) during the first trimester she has a 1-2% risk of having a child with spina bifida.¹ This risk becomes more evident with the decline in the overall prevalence of spina bifida.^{2,4} It may be prevented by avoiding the drug during pregnancy or by informed counselling followed by antenatal screening for spina bifida with high resolution ultrasonography, amniocentesis, and abortion of affected fetuses.⁵ In Britain few general practitioners seem to be aware of the risk of spina bifida and the special need for screening pregnant women taking valproate.

We report three cases of spina bifida in children born to women taking valproate as monotherapy who were unaware of the risk and were not offered prenatal diagnosis. All the children are currently receiving care.

Case reports

Case 1—A 27 year old woman had had her epilepsy well controlled with sodium valproate since the age of 22. In 1983 she had a miscarriage, but there were no details. In 1984, after a normal pregnancy, she gave birth at term to a 3020 g boy with open spina bifida at motor level L4. She had continued to take sodium valproate throughout her pregnancy. She had not been screened.

Case 2—In 1985 a 25 year old epileptic woman gave birth at term to a 3500 g girl with open spina bifida at

motor level L5. (She had had a previous termination of pregnancy for social reasons.) She had taken sodium valproate 400 mg twice daily throughout her pregnancy. She was not screened until she was admitted with raised blood pressure at 34 weeks, when an ultrasound scan showed spina bifida.

Case 3—In 1986 a 25 year old epileptic woman gave birth at term to a 3200 g boy with closed spina bifida at motor level L3 and sacral agenesis. She had taken sodium valproate 200 mg three times a day throughout her pregnancy. She had previously had two normal children while taking this drug. She was not screened until she had vaginal bleeding at 30 weeks, when an ultrasound scan showed placenta praevia and spina bifida.

Discussion

The first important epidemiological evidence that valproate might cause spina bifida came in 1982 from Robert and Guibaud in the Rhône-Alpes region of France.⁶ They found that of 72 children with neural tube defects, nine were born to epileptic mothers who had taken valproate during pregnancy. By including these data in a larger study the International Clearing House for Birth Defects Monitoring Systems decided "It is highly likely that valproate causes spina bifida in 1% of fetuses exposed to it in early pregnancy."

Jeavons, in Birmingham, collected data on 196 pregnancies in which the mother had taken valproate;

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157 were normal, but the 39 abnormal pregnancies included nine with spina bifida.⁸ It was suggested that women who have taken valproate in early pregnancy might be counselled about the risk of spina bifida and offered amniocentesis.^{9,10}

In 1983 the Centers for Disease Control analysed the data from Italy, France, and the United Kingdom and concluded: "Sodium valproate should be considered a human teratogen."¹¹ The Centers for Disease Control estimated the risk to a pregnant woman treated with valproate of having a child with spina bifida to be 1-2%, which is similar to the recurrence risk for spina bifida. Robert and Rosa similarly calculated the risk of spina bifida to be 40 times the expected rate after exposure to valproate.¹¹

In 1986 Lindhout and Schmidt published a prospective study of exposure to valproate in utero and neural tube defects.¹² One hundred and twenty epileptic mothers receiving valproate alone produced three infants with neural tube defects; 273 epileptic mothers taking valproate and other drugs also produced three infants with neural tube defects. The results confirmed that "Valproate exposure during the first trimester of pregnancy is causally associated with a considerably increased risk of neural tube defects of 1.5%." More recently Khoury and Holtzman compared the teratogenicity of valproate with thalidomide.¹³ They calculated the relative risks or strengths of the teratogens as 20-25 and 175 respectively and concluded that valproate is a strong teratogen.

The Committee on Safety of Medicines has received 97 reports by the yellow card system of fetal abnormalities possibly associated with mothers taking valproate during pregnancy (Committee on Safety of Medicines, personal communication, 1988). Of these, 26 were spina bifida. A further 20 cases were multiple malformations or hydrocephalus, which may have included some cases of spina bifida. The remaining 51 cases were of 25 other anomalies, most of which were less serious.

The induction of spina bifida by valproate has been confirmed by many animal studies, and valproate was the drug chosen by Michejda and McCullough to provide an animal model for research on spina bifida.¹⁴ They gave high doses of valproate to three pregnant monkeys for three days corresponding to the critical period of neural tube formation. One miscarried early but both the other fetuses developed spina bifida.

Any woman with epilepsy requiring treatment has a risk of having a child with a congenital malformation or mental retardation two to three times greater than average because of both her disease and its treatment.¹⁵ All epileptic drugs carry specific risks, and sodium valproate is a first choice anticonvulsant.¹⁶ It may cause a characteristic pattern of facial malformations in the fetus, but there is no substantial evidence that it causes any severe malformation other than spina bifida, for which screening is clearly essential.¹⁷

As shown by our three cases, few general practitioners seem to be aware of the risk of spina bifida due to valproate. In one study of general practitioners (including nine lecturers in general practice), most of whom were attending a postgraduate course, only four out of 55 knew of the risk of spina bifida, though most would have investigated the side effects. Consulting the British data sheet on sodium valproate, however, would not have helped, as this completely fails to mention the risk of spina bifida and merely states that the drug is teratogenic in animals and that "pregnancies should be monitored."¹⁸ Even the *British National Formulary* reference to valproate does not

mention spina bifida except separately in the section on prescribing in pregnancy, where it states that an increased risk of neural tube defects has been reported but fails to recommend specific screening.¹⁹

This contrasts with the United States, where the product information clearly states that the risk of women exposed to valproate having children with spina bifida is roughly 1-2%.²⁰ Increased awareness of the risk and the fact that in America valproate is used only for absence seizure disorders and is thus less commonly prescribed may have reduced the number of American babies born with spina bifida due to exposure to the drug in utero.¹⁷

The prenatal diagnosis of spina bifida in a mother treated with valproate enables an affected pregnancy to be terminated if she wishes. In France since 1983 women taking valproate during the first trimester have been counselled and offered amniotic fluid examination and fetal ultrasound.³ When done at 16-18 weeks of gestation this should detect 92-95% of all neural tube defects.^{21,22} In three years three cases of spina bifida were thus diagnosed and the pregnancies terminated. One other case escaped screening.

The three French cases of spina bifida which were diagnosed in utero and subjected to termination contrast with the three cases in our series, in which the infants were born during the same period (1983-6) when no special screening was done. They underline the need for awareness of the teratogenicity of valproate and for counselling and the offer of prenatal diagnosis of spina bifida for pregnant women using the drug.

Finally, as it is not so much a case of prescribing in pregnancy as a woman becoming pregnant while taking the drug, possibly general practitioners should review their routine repeat prescriptions of sodium valproate to epileptic women of childbearing age.

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